ToTem

Phase I study of transfer of effector memory T cells (Tem) following allogeneic stem cell transplantation.

Trial Sponsor:	University College London
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For the Sponsor:		
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Please note: This trial protocol must not be applied to patients treated outside the ToTem trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

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1. PROTOCOL SUMMARY

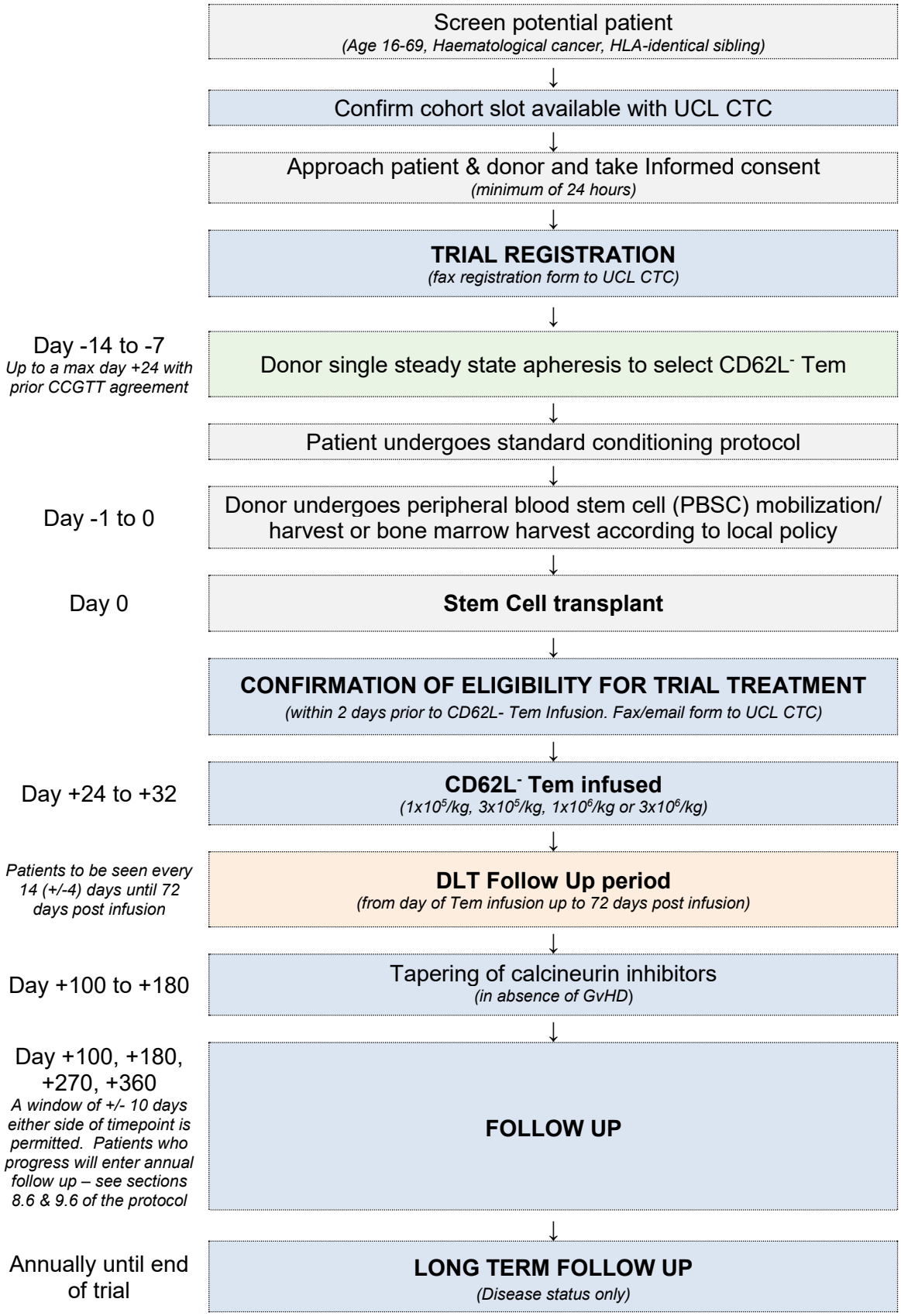
1.1. Summary of Trial Design

Title:	Phase I study of transfer of effector memory T cells (Tem) following allogeneic stem cell transplantation.
Short Title/acronym:	ToTem
Sponsor name & reference:	University College London – UCL/13/0372
Funder name & reference:	Medical Research Council (MR/R025436/1)
Clinicaltrials.gov no:	NCT03836690
Design:	Phase I study using a Bayesian Time-to-event continual reassessment method to determine safety and maximum tolerated dose (MTD).
Overall aim:	To determine the feasibility and safety of transfer of donor Tem following allogeneic stem cell transplantation
Primary endpoint:	Occurrence of dose-limiting toxicity (DLT, defined as acute-pattern GvHD grade II-IV)
Secondary endpoints:	1. Incidence and severity of acute GvHD (whether dose-limiting or not) 2. Incidence and severity of chronic GvHD 3. Non-relapse mortality at 1 year 4. Overall- and event-free survival at 1 year 5. Incidence/type of infection requiring inpatient admission at 1 year 6. Total number of inpatient days at 1 year
Exploratory Biological Studies:	1. T Cell Receptor (TCR) repertoire analysis by deep CDR3 sequencing 2. Chimerism and reconstitution of immune subsets 3. Reconstitution of virus- and bacterial-specific immunity 4. Relationship between donor demographics/immune profile with number of $CD62L^-$ Tem selected. 5. Alemtuzumab levels on the day of $CD62L^-$ Tem infusion
Target accrual:	Maximum 18 patients

Patient and Donor Registration Inclusion & exclusion criteria:	**Patient Inclusion criteria** *(At registration (pre-transplant; prior to commencement of transplant conditioning))* • Severe aplastic anaemia or • Primary immune deficiency or • Haematological cancer (one of following): ○ Non-Hodgkin's lymphoma in CR or PR (and VGPR if applicable for disease) ○ Hodgkin's lymphoma in CR or PR ○ Chronic (Pro-)Lymphocytic Leukaemia in CR, CRi or PR ○ Plasma cell myeloma in CR, sCR, VGPR or PR ○ Acute myeloid leukaemia in CR or CRi ○ Acute lymphoblastic leukaemia in CR or CRi ○ Myelodysplastic syndrome <10% blasts ○ Chronic myelomonocytic leukaemia <10% blasts • Suitable for HLA-identical sibling transplant using a standard alemtuzumab-based conditioning regimen with calcineurin-inhibitor based immunoprophylaxis • Aged ≥16 years, and <70 years • Written informed consent **Patient Exclusion Criteria** • Women who are pregnant or breastfeeding • Life expectancy of <8 weeks • Currently taking part in any other interventional clinical research study (involving any IMP, ATIMP or cellular therapy) • Proposed use of any other method of GvHD prophylaxis other than alemtuzumab and calcineurin inhibitor • Organ dysfunction: LVEF<45%, glomerular filtration rate (corrected) <50ml/min, bilirubin >50µmol/l, or AST/ALT > 2.5 x ULN **Donor inclusion criteria** • Aged ≥ 16 years • HLA-identical sibling • Have met transplant centre criteria regarding suitability for cell therapy donation

	• Negative for HIV 1 and 2, hepatitis B, hepatitis C, HTLV-1 and 2, syphilis serology (to be confirmed before registration) • Written informed consent **Donor exclusion criteria** • Pregnant/lactating women
Patient Pre-Treatment exclusion criteria:	**Pre-Treatment Exclusion Criteria** *(eligibility check prior to CD62L$^-$ Tem Infusion)* • Prior or active acute GvHD • Relapse or progressive disease • Primary or secondary graft failure • Other cellular therapies
Number of sites:	3
Treatment summary:	Donors will undergo a steady state apheresis for the collection of T cells between day -14 and day +24 of the allo-SCT according to logistics. Selection of Tem will be performed at UCL before distribution of cryopreserved cells to the trial centre; donor Tem will be transferred on day 28 ±4 following allo-SCT.
Duration of recruitment:	30 months
Duration of follow up:	Patients will be followed up for a minimum of 1 year post-stem cell transplant
Definition of end of trial:	The end of the trial will be when the final data item for the final patient is received by the Sponsor (i.e. it is anticipated that this will be when the final patient completes their day 360 follow-up visit).

1.3. Trial Schema



2. INTRODUCTION

2.1. Background

Following allogeneic stem cell transplantation (allo-SCT), a serious complication is graft-versus-host disease (GvHD) which occurs as a result of immune injury to patient tissues mediated by donor T cells reacting to alloantigens (1, 2). It causes death in about 10% of patients and has a major negative impact upon quality-of-life in surviving patients (1, 2). Prevention of GvHD relies upon depletion of donor T cells or drugs that block T cell function. However, these strategies delay immune recovery, increase the risk of life-threatening infection and lead to mortality in a further 10-15% of patients. A key challenge following allo-SCT is to accelerate immune reconstitution while at the same time avoiding GvHD. At UCL, we have run several trials to address this challenge involving the infusion of 1) positively selected, pathogen-specific T cells (e.g. CMV-IMPACT, NCT01077908) and 2) 'allo-depleted' T cells following in vitro removal cells activated upon exposure to recipient leukocytes (e.g. ICAT, NCT01827579). Routine use of these or other proposed strategies into normal clinical practice will not only depend upon their efficacy but also their complexity and cost; for this reason, there is an urgent need to test novel technologies that are both affordable and readily applicable.

Because alloreactivity is mainly derived from the naïve (or antigen inexperienced) T cell population (1, 2), one approach for separating GvHD-inducing T cells from pathogen-specific T cells is to select memory (or antigen experienced) T cells for adoptive transfer (3). Murine studies of allo-SCT have shown that memory T cells lacking surface expression of CD62L ($CD62L^-$) are able to engraft following transplant and respond to pathogen challenge, but unlike the CD62L-expressing ($CD62L^+$) T cells, do not induce GvHD (3). In addition to differences in T cell repertoire, memory T cells also possess repertoire-independent properties that limit their capacity to sustain effector cytokine synthesis and induce tissue injury (4). Human $CD62L^-$ memory T cells also demonstrate reduced responses to allogeneic antigenic stimulation in vitro compared with $CD62L^+$ T cells but maintain reactivity to viral antigens (5). These findings offer the opportunity of using memory T cells to enhance immune reconstitution following allo-SCT and provide broad immunity to multiple pathogens without the risk of GvHD.

An early phase US clinical trial published by our collaborator (Dr. M. Bleakley, Fred Hutchinson Cancer Research Center, USA) (6, 7) has demonstrated proof-of-concept that transfer of memory T cells selected using another marker (T cells lacking surface expression of CD45RA or $CD54RA^-$) is feasible following allo-SCT in human patients undergoing allo-SCT. In this single arm clinical trial, 35 patients with high-risk leukaemia received CD34-selected allogeneic peripheral blood stem cells (PBSC) and a defined dose of $CD45RA^-$ memory T cells obtained by negative immunomagnetic selection from the same graft (1×10^7 T cells/kg recipient weight) (7). The risk of acute GvHD was 66%, a rate similar to historical controls, indicating that the $CD45RA^-$ product still retains substantial alloreactivity. However, the cumulative incidence of chronic GvHD was very low at 9% compared to 50% in historical controls; this finding is difficult to interpret as the dose of $CD45RA^-$ T cells infused was over 10-fold less than usually transferred as part of an unmanipulated PBSC graft. Furthermore, the intended benefit of accelerating immune reconstitution may have been counteracted by the use of glucocorticoids in 62% of patients to treat acute GvHD. One potential explanation for the residual alloreactivity of the $CD45RA^-$ product is the continued presence of central memory T cells, especially amongst the $CD4^+$ T cell subset that constitutes the majority of the product (6); of note,

central memory phenotype T cells still cause GvHD in pre-clinical models of transplantation (8, 9).

Investigators from Stanford have reported a modified selection method that employs a negative selection of $CD45RA^+$ cells followed by a positive selection of $CD8^+$ T cells ($CD45RA^-CD8^+$) (10). They transferred escalating doses of $CD45RA^-CD8^+$ T cells to 15 patients with relapsed blood cancers after allo-SCT. No adverse infusional events or dose-limiting toxicities occurred; grade II acute GvHD occurred in one patient. Consistent with removal of $CD4^+$ T cells (that have a higher proportion of cells with a central memory phenotype), the majority of the remaining T cells in the final product possessed an effector memory T cell (Tem) phenotype (10).

Properties of selected $CD62L^-$ Tem cells

Because $CD62L^-$ T cells lack both naïve T cells and the central memory T cells, we reasoned that a selection method removing CD62L-expressing T cells may provide a product with favourable characteristics compared to $CD45RA^-$ product (11). To assess the feasibility of using CD62L depletion for removal of naïve and central memory T cells, we performed small-scale experiments using peripheral blood mononuclear cells from healthy volunteers and immune-magnetic depletion of $CD62L^+$ cells. CD62L expression upon T cells remains constant upon storage at room temperature for 24 hours allowing suitable transit time for cells before selection. Among un-manipulated cells, 19.6±8.7% of $CD3^+$-gated cells were $CD62L^-CD4^+$ and 17.0±8.4% were $CD62L^-CD8^+$ (n=16). In 5 donors who were CMV and/or EBV seropositive, the bulk of virus-specific $CD8^+$ T cells identified by pentamer were within the $CD62L^-$-gated population, and particularly for CMV, within the $CD45RA^+$ effector memory (Temra) fraction. Among $CD3^+$-gated cells, the CD62L-depleted fraction was almost completely depleted of $CD45RA^+CCR7^+$ naïve T cells indicating that substantial shedding of CD62L did not occur upon binding to magnetic beads. The $CD62L^-$ $CD4^+$ T-cell fraction contained predominantly $CD45RA^-$ Tem whereas the $CD62L^-$ $CD8^+$ T-cell fraction contained both CD45RA− Tem and CD45RA+ Temra.

Because impaired immunity to CMV and EBV following allo-SCT leads to major mortality and morbidity, we have evaluated the specificity of T cells retained in the $CD62L^-$ product (11). T-cell immunity to CMV was retained following CD62L depletion as demonstrated by similar frequencies of $CD4^+IFN\text{-}\gamma^+$ cells and increased frequencies of $CD8^+IFN\text{-}\gamma^+$ cells detected by intracellular staining following stimulation with a CMVpp65 peptide pool (mean 2.1±1.8-fold increase). We also observed moderately increased frequencies of EBV-specific $CD8^+IFN\text{-}\gamma^+$ cells detected by intracellular staining following stimulation with an EBNA-1 peptide pool (mean 2.7±1.7-fold increase). When compared with unmanipulated cells, CD62L depletion led to a marked reduction in the proportion of B cells and monocytes but maintenance of $CD4^+CD25^+Foxp3^+$ regulatory T cells and a relative increase in both natural killer and natural killer T cells.

Comparison of memory T cell selection through depletion of CD62L$^+$ versus CD45RA$^+$ cells

We have demonstrated favourable product characteristics compared to the CD45RA depletion method (11). The key product differences are summarized below:

- The CD62L$^-$ Tem product retains 2.5-fold more CD8$^+$ T cells than the product generated by the CD45RA-based selection method
- In contrast to the CD45RA$^-$ product, the CD62L$^-$ Tem product lacks central memory T cells which can promote GvHD in animal models
- Unlike the CD45RA$^-$ product which removes CD8$^+$ but not CD4$^+$ alloreactive T cells, the CD62L$^-$ Tem product depletes both alloreactive CD8$^+$ and CD4$^+$ T cells
- Unlike the CD45RA- product, the CD62L-based selection method does not remove CD45RA$^+$ Tem (Temra), a cell population that may be important in early control of certain pathogens (e.g. CMV).

Feasibility of clinical scale selection using CliniMACs-based depletion

We have now generated a clinical scale protocol suitable for CD62L depletion (11). Using steady-state leukapheresis products from allogeneic sibling donors, three clinical-scale runs for validation of CD62L depletion using the CliniMACs were performed under GMP conditions. All CD62L-depleted fractions tested negative for bacterial and fungal growth using aerobic and anaerobic blood culture bottles following 10-day incubation, and environmental monitoring and airborne particle counting were within the permitted range for current GMP. Processing time was ~2.5 hours with a median viability of 90% in CD62L-depleted fractions. The cell product characteristics in terms of phenotype, depletion of alloreactivity and retention of virus specific responses conformed to our findings in the small-scale selections. The MHRA have been consulted and confirmed that the CD62L$^-$ Tem product does not constitute an Advanced Therapy Investigational Medicinal Product (ATIMP).

Predicted numbers of virus-specific T cells in the CD62L$^-$ Tem product

On the basis of the current data set and historical data relating to total nucleated cell count and CD3$^+$ content of steady-state leukaphereses from allogeneic donors, we estimate that the CD62L-depletion procedure will yield a total $14.1 \times 10^6 \pm 9.1$ CD3$^+$CD62L$^-$ cells/kg recipient weight assuming an adult weight of 70 kg (11). Based upon our analysis of numbers of virus-specific CD8+ T cells in CD62L$^-$ Tem products, we estimate that 1 x 10^6/kg CD62L$^-$ Tem derived from CMV seropositive donors will contain a ~7.4 ± 3.2 x 10^4 CMV pp65-specific CD8$^+$ T cells/kg and 1.4 ± 1.4 x 10^4 EBV-specific T cells. This dose of cells is similar to or exceeds the dose of virus-specific T cells used in clinical trials for treatment of CMV or EBV infection (12-15). Importantly, the CD62L$^-$ Tem product contains memory T cells with multiple specificities and thus has the potential to allow re-constitution of broad immunity against multiple pathogens, but using a simpler technology with lower costs.

Rationale for trial and target population

We have chosen the strategy of CD62L$^-$ Tem to accelerate immune reconstitution because 1) the selection is of low cost and can be operated at all UK transplant centres under existing regulation and without additional infrastructure and 2) the CD62L$^-$ product has potentially favourable product characteristics compared to a CD45RA$^-$ memory T cell product also being evaluated in clinical trials (6, 11). At this early stage, it is not known

whether any one approach for memory T cell selection is superior to another. We are therefore collaborating with clinical investigators studying the CD45RA$^-$ T cells to determine the same biological endpoints for immune reconstitution to 1) determine whether transfer of different memory T cell populations have different activities in vivo and 2) to provide new knowledge regarding the mechanisms underlying these effects.

The target population in this trial is patients undergoing an HLA-identical sibling haematopoietic stem transplant. The number of patients undergoing this procedure is 470/year in the UK, 5900/year in Europe and 2500/year in the US. The intended benefit of CD62L$^-$ Tem transfer is to accelerate immune reconstitution in patients undergoing allo-SCT without incurring a greater risk of GvHD. Patients will therefore potentially benefit from improvements in clinical outcomes as a result of reduced non-relapse mortality secondary to infection. A reduction in hospital readmission and the need for additional treatments will help to improve the quality-of-life for patients. Reduced length-of-stay, re-admissions and drug costs could also reduce the financial burden to health care systems and increase value for money

3. TRIAL DESIGN

Phase I study using a Bayesian Time-to-Event Continual Reassessment Method (CRM) to determine safety and maximum tolerated dose (MTD) of CD62L$^-$ Tem. Eligible patients and HLA-identical sibling donors will be registered prior to transplant. Donors will undergo an additional steady state apheresis for the collection of T cells between day -14 and day +24 of the allo-SCT according to logistics. Selection of Tem at the required dose will be performed at UCL Centre for Cell, Gene and Tissue Therapeutics (CCGTT) before distribution of the cryopreserved cells to the trial centre. Donor Tem will be infused on day 24-32 following allo-SCT. Patients will be followed-up for a minimum of 1 year with specific evaluation points just prior to Tem infusion and at days +100, +180, +270 and +360 post-stem cell transplant. Patients are then seen annually until the end of the trial.

3.1. Trial Objectives

- To determine the safety and Maximum Tolerated dose (MTD) of donor Tem transfer following allogeneic stem cell transplantation and to recommend Phase II dose of Tem
- To determine the impact of Tem transfer upon the kinetics and breadth of T cell reconstitution

3.2. Trial Endpoints

Primary Endpoint

1. Occurrence of dose-limiting toxicity (DLT) (defined as acute-pattern GvHD grade II-IV)

Secondary Endpoints

1. Incidence and severity of acute GvHD (whether dose-limiting or not)
2. Incidence and severity of chronic GvHD
3. Non-relapse mortality at 1 year
4. Overall- and event-free survival at 1 year
5. Incidence/type of infection requiring inpatient admission at 1 year
6. Total number of inpatient days at 1 year

Biological Endpoints

1. TCR repertoire analysis by deep CDR3 sequencing
2. Chimerism and reconstitution of immune subsets
3. Reconstitution of virus- and bacterial-specific immunity
4. Relationship between donor demographics/immune profile with number of CD62L$^-$ Tem selected.
5. Alemtuzumab levels on the day of CD62L$^-$ Tem infusion

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- 'Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority, and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 (Timelines for Data Return)
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 14 (Trial Monitoring and Oversight)
- The Human Tissue Act 2004
- Human Tissue (Quality and Safety for Human Application) Regulations (SI 2007/1523) and the sites HTA license (for procurement, testing and distribution)

4.1.1. Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of a site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of treating haematological cancers and performing allogeneic stem cell transplants for haematological malignancies. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI plans to take a leave of absence UCL CTC **must be informed promptly.** For absences greater than three months, or where the PI is no longer able to perform his/her duties at the site, UCL CTC may terminate recruitment at site. A new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or two-yearly

where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site Initiation and Activation

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by form of on-site visit. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.2.2. Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A signed and dated copy of the PI's current CV (with documented up-to-date GCP training, or copy of GCP training certificate)

In addition, the following agreements must be in place:

- A signed model non-commercial agreement (mNCA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)
- A signed Service Level Agreement (SLA) between the Centre for Cell, Gene and Tissue Therapeutics (CCGTT) and relevant institution (usually an NHS Trust/Health Board)

4.2.3. Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion and return of CRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24 hour medical advice** for trial patients

5. INFORMED CONSENT

Sites are responsible for assessing a patient/donor's capacity to give informed consent.

Sites must ensure that all patients and donors have been given the current approved version of the patient/donor information sheets, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent forms.

Sites must assess a patient's and donor's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient and/or donor requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient and donor prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient, and the donor information sheet discussed with the donor.

A **minimum of twenty four (24) hours** must be allowed for the patient and donor to consider and discuss participation in the trial. Specifically, a minimum of 24 hours should pass between discussing the trial with the patient and donor (including providing them with the Patient Information Sheet (PIS)/Donor Information Sheet (DIS)) and them subsequently signing the Informed Consent Form.

Written informed consent on the current approved version of *both* the patient consent form and donor consent form must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient/donor notes. **Both the patient and the donor must consent in order for the patient to be registered into the trial.** The trial may be discussed with the patient and donor separately, however consent from both parties will be required prior to registration.

Site staff are responsible for:

- checking that the current approved version of the patient and donor information sheet and consent form are used
- checking that information on the consent forms are complete and legible
- checking that the patient and donor has completed/initialled <u>all</u> relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient or donor
- checking that an appropriate member of staff has made dated entries in the patient's and donor's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- giving the patient and donor a copy of their signed consent form and information sheet
- giving the patient a patient contact card with contact details for 24 hour medical care
- following registration, adding the patients' and donor's trial number to all copies of the consent form, which should be filed in the patient's/donor's medical notes and the original in the investigator site file

The right of the patient or donor to refuse to participate in the trial without giving reasons must be respected. All patients and donors are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

6. SELECTION OF PATIENTS AND DONORS

6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial and the reasons why they were not registered into the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2. Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria must be addressed prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation of eligibility must be documented in the patients' notes and on the registration CRF. Eligibility to receive trial treatment must also be confirmed prior to the patient receiving the $CD62L^-$ Tem infusion and verified with UCL CTC.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-Registration Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1. Patient Registration Inclusion criteria

- Severe aplastic anaemia or
- Primary immune deficiency or
- Haematological cancer which can be **ONE OF** the following (see Appendix 4 for complete response/remission (CR) and partial response/remission (PR) definitions):
    - Non-Hodgkin's lymphoma (NHL) in CR or PR (and VGPR in applicable disease types)
    - Hodgkin's lymphoma (HL) in CR or PR
    - Chronic (Pro-)lymphocytic leukaemia (CLL or PLL) in CR, CRi or PR
    - Plasma cell myeloma (PCM) in CR, sCR, VGPR or PR
    - Acute myeloid leukaemia (AML) in CR or CRi
    - Acute lymphoblastic leukaemia (ALL) in CR or CRi
    - Myelodysplastic syndrome (MDS) < 10 % blasts in bone marrow
    - Chronic myelomonocytic leukaemia (CMML) < 10% blasts in bone marrow
- Suitable for HLA-identical sibling transplant using a standard alemtuzumab-based conditioning regimen with calcineurin-inhibitor based immunoprophylaxis
- Aged ≥ 16 years, <70 years
- Written informed consent

6.2.2. Patient Registration Exclusion criteria

- Women who are pregnant or breast-feeding
- Life expectancy of < 8 weeks
- Currently taking part in any other interventional clinical research study (involving any IMP, ATIMP or cellular therapy)
- Proposed use of any other method of GvHD prophylaxis other than alemtuzumab and calcineurin inhibitor
- Organ dysfunction:
    - LVEF <45%
    - glomerular filtration rate (corrected) <50ml/min
    - Bilirubin > 50 µmol/l
    - AST or ALT >2.5 x ULN (NB: If both are performed then both must be ≤2.5 x ULN)

6.2.3. Patient Trial Treatment Exclusion criteria

Following the stem cell transplant the following exclusion criteria must be checked within 2 days prior to the planned CD62L$^-$ Tem infusion date. The patient's eligibility for trial treatment must be confirmed with UCL CTC prior to infusion taking place (see section 7.2) and continually assessed up to the point of Tem infusion.

- Prior or active acute pattern GvHD of any grade
- Relapse or progression
- Primary or secondary graft failure
- Has received other cellular therapies

6.3. Allogenic Donor Eligibility

There will be no exception to the eligibility requirements at the time of registration. Assessment of related donor eligibility is the responsibility of the site.

Donors must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-Registration Assessments) for the list of assessments and procedures required to evaluate the suitability of donors prior to entry.

6.3.1. Donor inclusion criteria

- Aged ≥ 16 years
- HLA-identical sibling
- Have met transplant centre criteria regarding suitability for cell therapy donation
- Negative for HIV 1 and 2, hepatitis B, hepatitis C, HTLV-1 and 2, syphilis serology (to be confirmed before both registration and at time of or up to 7 days following donation)
- Written informed consent

6.3.2. Donor exclusion criteria

- Pregnant/lactating women

6.4. Pregnancy and birth control

6.4.1. Definitions

Definition of women of childbearing potential (WOCBP) and fertile men

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who:

- Has not undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- Is not postmenopausal (a post-menopausal woman is a female who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- Has not had premature ovarian failure confirmed by a specialist gynaecologist

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

6.4.2. Risk of exposure to trial treatment during pregnancy

$CD62L^-$ Tem is a donor derived blood product with no manufacturing process and involves depletion of $CD62L^+$ cells via immune-magnetic depletion. Although similar T-cell products have been used in donor lymphocyte infusions following allogeneic stem cell transplantation, there is currently no pre-existing safety data for the specific use of $CD62L^-$ Tem in pregnant women. There is also a limited amount of data from the use of alemtuzumab in pregnant women and the exact drugs used during the alemtuzumab-based conditioning regimen will be dependent upon the treating site's standard of care. Side effects of allo-STC and $CD62L^-$ Tem (e.g. GvHD) could necessitate other treatment that could also be a risk to a foetus.

Therefore, as the safety implications are unknown treatment has been assessed as having a high risk of teratogenicity/fetotoxicity. Female patients who are pregnant or who are breast feeding are excluded from entry into the trial.

6.4.3. Pregnancy testing

All female trial patients and female donors who are WOCBP must have a negative serum or negative highly sensitive urine pregnancy test (minimum sensitivity 25 IU/l or equivalent units of HCG) at prior to registration (see section 9.1). Pregnancy testing is repeated prior to Tem-infusion in patients only (see section 9.2).

6.4.4. Contraceptive advice

<u>Requirement for female patients</u>

All female trial patients who are WOCBP must consent to use one of the following methods of highly effective contraception from the start of treatment (Tem cells infusion) until 6 months post Tem infusion. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral

    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral (e.g. desogestrel)
    - injectable
    - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1, 2]
- sexual abstinence[3]

1. Contraception methods that are considered to have low user dependency.

2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial patient and that the vasectomised partner has received medical assessment of the surgical success.

3. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Requirement for male patients with female partners who are pregnant or WOCBP

Due to the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including male patients who have had vasectomies) must consent to use condoms with female partners who are WOCBP or partners who are pregnant, during treatment (inclusive of the conditioning regime) and until 6 months post Tem infusion.
- Male patients must also advise their female partners who are WOCBP regarding contraceptive requirements as listed for female patients who are WOCBP.

For female and male patients

The method(s) of contraception used must be stated in the patient medical notes. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

6.4.5. Action to be taken in the event of a pregnancy

Female patients:

If a female patient becomes pregnant:

- prior to Tem infusion, the patient will be withdrawn from the trial and will not receive trial treatment.
- after Tem infusion, during the pregnancy at-risk period (until 6 months post infusion), the patient (or their female partner) will be followed up until 6 weeks after the end of the pregnancy if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant, or a pregnant female partner is exposed to trial treatment after Tem infusion and until 6 months post infusion, the male

patient can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

Female donor:

If a female donor becomes pregnant prior to apheresis, the donor and respective patient will be withdrawn from the trial and the patient will not receive trial treatment.

Notification to UCL CTC

Refer to Pregnancy Report Processing (see Pharmacovigilance section 12.6)

6.4.6. Long term infertility

Studies to evaluate the effect of $CD62L^-$ Tem on fertility have not been performed and the risk on male and female fertility is unknown. Patients who wish to have children in the future should be given advice regarding sperm or oocyte cryo-conservation prior to treatment in line with standard local policy.

6.4.7. Lactation

The effect of $CD62L^-$ Tem in lactating females is currently unknown. In pre-clinical studies alemtuzumab was detected in the milk and offspring of lactating female mice. It is unknown whether alemtuzumab is excreted in human milk, and a risk to the suckling newborn/infant cannot be excluded. Therefore, females who are breast feeding are excluded from trial entry.

7. REGISTRATION PROCEDURES

There is a two-step registration process for ToTem:

1. Trial Registration – Initial registration into the trial of the patient and donor prior to donor apheresis and patient transplant conditioning.
2. Confirmation of eligibility for trial treatment – after patient stem cell transplant and within 2 days prior to CD62L$^-$ Tem infusion, patient eligibility for trial treatment should be reassessed (see section 6.2.3) and confirmed with UCL CTC.

7.1. Trial Registration

Registration will be undertaken centrally at UCL CTC and this must be performed **prior to donor apheresis and patient transplant conditioning**. Pre-registration evaluations for patients and donors should be carried out at sites as detailed in section 9.1 (Pre-Registration Assessments).

Following the pre-registration assessments, confirmation of eligibility, and the consent of the patient and donor at a site, the registration CRF must be fully completed and faxed to UCL CTC. This will be used to confirm patient and donor eligibility. If further information is required UCL CTC will contact the person submitting the registration form to discuss the patient and request updated forms to be faxed.

N.B. If the site is unable to fax, registration forms may be sent by email. If emailing forms, identifiable information on the form (e.g. date of birth) must be redacted before it is emailed to ctc.ToTem@ucl.ac.uk. The identifiable information must be provided to UCL CTC via telephone so that UCL CTC can transcribe this information onto the form. The un-redacted form must then be posted to UCL CTC, and a copy kept in the patient file at site.

Once eligibility has been confirmed a trial number (e.g. TOT-01) and cohort dose allocation will be assigned to the patient. The donor will also be assigned a trial number (e.g. TOT-01-D) which will link them to the trial patient.

UCL CTC will e-mail confirmation of the patient's inclusion in the trial, their trial number and cohort allocation to the PI, main contact and main research nurse (if different from main contact) and the cell processing laboratory (CCGTT). Details of this should be added to the registration form by the site.

Registration fax number:	020 7679 9861
Registration email address:	ctc.ToTem@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once registration has been completed the **patient and the donor** must be provided with the following:

- A copy of their signed consent form and patient/donor information sheet
- A patient contact card. Site contact details for 24 hour medical care must be added to this card. Patients should be advised to carry this with them at all times while participating in the trial.

After registration the ToTem GP letter **must be sent to the patient's GP** by the site to inform them they are participating in the trial.

7.2. Confirmation of eligibility for trial treatment

Eligibility for trial treatment must be confirmed with UCL CTC **prior to CD62L$^-$ Tem infusion** (trial treatment) (see patient trial treatment exclusion criteria section 6.2.3). The Confirmation of Eligibility for trial treatment CRF must be faxed to UCL CTC **within 2 days prior to** the infusion taking place, allowing sufficient time for UCL CTC to process the CRF. If confirmation is required urgently (e.g. the CRF is faxed on the same day as the infusion) provide as much advance notice as possible and telephone the ToTem Trial Coordinator to inform them of this.

N.B. If the site is unable to fax, the Confirmation of eligibility for trial treatment CRF may be sent by email to ctc.ToTem@ucl.ac.uk. The identifiable information must be provided to UCL CTC via telephone so that UCL CTC can transcribe this information on to the form. The un-redacted form must then be posted to UCL CTC, and a copy kept in the patient file at site.

Once eligibility for trial treatment has been confirmed, UCL CTC will e-mail the PI, main contact and main research nurse (if different from main contact) confirming that the patient may proceed with trial treatment.

Registration fax number:	020 7679 9861
Registration email address:	ctc.ToTem@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Evaluations for eligibility should be undertaken up until the time of the infusion and if the eligibility status of the patient changes (as per section 6.2.3 and section 15), treatment should be withheld and UCL CTC contacted immediately. Pre-treatment assessments should be performed as per section 9.3.

8. TRIAL TREATMENT

Investigational treatments

The investigational treatment is: Donor T cells depleted of CD62L$^+$ cells (CD62L$^-$ Tem).

8.1. Treatment Summary

Day number	Task
Day -14 to -7 (recommended) *up to +24 permissible (with prior agreement from CCGTT lab)*	Donor Tem Apheresis - Perform steady state lymphocyte collection
	Patient undergoes standard conditioning protocol
Day-1 to 0	Donor peripheral blood stem cell (PBSC) mobilization/ harvest or bone marrow harvest as per local policy
Day 0	Stem Cell Transplant
Day +24 to +32	Trial Treatment - Infuse CD62L$^-$ Tem
Day +100 to +180 *(start taper at day +100 and aim to complete taper by day +180)*	Tapering of calcineurin inhibitor in absence of GvHD

8.2. Treatment Details

8.2.1. Donor CD62L$^-$ Tem Apheresis and PBSC/Bone marrow harvest

Following Trial Registration, the donor may undergo single steady state apheresis for the purpose of selecting CD62L$^-$ Tem. The trial site must arrange the time and date of leukapheresis with the Centre for Cell, Gene and Tissue Therapeutics (CCGTT) as soon as possible after registration (see **Error! Reference source not found.**)

The preferred schedule is for donors to undergo apheresis between -14 to -7 days prior to day 0 of the stem cell transplant (the day when the stem cells are infused). The apheresis product will then be couriered to CCGTT and processed according to the patient's cohort. Following the steady state apheresis, donors will then undergo peripheral blood stem cell (PBSC) mobilization/harvest or bone marrow harvest according to local policies.

Because of the logistics involved in scheduling apheresis appointments and processing laboratory availability at each trial centre, it will also be permissible for donors to undergo a steady state apheresis after PBSC or bone marrow donation. Therefore, a maximum window for apheresis is allowed between -14 days prior to and up to +24 days following day 0 of the transplant with prior agreement from CCGTT.

8.2.2. Patient Conditioning and Stem Cell transplant

All patients will undergo a standard conditioning protocol employing immunoprophylaxis with alemtuzumab, in combination with a calcineurin inhibitor. This is standard treatment and the conditioning drugs and post-transplant immunosuppression are not considered IMPs for the purposes of the trial; nor is the transplant considered a trial-specific

procedure. Conditioning, transplant, post-transplant anti-microbial/anti-viral prophylaxis will be given in accordance with local policies.

8.2.3. Investigational Treatment - CD62L$^-$ Tem infusion

Following the completion of the pre-treatment assessments (see section 9.3) and confirmation of eligibility for trial treatment (see section 7.2 and 6.2.3) patients may receive the CD62L$^-$ Tem product.

The patient will have the donor CD62L$^-$ Tem as a single infusion between day +24 and day +32 post-transplant. The site should request the CD62L$^-$ product from CCGTT as described in **Error! Reference source not found.** of the Laboratory Manual. The product for re-infusion will be recovered from cryopreservation, thawed rapidly at 37°C and re-infused in less than 30 minutes after the thawing process is complete following local policy for infusion of T-cell by a suitably trained and accredited staff.

8.2.4. Post-Trial Treatment

In the absence of GvHD, tapering of calcineurin inhibitors will be from day +100 onwards with the aim that they are discontinued by day +180.

8.3. CD62L$^-$ Tem Dose Levels

We will investigate 4 CD62L$^-$ Tem dose levels ($1x10^5$/kg, $3x10^5$/kg, $1x10^6$/kg and $3x10^6$/kg). At the time of patient registration, UCL CTC will send an e-mail confirming the cohort the patient is in and the dose level they will receive.

The first two patients will receive dose level 3 ($1x10^6$/kg), and then be followed for 72 days post Tem infusion to monitor for GvHD onset. Data from patients 1 and 2 will be used to update the prior DLT risks, and a formal Safety Review Committee (SRC) meeting will be held to recommend the dose to be given to patients 3 and 4. After following up patients 3 and 4 for 72 days post infusion to monitor for GvHD onset, another formal SRC meeting will be held to recommend the dose to be given to patients 5 and 6. From then, partial follow-up data from the 72 day DLT window will be used to estimate DLT risks on an ongoing basis, so that new patients who are recruited before previous patients have completed follow-up may be entered onto the trial and receive CD62L$^-$ Tem. A minimum of two patients will be treated at open dose cohorts.

Dose Level	1	2	3	4
Dose:	$1x10^5$/kg	$3x10^5$/kg	$1x10^6$/kg	$3x10^6$/kg

We will use a two-parameter logistic model to describe the relationship between the dose of Tem and the probability of observing a DLT (acute GvHD grade II-IV). The MTD is the largest dose that can be given to trial patients that has an estimated probability of DLT no more than the target toxicity level of 20%. Skipping untested doses when escalating dose is prohibited.

The dose of cells infused will be determined in advance by the SRC. In all cases, the dose will be capped according to the total number of contaminating naïve T cells in the CD62L$^-$ Tem product so that the dose of naïve T cells infused is < 0.05 x 10^6/kg recipient weight.

No dose reductions are permissible in this study. If the patient does not receive the full dose of the Tem product for any reason UCL CTC should be contacted immediately.

8.4. Dose-limiting toxicity follow up period

The dose-limiting toxicity period is defined from the day of $CD62L^-$ Tem infusion up to 72 day post infusion. **All** patients receiving the Tem-infusion are required to be followed for the full dose-limiting toxicity period.

Any patients experiencing the following adverse event during this time will be considered to have experienced a dose-limiting toxicity:

- Grade II-IV, acute-pattern Graft-versus-host disease (GvHD)

In the event of a DLT, UCL CTC should be contacted immediately and a **GvHD (DLT) Urgent Notification** CRF submitted within 24 hours see section 12 (Safety Reporting). The time of onset will be the date of the decision to treat or date of confirmatory biopsy whichever is earlier.

Rolling GvHD and GvHD assessment forms should be submitted to record the details of each incidence of GvHD (including those not meeting the definition of a DLT) and re-submitted if the grade/type of GvHD changes. These are non-urgent forms and can be posted as per section 11 (Data management and data handling Guidelines).

The severity of acute pattern GvHD is graded upon modified Glucksberg criteria as outlined below (16):

Individual target organ stage:

Stage	Skin	Liver (Bilirubin)	Upper GI [1]	Lower GI (diarrhoea output[3])
0	No active erythematous rash	<35 micromol/l	No symptoms	<500ml day or <3 episodes/day
1	Maculopapular rash <25% BSA	35 - 50 micromol/l	Persistent nausea, vomiting or anorexia[2]	500-999ml/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	51-100 micromol/l		1000-1500ml/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	101-250 micromol/l		>1500ml/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) PLUS desquamation or bullae 5% > BSA	>250 micromol/l		Severe abdominal pain ± ileus or gross bloody stool (regardless of volume)

[1] Diagnosis of upper gut GVHD is based upon endoscopy and biopsy or clinical exclusion of other causes

[2] Nausea >2 days and vomiting >1 day or anorexia with weight loss

[3] Assume volume per individual diarrhoea episode is 200ml

Overall GvHD Grade:

Grade 0: No stage 1-4 for any organ

Grade 1: Stage 1-2 skin without liver, upper GI, or lower GI involvement

Grade 2: Stage 3 skin and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI

Grade 3: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 1 upper GI

Grade 4: Stage 4 for skin and/or stage 4 liver and/or stage 4 lower GI, with stage 0-1 upper GI

8.5. Post-DLT Period Follow Up

After completing the Dose-Limiting Toxicity Follow Up Period (72 days post-Tem infusion), patients are followed up at days +100, +180, +270 and +360 post-stem cell transplant. Following the day +360 visit, the patient's status will be collected on an annual basis. See section 9 for assessment details.

8.6. Follow Up after Graft Failure, Progression or Relapse

Patients with graft failure or that progress or relapse **during** the dose-limiting toxicity period will be followed up for the full 72 day DLT Follow Up Period (as per sections 8.4 and 9.4). Upon completing the DLT Follow Up Period these patients will no longer be required to attend days +100, +180, +270 and +360 post-stem cell transplant visits. The patient's status will continue to be collected on an annual basis from their stem cell transplant date.

Patients with graft failure or that progress or relapse **after** the dose-limiting toxicity period will no longer be required to attend the relevant remaining days +100, +180, +270 and +360 post-stem cell transplant visits. The patient's status will continue to be collected on an annual basis from their stem cell transplant date.

8.7. Management of Adverse Events

Patients with acute pattern or chronic GvHD should be treated according to local policies. For patients developing acute-pattern GvHD grade II-IV, a standard treatment involves systemic methylprednisolone at a dose of 1-2mg/kg intravenously followed by a taper and switch to oral prednisolone according to response. Such patients are usually maintained or re-started on a calcineurin inhibitor with the aim of achieving therapeutic levels. Subsequent taper of immunosuppression is according to clinical response. Patients failing to respond to such therapy should be managed according to local practice.

For patients who develop moderate-severe chronic GvHD, a combination of cyclosporine/ prednisolone is also a standard therapy. Alternative or additional therapies may be initiated in patients who fail to respond or who are steroid-dependent or who are intolerant of this treatment according to local practice.

Where patients develop corticosteroid treatment-refractory acute grade II-IV GvHD or moderate-severe chronic GvHD, they will be eligible to enter other clinical trials if appropriate.

8.8. Management of Investigational Treatment Error, or Occupational Exposure

Investigational treatment error

An investigational treatment error is any unintentional error in prescribing, dispensing, or administration of an investigational treatment while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

Investigational treatment errors should be reported on in incident report (see section 13.1). Any adverse events resulting from an investigational treatment error should be reported as an SAE (see section 12.2.2 for reporting procedures).

Occupational exposure

Exposure to an investigational treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1).

8.9. Supportive Care

Prevention and management of infection
All patients should receive standard anti-microbial and anti-viral prophylaxis according to local policy to prevent infection by Pneumocystis carinii, encapsulated bacteria and herpes or varicella zoster re-activation. All at risk patients should undergo regular monitoring for CMV, EBV and adenoviral infection by peripheral blood PCR with pre-emptive therapy commenced according to local policy. All new respiratory infections should be screened by respiratory viral screening and where relevant sputum culture or bronchiolar lavage. Use of anti-fungals drugs as primary treatment or secondary prophylaxis will be according to local policy.

Relapse or progression
In the event of relapse or progression at any time point, patients will be eligible to receive additional therapy. Suitable therapies might include unmanipulated donor lymphocyte infusion (DLI), therapeutic antibody, small molecular inhibitors, epigenetic modifying agents, chemo- or radiotherapy or any combination thereof, according to local policy. Patients that progress or relapse post-Tem infusion will continue to be followed up as per sections 9.4 and 9.5.

Mixed chimerism
Determination of chimerism will be performed at Great Ormond Street Hospital NHS Trust to ensure uniformity throughout the trial and will be performed by PCR-STR. These assays will be performed according to standard operating procedures of the Central Laboratory and subject to internal quality control and quality assurance. The Central

Laboratory participates in an external quality assurance scheme (UK NEQAS). Any patient who subsequently develops a significant fall in donor chimerism (defined as <50% donor chimerism) will be eligible to receive unmanipulated DLI or any alternative treatment as decided by the PI at each centre.

Unmanipulated DLI

In accordance with standard UK practice, all registered patients will be eligible to receive unmanipulated DLI from 6 months post-transplant if investigations confirm persistent disease or mixed chimerism. From 6 months post-transplantation, the risk of unmanipulated DLI causing GvHD is low if given according to an escalated dose regimen. An example of a conventional escalated dose regimen of unmanipulated DLI is 1 x 10^6, 3 x 10^6, 1 x 10^7, 3 x 10^7 and 1 x 10^8 CD3 cells/kg at 10 week intervals provided patients have no evidence of active GvHD or prior acute GvHD grade II-IV.

Management of acute and chronic GvHD

See section 7

8.10. Contraindications

Patients are not permitted to receive any other cellular therapy from the time of informed consent up to 72 days post $CD62L^-$ Tem infusion. Patients will not be permitted to enter additional trials involving cellular therapies, ATIMP or IMPs **UNLESS** they develop corticosteroid treatment-refractory acute grade II-IV GvHD or moderate-severe chronic GvHD, where they will be eligible to enter other clinical trials if appropriate.

8.11. Cell Laboratory Responsibilities

Site Cell Laboratory responsibilities

Sites performing steady state apheresis are responsible for ensuring the donor biological screening, leucapheresis procedures, including the labelling and issue of the leucapheresis product are carried out according to the Human Tissue (Quality and Safety for Human Application) Regulations (SI 2007/1523) and in line with local procedures. Sites are also required to have implemented the Single European Coding system (SEC) when labelling the apheresis products.

The management of the Tem product at participating sites is the responsibility of the PI, who may delegate this responsibility to appropriately qualified personnel in the Cell Therapy Lab. The delegation of duties must be recorded on the site staff delegation log.

8.11.1. Temperature Excursions

All temperature excursions outside the storage conditions specified in **Error! Reference source not found.** must be reported to UCL CTC as per the 'Cell Therapy Laboratory Procedure for Reporting Temperature Excursions'

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY

- the 'Notification of Temperature Excursion' form must be completed and e-mailed to ctc.excursions@ucl.ac.uk or faxed to 020 7679 9861.

Please note that UCL CTC must be informed immediately if a patient has been administered CD62L$^-$ Tem affected by a temperature excursion.

8.11.2. CD62L$^-$ Tem accountability

Accountability for the Tem product, is the responsibility of the Principal Investigator, who may delegate this responsibility to appropriately qualified personnel. The responsible person will ensure that CD62L$^-$ Tem is used only in accordance with this protocol and that appropriate records are maintained.

The Principal Investigator (or other appropriately qualified personnel) must maintain accountability records which includes receipt, issuing, unused CD62L$^-$ Tem, storage conditions and destruction of unused CD62L$^-$ Tem. Template accountability logs will be supplied by UCL CTC.

Copies of completed accountability logs must be sent to the CTC for all patients receiving Tem at the end of trial treatment or upon request. Also refer to section 14.2 (centralised monitoring).

Accountability for other Non Investigational Medicinal Products (NIMPs) (pre-medication and/or other concomitant medication) is to be performed according to institutional guidelines.

8.12. Out-of-Office Hours Emergency Advice

Site staff will provide all registered patients with the latest approved version of the patient contact card for the trial. Site staff will need to add the name of the subject, trial number, the investigator contact details, on-call 24 hour medical care contact number. Patients/donors must be reminded to carry the card at all times whilst participating in the trial.

8.13. Clinical Management after Treatment Discontinuation

If a patient withdraws from the trial after trial treatment, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Also refer to sections 9.4, 9.5 and 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9. ASSESSMENTS

Please also see Schedule of Events table in Appendix 2.

9.1. Pre-Registration Assessments

Patients and donors must give written informed consent **before** any trial specific screening investigations may be carried out. If any are carried out as part of standard of care they do not need to be repeated.

Patient Pre-registration assessments

- Disease assessment as per local policy

An evaluation of disease status as appropriate to the type of disease and to local policies should be performed prior to registration. Assessments carried out as per local policy must be sufficient to determine the response criteria for each disease as per appendix 5. Patients not meeting the criteria for trial entry as per appendix 5 will be not be registered.

The following investigations should be performed within 4 weeks prior to registration:

- Medical history (including concomitant medication assessment)
- Haematopoietic Cell Transplantation Specific Co-morbidity Index (34)
- Physical examination & weight
- Full blood count with differential
- Biochemistry (sodium, potassium, urea, creatinine, calcium, phosphate, albumin, total protein, bilirubin, AST/ALT, alkaline phosphatase)
- Glomerular filtration rate in ml/min (estimated GFR is acceptable)
- Echocardiogram or MUGA scan
- Urine or serum pregnancy test (for women of childbearing potential see section6.4.3)

The following should be performed **after** patient has given consent to the participation of the trial and trial registration.

- Peripheral blood (PB) sample for central lab (4ml in EDTA - chimerism analysis)

Please refer to the ToTem laboratory manual for details of sample shipment.

Donor Pre-registration assessments

The following tests should be performed for all donors as a minimum requirement within 4 weeks prior to registration. Additional testing may be required depending on the donor's history.

- Urine or serum pregnancy test (for women of childbearing potential see section 6.4.3)
- Infectious Disease screening tests:

HIV	Anti-HIV-1, 2
	HIV-1 & 2 RNA PCR
Hepatitis B	HBsAg Anti HBc

	HBV DNA
Hepatitis C	Anti-HCV-Ab
	HCV RNA PCR
HTLV	HTLV 1&2
Syphilis	A validated testing algorithm must be applied to exclude the presence of active infection with Treponema pallidum. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

The above results should be e-mailed to the Centre for Cell, Gene & Tissue Therapeutics as soon as possible after the results have been obtained and at least 24 hours before apheresis is carried out. Please refer to the Protocol **Error! Reference source not found.**, the laboratory manual and the service level agreements with UCL Centre for Cell, Gene & Tissue Therapeutics for details.

Demographic data (e.g. age, height/weight, gender, and ethnicity) will be also collected. Donors consent will be obtained for this.

The following should also be performed **after** donor has given consent to the participation of the trial and trial registration.

- Peripheral blood sample for central lab (4ml in EDTA - chimerism analysis)

Please refer to the ToTem laboratory manual for details of sample shipment.

9.2. Donor CD62L$^-$ Tem Apheresis Assessments

Donor assessments prior to CD62L$^-$ Tem apheresis
The following assessments must be repeated on the day of, or up to 7 days after donor apheresis.

- Infectious Disease screening tests:

HIV	Anti-HIV-1, 2
Hepatitis B	HBsAg Anti HBc
Hepatitis C	Anti-HCV-Ab
HTLV	HTLV 1&2
Syphilis	A validated testing algorithm must be applied to exclude the presence of active infection with Treponema pallidum. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

The above results should be emailed to the RFH Centre for Cell, Gene & Tissue Therapeutics as soon as possible after the results have been obtained. Please refer to

the Protocol **Error! Reference source not found.**, the laboratory manual and the service level agreements with RFH Centre for Cell, Gene & Tissue Therapeutics for details

Monitoring of donors during apheresis
Apheresis should be performed on a day unit or ward in the presence of trained medical and nursing staff. Donors should be monitored regularly for any adverse effects. Monitoring and treatment should be in accordance with local policy for any adverse effects that occur.

9.3. Patient Pre-treatment Assessments

The following investigations should be performed within 2 days prior to infusion of CD62L$^-$ Tem to confirm the patient is eligible to receive trial treatment and meets none of the trial treatment exclusion criteria (see section 6.2.3). **The patient's eligibility must be confirmed with UCL CTC prior to infusion taking place** (see section 7.2) and continually assessed up to the point of CD62L$^-$ Tem infusion:

- Adverse event assessment (including GvHD assessment)
- Physical examination & weight
- Full blood count with differential
- Biochemistry (sodium, potassium, urea, creatinine, calcium, phosphate, albumin, total protein, bilirubin, AST/ALT, alkaline phosphatase)
- Peripheral blood sample for central lab (5ml in serum tube - alemtuzumab levels)
- Urine or serum pregnancy test (for women of childbearing potential see section 6.4.3)

Monitoring of patients during infusion of donor CD62L$^-$ Tem
Donor CD62L$^-$ Tem should be administered on a day unit or ward in the presence of trained medical and nursing staff. The patient should be monitored regularly for any adverse effects. Treatment should be given in accordance with local policy for any adverse effects that occur. Adverse events occurring during the donor CD62L$^-$ Tem infusion should be reported on the trial adverse event form (see section 12.2). Patients should be advised to contact the hospital if they experience any adverse effects after the infusion has been carried out.

9.4. Assessments on Completion of Trial Treatment (DLT period)

Following CD62L$^-$ Tem infusion, patients should be assessed as per standard of care for safety purposes. The trial assessments below should be carried out every 14 days (+/- 4 days) from the date of Tem infusion until 72 days post Tem infusion:

- Adverse event assessment (including GvHD assessment)
- Physical examination & weight
- Full blood count with differential
- Biochemistry (sodium, potassium, urea, creatinine, calcium, phosphate, albumin, total protein, bilirubin, AST/ALT, alkaline phosphatase)

Note: A window of +/- 4 days is permitted for the first 4 visits in the DLT window (e.g. days +14, +28, +42 and +56) but to ensure the full DLT period of 72 days post-Tem

infusion is captured, a window of +4 days only is permitted for the final visit at day +72 (i.e. the final visit should take place between day +72 and +76 post-Tem infusion).

Where the day +72 post-Tem infusion visit coincides with the day +100 post-stem cell transplant visit, relevant tests do not need to be performed twice, however all required assessments for each timepoint should be carried out and both timepoint CRFs should be completed.

9.5. Assessments during Follow Up

The following investigations should be performed at days +100, +180, +270 and +360 post-stem cell transplant (+/- 10 days):

- Disease assessment as per local policy
- Adverse reaction assessment (including GvHD assessment)
- Physical examination & weight
- Full blood count with differential
- Biochemistry (sodium, potassium, urea, creatinine, calcium, phosphate, albumin, total protein, bilirubin, AST/ALT, alkaline phosphatase)
- Lymphocyte subset analysis (to include percentages and absolute numbers of CD3 T cells, CD4 T cells, CD8 T cells, B cells and NK cells); *N.B. this sample must be taken on the same day as the central lab samples below.*
- Peripheral blood samples for central labs:
    - 25ml in lithium heparin - Viral and antigen-specific immunity & immune reconstitution
    - 10ml in EDTA - chimerism analysis

The following samples should also be taken at days +100 and +360 post-stem cell transplant (+/- 10 days):

- Peripheral blood samples for central labs:
    - 10ml in EDTA - TCR analysis

9.6. Assessments during Long Term Follow Up

After the patient has completed the initial 360 days post-stem cell transplant follow up, or following progression, the following information should be collected annually (+/- 28 days):

- Patient status (including disease status)

Please note that the annual follow up for all patients is based on the stem cell transplant date, e.g. 1 year post-transplant, 2 years post-transplant, etc.

10. EXPLORATORY BIOLOGICAL STUDIES

Peripheral blood samples for exploratory analysis are a mandatory part of the trial and patients need to consent to these on the ToTem Informed Consent form before any samples are taken. The following analysis will be performed:

TCR repertoire analysis by deep CDR3 sequencing

To test for T cell repertoire diversity, we will perform deep sequencing of the TCRB CDR3 region using genomic DNA. The RFH Centre for Cell, Gene & Tissue Therapeutics will obtain a minimum of 1 $x10^7$ CD3+ from the donor apheresis and 1 $x10^7$ CD3+ following the CD62L negative selection for TCR repertoire analysis. Samples will be kept at the CCGGT until the end of the study at which point they will be will be sent to Adaptive Biotechnologies for analysis.

Peripheral blood (10ml in EDTA) should also be collected from the patient at days +100 and +360 post-transplant and sent to UCL Biobank at Royal Free. See lab manual for detailed instructions on the sample kits provided, sample collection and sample shipping.

UCL Biobank will process the peripheral blood to isolate PBMCs; at the end of the study these will be sent to Adaptive Biotechnologies for analysis.

Chimerism

To evaluate donor-recipient chimerism, we will perform polymerase chain reaction-based analysis of Short Tandem Repeat sequences using genomic DNA. Peripheral blood (4ml in EDTA) should be collected from the donor during the pre-registration assessment and from the patient at pre-registration, and 10ml at days +100, +180, +270 and +360 post-transplant. These samples should be sent to Great Ormond Street Hospital (GOSH) Clinical Pathology. See lab manual for detailed instructions on sample collection and shipping.

GOSH will analyse these samples to determine chimerism and forward the results to the CTC. The PIs at each centre will also receive these results.

Reconstitution of immune subsets and virus- and bacterial-specific immunity

To evaluate immune recovery, we will perform multi-parametric flow cytometry of peripheral blood mononuclear cells to identify immune subsets, and use pentamer or functional assays to identify pathogen-specific T cells. Peripheral blood (25ml in lithium heparin) should be collected from the patient at days +100, +180, +270 and +360 post-transplant and sent to UCL Biobank at Royal Free. See lab manual for detailed instructions on the sample kits provided, sample collection and sample shipping.

UCL Biobank will process the peripheral blood to isolate PBMCs and these will be sent at the end of the study to the Transplantation Immunology Research group at UCL, RFH for analysis

Relationship between donor demographics/immune profile with number of CD62L$^-$Tem selected.

Data relating to donor demographics (age, height/weight, ethnicity and sex) will be analysed in relation to immunophenotypic analysis of donor apheresis and post-selection samples. The RFH Centre for Cell, Gene & Tissue Therapeutics will obtain a minimum of 1 x10^7 CD3+ from the donor apheresis and 1 x10^7 CD3+ following the CD62L negative selection for immune phenotypic analysis. Samples will be sent to the UCL/RFH BioBank for storage before release to the Transplantation Immunology Research group at UCL, RFH at the end of the study.

Alemtuzumab levels on the day of CD62L$^-$ Tem infusion

To test alemtuzumab levels, we will perform an enzyme-linked immunoabsorption assay. Peripheral blood (5ml in serum tube) should be collected from the patient within 2 days prior to Tem infusion and sent to UCL/RFH Biobank at Royal Free. See lab manual for detailed instructions on the sample kits provided, sample collection and sample shipping.

UCL/RFH Biobank will process the peripheral blood to collect and store serum; at the end of the study, the samples will be sent to the Transplantation Immunology Research group at UCL, RFH for analysis of alemtuzumab levels.

11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected by sites on version-controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed onto trial CRFs and must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending, to maintain confidentiality.

11.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the CRFs must be sent to UCL CTC and a copy kept at site.

11.2. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (should only use if every effort has been made to obtain the data).

11.3. Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit and **within 1 week of the patient being seen**. Prompt data return is essential in the trial so that dosing escalation/de-escalation decisions can be made accurately.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'triggered' monitoring visit. See section 14.3 ('Triggered' On-Site Monitoring) for details.

11.4. Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests will be sent to the data contact at site. Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Request forms.

There may be times in which data queries require a rapid response particularly if there is a safety review committee meeting due to determine dosing levels. The trial data manager will contact you if this is the case providing you with as much prior notice as possible.

12. SAFETY REPORTING

12.1. Definitions

The ToTem study does not fall under the definition of interventional clinical trial as intended by article 2 of the European Directive 2001/20/EC. Therefore, the following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Please note that the EU Tissue and Cells Directive has different definitions and reporting requirements of SAEs and SARs – please see section 12.7 for reporting requirements for untoward events associated with donor apheresis, procurement, testing, processing, storage and distribution of cells.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with an investigational treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational treatment, whether or not related to that investigational treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to an investigational treatment related to any dose administered. A causal relationship between an investigational treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See section 12.2.2 for SAE reporting procedures.

Related and Unexpected Serious Adverse Reaction

A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information.

i.e. an adverse event that meets all the following criteria:

- Serious – meets one or more of the serious criteria, listed under the definition of SAE above
- Related – assessed by the local PI or designee, or Sponsor as causally related to one or more elements of the trial treatment
- Unexpected – the event is not consistent with the applicable reference safety information

See section 12.3 for reporting procedures for these events.

Investigational treatment error, or Occupational exposure

Refer to section 8.8 for details on reporting of these events.

12.2. Reporting Procedures

A table summarising the reporting requirements for AEs, ARs, SAEs, GvHD, infections and pregnancies can be found in section 12.8.

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

http://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

Severity grade

The severity grade of each adverse event must be determined by using CTCAE v5.0.

Severity of acute pattern GvHD will be determined using the modified Glucksberg criteria as described in section 8.4.

Chronic GvHD will be evaluated according to NIH criteria as outlined in Appendix 6.

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs (including SAEs) the local PI or designee will assess whether the event is causally related to the investigational treatment.

For SAEs a review will also be carried out by the Sponsor's delegate and CCGTT.

Causal relationship to each investigational treatment must be determined as follows:

- Related (reasonable possibility) to the investigational treatment
- Not related (no reasonable possibility) to the investigational treatment

UCL CTC and CCGTT will consider events evaluated as related to be adverse reactions.

12.2.1. Reporting of Adverse Events (AEs) and Adverse Reactions (AR)

All adverse events (except GvHD and infections requiring hospitalisation) that occur between the day of CD62L$^-$ Tem infusion and 72 days post CD62L$^-$ Tem Infusion must be recorded in the patient notes and the AE rolling CRF.

Adverse reactions (related to CD62L$^-$ Tem infusion only) should be continued to be recorded in the patient notes and the AE rolling CRF during follow up until +360 days post stem cell transplant (see summary table in section 12.8).

Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC and CCGTT using the trial specific SAE Report. Also see section 12.2.2 (Reporting of Serious Adverse Events (SAEs)).

Adverse events meeting the definition of dose-limiting toxicity (DLT) must be reported on a **GvHD (DLT) Urgent Notification** CRF (see section **Error! Reference source not found. Error! Reference source not found.**).

Please note: GvHD and infection requiring inpatient admission do not need to be reported on the rolling AE form (see sections 12.4 and 12.5 for GvHD and infection reporting mechanisms) but do need to be reported as SAEs if meeting the definition of an SAE as per sections 12.1 and 12.2.2.

Pre-existing conditions (i.e. conditions present on the day prior to CD62L$^-$ infusion) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again). For example, an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).

NB the disease(s) under study and its anticipated day-to-day fluctuations would not be an AE.

12.2.2. Reporting of Serious Adverse Events (SAEs)

SAEs may occur in the patient or donor. Under the HTA SAEs may also only affect the apheresis material or CD62L$^-$ Tem cells. All SAEs must be recorded in the patient notes and submitted to UCL CTC by fax or email within **24 hours,** and to CCGTT by email immediately after observing or learning of the event, using the trial specific SAE Report.

All SAEs in the patient that occur between the date of CD62L$^-$ Tem Infusion and 72 days post CD62L$^-$ Tem Infusion **(or after this date if the site investigator feels the event is related to the investigational treatment and/or trial procedure)** are reportable.

SAEs in a donor that occur at any point after the date of apheresis and the site investigator feels the event is related to the procurement process are reportable.

Relevant sections on the SAE Report must be completed dependent on the trial participant and event reported. If the event is **not being reported to UCL CTC within 24 hours and CCGTT immediately**, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

For information on the Human Tissue Authority (HTA) safety reporting requirements of untoward events associated with the procurement, testing, processing, storage and distribution of cells under EU Tissue and Cells Directives see section 12.7.

Exemptions from SAE Report submission in the patient

For this trial, the following events are exempt from requiring submission on an SAE Report **unless considered to be related to the investigational treatment**. However, the events must be recorded in the relevant section of the trial CRFs:

- events that occur more than **72 days** post CD62L$^-$ Tem Infusion. Note: this does not include pregnancy related events (see section 12.6) or SAEs reportable under the EU Tissue and Cells Directive (see section 12.7).
- disease progression or relapse
- infection requiring inpatient admission (must be reported on the trial-specific infection form – refer to section 12.5 below)

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAE.

Completed SAE Reports must be sent to UCL CTC within 24 hours of becoming aware of the event

Fax: 020 7679 9861
Email: ctc.ToTem@ucl.ac.uk

Completed SAE Reports must be sent to CCGTT immediately upon becoming aware of the event

Email: m.lowdell@ucl.ac.uk
Phone: 07808 172026

SAE Follow-Up Reports

UCL CTC and CCGTT will follow up all SAEs until resolution and there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC and CCGTT promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAE Report to avoid unnecessary queries.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness to the trial treatment or procurement process will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved reference safety information (i.e. the list of expected adverse events in Appendix 3 of the protocol).

The CI, or their delegate (e.g. a clinical member of the TMG) will review the SAE and perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered

expectedness difficult to determine, the reviewer will be consulted for their opinion at this time.

SAE Processing at CCGTT

On receipt of the SAE Report, CCGTT will determine any requirement to report the SAE/SAR to the HTA under the EU Tissue and Cells Directive (2004/23/EC) (see section 12.7).

12.3. Related and Unexpected Serious Adverse Events

If the event is evaluated as a Related and Unexpected Serious Adverse Reaction, UCL CTC will submit a report to the REC within the required timeline.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

Informing Sites of Related and Unexpected Serious Adverse Events

UCL CTC will inform all PIs of any related and unexpected SAEs that occur on the trial. PIs will receive expedited Related and Unexpected Serious Adverse Events reports that must be processed according to local requirements.

12.4. Reporting of Graft versus Host Disease (GvHD)

Acute GvHD should be graded using the modified Glucksberg criteria as described in section 8.4. Chronic GvHD will be evaluated according to the NIH criteria as outlined in Appendix 6.

All cases of GvHD occurring from the date of $CD62L^-$ Tem infusion to 360 days post stem cell transplant should be recorded in the patient notes and on the GvHD rolling CRF. The GvHD rolling CRF is to be submitted at each scheduled trial visit (if no cases of GvHD occurred, only the cover sheet needs to be submitted). A GvHD Assessment CRF should be completed at the onset of each GvHD case and a new form submitted alongside the GvHD rolling CRF with every grade change.

GvHD cases meeting the definition of serious (e.g. the patient is hospitalised) should also be reported using the trial-specific SAE report as per section 12.2.2.

12.4.1. Reporting of Dose-Limiting Toxicities

In addition to the above reporting procedures, grade II-IV, acute GvHD occurring between the date of $CD62L^-$ Tem infusion and 72 days post $CD62L^-$ Tem infusion must be reported within **24 hours of becoming aware of the event** on the GvHD (DLT) Urgent Notification Form.

All Dose-Limiting Toxicities must be reported by faxing a completed GvHD (DLT) Urgent Notification CRF to UCL CTC within 24 hours of becoming aware of the event
Fax: 020 7679 9861
Email: ctc.ToTem@ucl.ac.uk

12.5. Reporting of Infections

Reporting of infections requiring inpatient admission is outlined in section 12.5.1.

All infections not requiring inpatient admission occurring from the date of CD62L$^-$ Tem infusion to 72 days post CD62L$^-$ Tem infusion should be recorded in the patient notes and on the AE rolling CRF as per section 12.2.1. Infections not requiring inpatient admission and the investigator feels is related to the trial/treatment should continue to be recorded in the patient notes and on the AE rolling CRF until 360 post stem cell transplant.

12.5.1. Reporting of Infections Requiring Inpatient Admission

Details of infections requiring inpatient admission from the date of CD62L$^-$ Tem infusion to 360 days post stem cell transplant must be reported on the Infection rolling form. The infection rolling form is to be submitted to UCL CTC with each scheduled trial visit (if no infections requiring inpatient admission occurred, only the cover sheet needs to be submitted).

For the purposes of the ToTem trial, infections requiring admission to hospital (**unless considered to be related to the investigational treatment)** do not need to be reported on the trial SAE report form. If the infection is fatal, life-threatening, prolongs an existing hospitalisation or meets any other seriousness criteria an SAE report must be submitted as per section 12.2.2.

12.6. Pregnancy

Reporting Period

For any pregnancy exposure to trial treatment, the site must submit a trial specific Pregnancy Report to UCL CTC by fax or email within **24 hours of learning of its occurrence**.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient
- Pregnancy in a partner of a male trial patient
- Exposure to treatment in a partner of a male trial patient who was pregnant at the start of the trial occurring between the date of CD62L$^-$ Tem infusion and 6 months post CD62L$^-$ Tem Infusion.

The site must request consent from the pregnant trial patient or pregnant female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of trial patients

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by faxing or emailing a completed Pregnancy Report to UCL CTC within 24 hours of becoming aware of the pregnancy
Fax: 020 7679 9861
Email: ctc.ToTem@ucl.ac.uk

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up **at least monthly** for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the new information. In case of adverse outcome to the pregnancy reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific pregnancy SAE Report, according to SAE reporting procedures. Refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the REC if the pregnancy outcome meets the definition of a related and unexpected SAE. Refer to section 12.3 (Related and Unexpected Serious Adverse Events) for details.

12.7. HTA reporting - EU Tissue & Cells Directive

The definition and reporting requirements of SAEs and SARs under the EU Tissue and Cells Directive (2004/23/EC) differ from those adapted from European Directive 2001/20/EC as specified above.

12.7.1. SAEs

The EU Tissue and Cells Directive (2004/23/EC) defines an SAE as follows:

"'Serious Adverse Event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity."

12.7.2. SARs

The EU Tissue and Cells Directive (2004/23/EC) defines a SAR as follows:

"'Serious Adverse Reaction' means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity."

SARs as defined in the Tissue and Cell Directive may occur a considerable time after administration. This is particularly the case with communicable diseases.

12.7.3. Reporting requirements

Event	Reporting requirements
SAE/SAR in donor at apheresis donation	Designated Individual (DI) (or equivalent) at the study site reports to HTA as per regulatory requirements. The trial site should also notify the CTC and CCGTT via the trial SAE report as per protocol section 12.2.2. Based on the received information the CTC and CCGTT will assess whether any trial and/or donation procedures should be amended.
SAE occurring from the time Material leaves the study site, during transit, and whilst at CCGTT	The CCGTT DI will report the SAE to the HTA as required under the EU Tissue and Cells Directive. CCGTT to inform CTC of SAE within 2 business days of the event. CTC to inform trial site of SAE. Based on the received information the CTC and CCGTT will assess whether any trial and/or donation procedures should be amended.
SAE event of $CD62L^-$ Tem during distribution to study site	The trial site should notify the CTC and CCGTT via the trial SAE report as per protocol section 12.2.2. The CCGTT DI will report the SAE/SAR to the HTA as required under the EU Tissue and Cells Directive. Based on the received information the CTC will assess whether any trial and/or donation procedures should be amended.
SAE/SAR in patient post $CD62L^-$ Tem Infusion	The study site should report the SAE/SAR to the CTC and CCGTT via the trial SAE report as per protocol section 12.2.2. The CCGTT DI will determine the relatedness to the trial treatment and report the SAE/SAR to the HTA as required under the EU Tissue and Cells Directive. Based on the received information the CTC will assess whether any trial and/or donation procedures should be amended.

12.8. Summary of study site safety reporting requirements

Event	Timeframe	Form required	How/when to send
Adverse events and reactions			
AEs	From the date of Tem infusion **until 72 days post Tem Infusion**	AE rolling form	Post/email/fax to CTC at each trial visit
ARs	From the date of Tem infusion **until 360 days post SCT**		
Serious adverse events			
SAEs in donor related to apheresis procurement	From date of procurement until the end of the trial	SAE report	Email to CCGTT **immediately** upon becoming aware of the event Fax/email to CTC **within 24 hours** of becoming aware of the event
SAEs and SARs as defined by HTA (see section 12.7)	At any point during the trial		
SAEs in patient after Tem infusion	From the date of Tem infusion **until 72 days post Tem Infusion** (or until end of the trial if related to Tem infusion)		
GvHD			
DLTs (aGvHD Grade II-IV)	From the date of Tem infusion **until 72 days post Tem Infusion**	GvHD (DLT) Urgent Notification CRF	Fax to CTC **within 24 hours** of awareness
		GvHD rolling form	Post/email/fax to CTC at each trial visit
		GvHD assessment form *(only required for subsequent grade changes)*	Post/email/fax to CTC with rolling GvHD form
Any GvHD (acute and chronic)	From the date of Tem infusion **until 360 days post SCT**	GvHD rolling form	Post/email/fax to CTC at each trial visit
		GvHD assessment form *(at onset and subsequent grade/type changes)*	Post/email/fax to CTC with rolling GvHD form

Any GvHD meeting the criteria of serious	From the date of Tem infusion **until 72 days post Tem Infusion** (or until end of the trial if related to Tem infusion)	SAE report (in addition to the rolling and assessment forms)	Email to CCGTT **immediately** upon becoming aware of the event Fax/email to CTC **within 24 hours** of becoming aware of the event
Infection			
Infection requiring inpatient admission	From the date of Tem infusion **until 360 days post SCT**	Infection rolling form	Post/email/fax to CTC at each trial visit
Infections not requiring inpatient admission	As per the relevant AE or AR timeframes	AE rolling form	Post/email/fax to CTC at each trial visit
Infection meeting the criteria of serious (except requiring inpatient admission) OR infections requiring inpatient admission **and** related to Tem infusion	From the date of Tem infusion **until the end of the trial**	SAE report (in addition to the rolling form)	Email to CCGTT **immediately** upon becoming aware of the event Fax/email to CTC **within 24 hours** of becoming aware of the event
Pregnancy			
Pregnancy (in patients or partners of male patients)	From the date of Tem infusion **until 6 months post Tem Infusion**	Pregnancy report form	Fax to CTC **within 24 hours** of awareness

12.9. Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG), Safety Review Committee (SRC) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

Trial safety data will be monitored to identify:

- Whether disease-related events (exempt from SAE reporting as per section 12.2.2) appear to be enhanced by the investigational treatment
- new adverse reactions to the investigational treatment

- trial related events that are not considered related to the investigational treatment, but may lead to changes to the trial documents.
- Review of incidence of DLTs as outlined in section 8.4 of the protocol
- Review of other safety issues such as:
    - Infection rates are higher than expected
    - Adverse events related to the product application process

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

13. INCIDENT REPORTING AND SERIOUS BREACHES

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2. Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with the principles of GCP and/or the protocol, including failure to report SAEs occurring on study within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the REC within 7 calendar days of becoming aware of the breach.

14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor and Manufacturer audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1. On-Site Monitoring

Sites will be sent a letter in advance of any on-site monitoring visits, confirming when a visit is scheduled to take place. The letter will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Monitoring Follow Up

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.2. Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of the following documents by sites to UCL CTC for review:

- Delegation Logs
- Investigator CV & evidence of GCP training
- Screening Logs
- Patient Accountability Logs
- Laboratory Sample Shipment Log

Expectations for document submission will be explained during site initiation and UCL CTC will send emails to sites requesting the documentsData received at UCL CTC will be subject to review in accordance with section 11.4 (Data Queries).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Where centralised monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk, for example a patient was given CD62L$^-$ Tem prior to confirming eligibility for trial treatment, the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting and Serious Breaches

) and 14.3 ('Triggered' On-Site Monitoring) for further details).

14.3. 'Triggered' On-Site Monitoring

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit and confirming when it will take place. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.4. Oversight Committees

14.4.1. Project Management Group (PMG)

The PMG will include the Chief Investigator, lead of the CCGTT, the UCL senior business manager, independent clinicians, and ToTem trial staff from UCL CTC. The main role of the PMG is to design and set up the trial, ensure that the project remains focused on delivering against its objectives and milestones and review project risks and how they are being managed. The group will meet regularly, approximately every 3 months.

Members of the PMG will be required to sign a PMG charter outlining their duties and responsibilities.

14.4.2. Trial Management Group (TMG)

The TMG will include the Chief Investigator, Principle Investigators at site and experts from relevant specialties, and the ToTem trial staff from UCL CTC). The TMG will be responsible for overseeing the trial. The group will meet regularly approximately twice a year and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Lymphoma & Haematological Oncology Clinical Studies Groups.

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

Members of the TMG will be required to sign a TMG charter outlining their duties and responsibilities.

14.4.3. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration

of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

14.4.4. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held as required during the trial. This will include an assessment of safety once the maximum tolerated dose has been established, at which point toxicity data from the trial will be summarised in a report for the IDMC to review. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

Members of the IDMC will be required to sign an IDMC charter outlining their duties and responsibilities.

14.4.5. Safety Review Committee (SRC)

The Safety Review Committee will be comprised of the Chief Investigator, the clinical members of the TMG, 2 independent clinicians, the trial statistician and other relevant staff from UCL CTC. Their role is to perform DLT evaluation and review other relevant safety data to inform the decision of whether to escalate or de-escalate a cohort, continue recruitment in the current cohort or to suspend recruitment.

The SRC will meet in person and/or by teleconference as required to discuss safety data and to make decisions about dose escalation or de-escalation.

Members of the SRC will be required to sign a SRC charter outlining their duties and responsibilities.

14.4.6. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to safety reporting which are conducted in accordance with section 12 (Safety Reporting).

15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1. Withdrawal prior to Trial Treatment

If a patient will not have trial treatment, UCL CTC should be informed as soon as possible so that the cohort slot can be reallocated to another patient. The reason the patient was withdrawn must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons that a patient may not have trial treatment include:

- Issue with donor Tem apheresis or Tem product
- Patient does not have stem cell transplant
- Patient does not meet eligibility criteria for trial treatment (see section 6.2.3)
- Deterioration in health
- Patient or donor decision to withdraw consent

If a patient does not receive trial treatment, the Change of Status form should be completed and submitted to UCL CTC. The patient will be withdrawn from the trial and followed according to local practice. No further data will be collected.

15.2. Withdrawal of consent after Trial Treatment

If a patient withdraws consent for any aspect of study conduct after they have received treatment, the Change of Status form should be completed and submitted to UCL CTC.

15.2.1. Withdrawal of consent for follow up

If a patient withdraws consent for trial follow up, but is happy to continue with future data collection from hospital notes:

- They will remain on trial for follow up.
- The patient will no longer have trial-specific visits and assessments. Follow up forms should be completed based on the routine visit nearest the due date for the follow up form.
- The following CRFs must be submitted at time of withdrawal:
    - Change of Status form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report AEs/SAEs and DLTs as per sections 12.2 and 12.4 respectively, and all follow up forms, including notifications of relapse/progression and death.

15.2.2. Withdrawal of consent for data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected:

- The following CRFs must be submitted at the time of withdrawal:

- Change of Status Form
- All CRFs up to and including the date of withdrawal of consent

- Thereafter no further data should be submitted, with the exception of SAE reports and DLT notifications as per section 12.2 and 12.4 (due to the requirements for oversight of safety)

15.2.3. Withdrawal of consent for use of samples

If a patient withdraws consent for the use of some or all of their samples in the trial or for future research, this should be reported on the Change of Status form. Unless the patient has also withdrawn consent for treatment/follow up, management and data collection should continue as per protocol.

15.3. Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to a participating site, the registering site remains responsible for submission of forms.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be when the final data item for the final patient is received by the UCL CTC (i.e. it is anticipated that this will be when the final patient completes their day 360 follow-up visit).. At this point the 'declaration of end of trial' form will be submitted to the Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 25 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 25 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.4.3 Trial Steering Committee (TSC) and 14.4.4 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the mNCA.

17. STATISTICS

17.1. Sample Size Calculation

The trial will be conducted as a dose-escalation study and use the Time-to-event Continual Reassessment Method (TITE-CRM; (17)) to guide dose-escalation decisions. The study aim is to identify the Maximum Tolerated Dose (MTD) and thus the Recommended Phase II Dose (RP2D) of Tem when given following allogenic stem cell transplantation. Four dose levels will be available for investigation ($1x10^5$/kg, $3x10^5$/kg, $1x10^6$/kg, $3x10^6$/kg). The MTD is defined as the largest dose of Tem that has an estimated risk of causing DLT (acute-pattern GvHD grade II-IV) equal or closest to 20% (the target toxicity level). We assume the relationship between DLT risk and Tem dose can be estimated using a two-parameter logistic model. Before the trial, we assume that the prior risk of DLT at the highest dose ($3x10^6$/kg) is 20%. We then use the prior calibration method of (18) to provide working prior beliefs for dose-toxicity risks at the other doses; this gives median DLT risks (and 90% credible intervals) shown in Table 1.

Dose	**$1x10^5$/kg**	**$3x10^5$/kg**	**$1x10^6$/kg**	**$3x10^6$/kg**
Prior median	8%	11%	15%	20%
90% Credible Interval	(0, 56)	(1, 63)	(1, 71)	(2, 78)

Table 1: Prior median probabilities of DLT risk per dose (90% credible interval). Model parameters (intercept and log-slope) from bivariate Normal distribution with means (-1.39, -1.17) and independent variances (2.60, 0.22) respectively.

A minimum of two patients will be treated at open dose cohorts. The first two patients will receive dose level 3 ($1x10^6$/kg), and be followed for 72 days post infusion to monitor for GvHD onset. Data from patients 1 and 2 will be used to update the prior DLT risks, and a formal SRC meeting will be held to recommend the dose to be given to patients 3 and 4. After following up patients 3 and 4 for 72 days post infusion to monitor for GvHD onset, another formal SRC meeting will be held to recommend the dose to be given to patients 5 and 6. From then (after patient 5 and 6 begin treatment), partial follow-up data from the 72 day DLT window will be used to estimate DLT risks on an ongoing basis, so that new patients who are recruited before previous patients have completed follow-up may be entered onto the trial and receive Tem. Computations for updating the model will be performed in R Software(19).

The maximum sample size for this study is 18 patients. This was chosen based on projected recruitment timelines for eligible patients, and obtaining sensible operating characteristics from the design. The trial may be terminated early if either i) Tem dose is escalated to dose level 4 without any DLTs occurring and 6 patients are dosed at dose level 4 without experiencing DLT – dose level 4 will be declared as the MTD (total of 8 patients), or ii) the chance that the risk of DLT at the lowest dose being above the target toxicity level is at least 90% – the trial will be stopped for safety.

17.2. Statistical Analysis

17.2.1. Analysis of main endpoint

Occurrence of dose-limiting toxicity (DLT, defined as acute-pattern GvHD grade II-IV)
For DLT analysis, all patients deemed eligible for toxicity assessment will form the analysis population. Incidence of DLT per dose will be described in tables. GvHD data will be used to provide final estimates of DLT risks and their uncertainty using the dose-toxicity model. These estimates, along with SRC recommendations, will determine the MTD and thus RP2D of Tem.

17.2.2. Analysis of secondary endpoints and secondary analyses

Incidence and severity of acute GvHD (whether dose-limiting or not)
Incidence and severity of acute GvHD (dose-limiting or not), as defined by the Glucksberg Scale, will be reported per dose level in frequency tables.

Incidence and severity of chronic GvHD
Incidence and severity of chronic GvHD will be reported per dose level in frequency tables.

Non-relapse mortality at 1 year
Non-relapse mortality (NRM) is defined as the time from registration to time of death without relapse. NRM will be presented using a Kaplan-Meier (KM) plot (grouped across dose level and per dose level), and 1-year NRM rate will be estimated (with 95% confidence intervals).

Overall- and Event-free survival at 1 year
Overall survival (OS) is defined as the time from registration to time of death from any cause. Event-free Survival (EFS) is defined as time from registration to the occurrence of any of the following events: graft failure, disease relapse, disease progression, or time of death from any cause. OS and EFS will be presented using KM plots (grouped across dose level and per dose level), and 1-year OS and EFS rates will be estimated (with 95% confidence intervals).

Incidence/type of infection requiring inpatient admission at 1 year
Infections that require inpatient admissions from date of Tem Infusion until +360 days post-stem cell transplant will be documented, and the type of infection and duration of inpatient stays will be reported per dose level.

Total Number of inpatient days at 1 year
The median and range for the total number of days that patients spend in hospital as inpatients from the date of Tem Infusion up to 1 year post allo-SCT will be reported.

17.2.3. Exploratory Biological studies

See Section 10 for full details on the exploratory biological studies.

17.3. Interim Analyses

No formal interim analysis for efficacy or futility will be performed. Data relating to DLTs (acute pattern grade II-IV GvHD) and other safety data will be reviewed on an ongoing basis by the statistician and CI and reviewed formally by the SRC prior to dose escalation/de-escalation decisions being made. Data will also be reviewed by the IDMC and the study may be stopped early if the incidence of DLTs or other toxicity is judged to be unacceptably high in the judgement of both the IDMC and the SRC.

18. ETHICAL CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of Good Clinical Practice
- Human Rights Act 1998
- Data Protection Act 2018, and General Data Protection Regulation (EU)2016/679 (GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Mental Capacity Act 2005
- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority

18.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

18.2. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.3. Protocol Amendments

UCL CTC will be responsible for gaining ethical approval for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.4. Patient Confidentiality & Data Protection

Patient and donor identifiable data, including initials and date of birth will be collected by UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a

secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL

In addition certain identifiable information will be held on file at the central laboratory where the Tem cells are manufactured. This is necessary in order to ensure the correct Tem cells are matched to the correct patient. The information that will be used by the central lab will be: the patient's name, date of birth and trial number, and the donor's name, date of birth and hospital number. The study team at UCL CTC will not have access to these identifiers. Patients and donors will be informed of this on the trial information sheets and asked to consent for their identifiers to be used.

19. SPONSORSHIP AND INDEMNITY

19.1. Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2. Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20. FUNDING

The Medical Research Council (MRC) is supporting the central coordination of the trial through UCL CTC.

Research A and B costs will be reimbursed to sites as per the finance section of the mNCA.

21. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group and authorship will be determined by mutual agreement. Any secondary publications and presentations prepared by investigators must be reviewed by the TMG and must not be published prior to the first publication by the TMG.

Data generated by the study belong to the Sponsor, University College London. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. Please refer to the model non-commercial agreement (mNCA) between the Sponsor and Site gives further information on intellectual property rights.

The ClinicalTrials.gov number should be quoted in any publications resulting from this trial.

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Appendix 1 ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate aminotransferase
ATIMP	Advanced Therapy Investigational Medicinal Products
CCGTT	Centre for Cell, Gene and Tissue Therapeutics
CI	Chief Investigator
CR	Complete Response
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease Free Survival
DI	Designated Individual
DIS	Donor Information Sheet
DLI	Donor Lymphocyte Infusion
DPA	Data Protection Act
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EFS	Event Free Survival
FBC	Full Blood Count
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GvHD	Graft versus Host Disease
aGvHD	Acute Graft versus Host Disease
cGvHD	Chronic Graft versus Host Disease
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IV	Intravenous
LCRN	Local Clinical Research Network
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
MRC	Medical Research Council
MRI	Magnetic Resonance Image
MTD	Maximum Tolerated Dose
NCRI	National Cancer Research Institute
NRM	Non-relapse mortality
OS	Overall Survival
PB	Peripheral Blood

PD	Progressive Disease
PI	Principal Investigator
PIS	Patient Information Sheet
PMG	Project Management Group
PO	By mouth
PR	Partial Response
REC	Research Ethics Committee
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCT	Stem Cell Transplant
SD	Stable Disease
SLA	Service Level Agreement
SRC	Safety Review Committee
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEM	Effector Memory T cells
TCR	T Cell Receptor
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cells
WOCBP	Woman of Childbearing Potential

Appendix 2 QUICK REFERENCE GUIDE TO PATIENT VISITS

Assessment/ procedure	**Pre-Registration** *(within 4 weeks prior to registration)*		**CD62L$^-$Tem Apheresis** *(Day of apheresis or up to 7 days after)*	**Pre- Tem Treatment** *(within 2 days prior to Tem infusion)*	**DLT Period Follow Up** *every 14 days (+/- 4 days) until 72 days post Tem infusion*	**Follow Up** - D+100 - D+180 - D+270 - D+360 *(+/- 10 days)*	**Footnotes**
	Patient	Donor	Donor	Patient	Patient	Patient	1. *Required for trial eligibility. Scans/procedures may take place greater than 4 weeks prior to registration however current disease status must be confirmed at registration.*
Demographic data	x	x					2. *Biochemistry: Sodium, potassium, urea, creatinine, calcium, phosphate, albumin, total protein, bilirubin, AST, ALT, alkaline phosphatase and GFR*
Medical history	x						3. *For women of childbearing potential (see section 6.4.1)*
Disease assessment (as per local policy)	x[1]					x	4. *HIV (Anti-HIV-1, 2 & HIV-1 & 2 RNA PCR), Hepatitis B (HBsAg, Anti HBc, HBV DNA), Hepatitis C (Anti-HCV-Ab, HCV RNA PCR), HTLV (HTLV 1&2), Syphilis*
Haematopoietic Cell Transplantation Specific Co-morbidity Index	x						5. *4ml EDTA donor & recipient at registration and 10ml peripheral blood in EDTA during follow up*
Physical examination & weight	x			x	X	x	6. *5ml peripheral blood in serum tube*
Echocardiogram or MUGA scan	x						7. *25ml peripheral blood in Lithium heparin tube*
Eligibility for **CD62L$^-$Tem infusion**				x			8. *10ml peripheral blood in EDTA*
Full blood count + differential	x			x	X	x	9. *Adverse Reactions required during follow up*
Biochemistry[2]	x			x	X	x	10. *Performed on D+100 and +360 only*
Urine or serum pregnancy test[3]	x	x		x			
Infectious Disease Screen[4]		x	x				
Adverse Event Assessment (incl. GvHD)				x	X	x[9]	
Lymphocyte subset analysis (performed locally)						x	
Exploratory blood for chimerism[5]	x	x				x	
Exploratory blood for alemtuzumab levels[6]				x			
Exploratory blood for viral & immune reconstitution[7]						x	
Exploratory blood for TCR[8]						x[10]	

Appendix 3 EXPECTED ADVERSE EVENTS (20-22)

The following AEs are commonly associated with CD62L$^-$ Tem DLI and will be considered expected for this treatment:

- Fever
- Chills
- Hypotension
- GvHD (CTCAE v5.0 term: Immune system disorders – other: GvHD)*
- Bone Marrow Hypocellular
- Aplastic crisis* (CTCAE v5.0 term: Blood & lymphatic system disorders – other: pancytopenia)
- Neutropenia
- Anaemia
- Thrombocytopenia
- Vomiting

***Should this adverse event result in death, it should be considered expected for this procedure.**

The following ARs are commonly associated with apheresis and will be considered expected in donors:

- Citrate-induced hypocalcaemia
- Vasovagal syncope
- Hypovolaemia (CTCAE v5.0 term: Metabolism & nutrition disorders – other: hypovolemia)
- Hypotension Thrombocytopenia
- Deep vein thrombosis

The following ARs are also expected in donors who have placement of a central venous catheter:

- Bleeding
- Infection
- Air embolism
- Pneumothorax
- Cardiac arrhythmia

Appendix 4 RESPONSE CRITERIA

CLL and PLL *- modified from Hallek et al.(33)*

CR, CRi or PR for trial entry

CR (complete remission): all the criteria have to be met, and patients have to lack disease-related constitutional symptoms;

CRi is a category defined by failure to recover satisfactory counts but other criteria for CR are met;

PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of PD and failure to achieve PR.

Parameter	Group	CR*	PR	PD
Lymphadenopathy	A	None >1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	A	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	A	None	Decrease ≥50%	Increase ≥50%
Blood lymphocytes	A	>4,000/µl	Decrease ≥50% from baseline	Increase ≥50% over baseline
Marrow	A	Normocellular, <30% lymphocytes, no B-lymphoid nodules	50% reduction in marrow infiltrate or B-lymphoid nodules	
Platelet count	B	>100.000/µl	>100.000/µl or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Haemoglobin	B	>11.0g/dl	>11g/dl or increase ≥50% over baseline	Decrease of >2g/dl from baseline secondary to CLL
Neutrophils	B	>1,500/µl	>1,500/µl or >50% improvement over baseline	

Malignant lymphoma *- from Cheson et al.(29)*

CR or PR for trial entry

	Site	PET-CT-Based Response	CT-Based Response
Complete Response		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in long diameter No extralymphatic sites of disease
	Nonmeasured lesion	Not Applicable	Absent
	Organ enlargement	Not Applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5x5 mm as the default value When no longer visible, 0 x 0 mm

		At end of treatment, these findings indicate residual disease	For a node > 5 x 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	Not Applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not Applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No Response Or Stable Disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	Not Applicable	No increase consistent with progression
	Organ enlargement	Not Applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not Applicable
Progressive Disease		**Progressive metabolic disease**	**Progressive Diseased requires at least 1 of the following PPD progression:**
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of	An individual node/lesion must be abnormal with:

	Extranodal lesions	uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate

regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Lymphoplasmacytic lymphoma and Waldenstrom's macroglobulinaemia - *from Owen et al.(30)*

CR, VGPR or PR for trial entry

Response	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor Response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease
Stable Disease (SD)	Monoclonal IgM protein is detectable

	<25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive Disease (PD)	≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease
*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.	

Myeloma - *adapted from Rajkumar SV, Harousseau J-L, Durie B et al.(31)*

CR, sCR, VGPR or PR for trial entry

The IMWG response criteria for myeloma should be used for defining response:

Complete remission (CR)	Negative immunofixation on serum and urine Disappearance of any soft tissue plasmacytomas <5% plasma cells in bone marrow
Stringent complete remission (sCR)	As above and: Normal SFLC ratio and no evidence of clonal plasma cells on immunohistochemistry or flow cytometry
Very good partial response (VGPR)	>90% reduction in serum paraprotein and <100mg/24h BJP
Partial response (PR)	>50% reduction in serum paraprotein and/or >90% reduction in BJP and/or ≥50% decrease in difference between involved and uninvolved SFLC and/or >50% decrease in bone marrow plasma cells (if non-secretory multiple myeloma)
Stable disease/no response (SD)	None of the above and not progressive disease Define the time to progression
Progressive disease (PD)	>25% increase in serum paraprotein (absolute increase >5g/L) Urinary BJP (absolute increase >200mg/24h) Difference between SFLC (absolute increase >100mg/L) Bone marrow plasma cells (absolute >10%) New bone lesions/plasmacytomas Myeloma-related hypercalcaemia
Primary refractory	Defined as having never achieved partial response on therapy (PR) Non-responding, non-progressive Progressive disease
Relapsed/refractory	Achieved partial response on therapy (PR) then progressed within 60 days
Relapsed	Developed progressive disease after initially achieving partial response with >60 days duration and occurs off therapy

AML and ALL *- adapted from Cheson et al.(32)*

CR or CRi for trial entry

Complete remission (CR)	The marrow is regenerating normal haematopoietic cells and contains <5% blast cells by morphology on the aspirate film. ANC ≥1.0 × 109/L; platelet count ≥100 × 109/L
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 109/L) or thrombocytopenia (<100 × 109/L)
Relapse	Not meeting criteria for CR or CRi

MDS and CMML

Note that response criteria are based upon eligibility of <10% blasts at study entry

Complete remission (CR)	The marrow is regenerating normal haematopoietic cells and contains <5% blast cells by morphology on the aspirate film. ANC ≥1.0 × 109/L; platelet count ≥100 × 109/L
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 109/L) or thrombocytopenia (<100 × 109/L)
Relapse	Not meeting criteria for CR or CRi

Appendix 5 CHRONIC GvHD

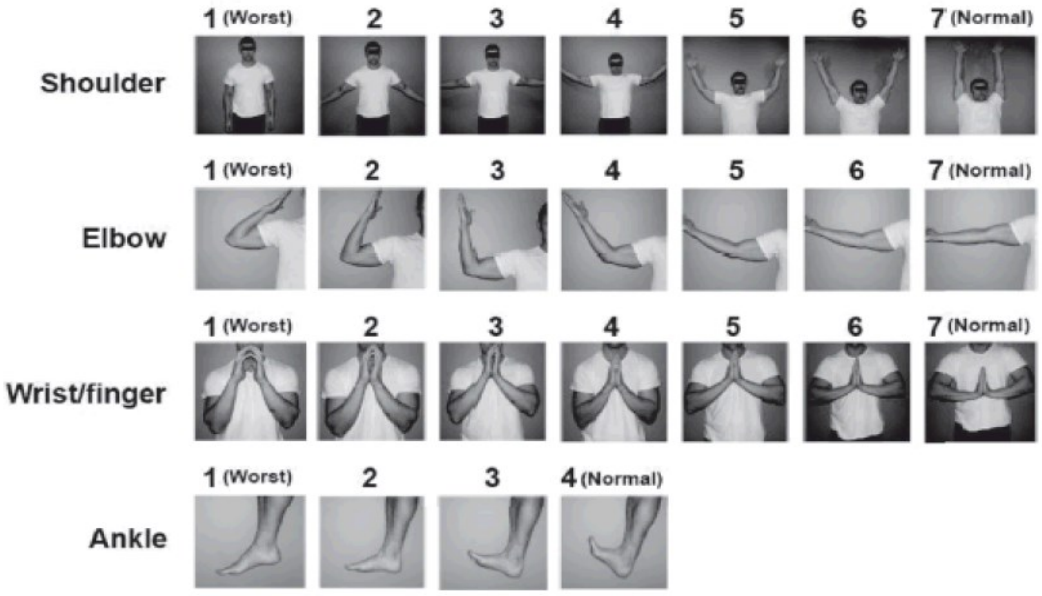
Chronic GvHD (cGvHD) will be evaluated according to NIH criteria [28].

Performance Score ***(ECOG):***			
0 Asymptomatic and fully active (ECOG 0)	**1** Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1)	**2** Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2)	**3** Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4)
Genital Tract:			
0 No Signs	**1** Mild signs and females with or without discomfort on exam	**2** Moderate signs and may have symptoms with discomfort on exam	**3** Severe signs with or without symptoms
Eyes:			
0 No Symptoms	**1** Mild eye symptoms not affecting ADL (requirement of eye drops ≤ 3 times per day)	**2** Moderate dry eye symptoms partially affecting ADL (requiring eye drops > 3 times per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	**3** Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
GI Tract:			
0 No symptoms	**1** Symptoms without significant weight loss* (<5%)	**2** Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhoea without significant interference with daily living	**3** Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** oesophageal dilation **OR** severe diarrhoea with significant interference with daily living
Liver:			
0 Normal total bilirubin and ALT or AP < 3 x ULN	**1** Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	**2** Elevated total bilirubin but ≤3mg/dL or ALT > 5 x ULN	**3** Elevated total bilirubin >3mg/dL

Lungs:			
Symptoms:			
0 No Symptoms	**1** Mild symptoms (shortness of breath after climbing one flight of steps)	**2** Moderate symptoms (shortness of breath after walking on flat ground)	**3** Severe symptoms (shortness of breath at rest; requiring O_2)
% FEV1:			
0 FEV1 ≥ 80%	**1** FEV1 60-79%	**2** FEV1 40-59%	**3** FEV1 ≤39%
Mouth:			
0 No symptoms	**1** Mild symptoms **with** disease signs but not limiting oral intake significantly	**2** Moderate symptoms with disease signs **with** partial limitation of oral intake	**3** Severe symptoms with disease signs on examination **with** major limitation of oral intake
Skin:			
Score %BSA:			
0 No BSA involved	**1 1** 1-18% BSA	**2** 19-50% BSA	**3** >50% BSA
Skin features:			
0 No sclerotic features	**1**	**2** Superficial sclerotic features “not hidebound” (able to pinch)	**3** Deep sclerotic features, “hidebound” (unable to pinch), Impaired mobility, Ulceration

Joints and Fascia :			
0 No Symptoms	**1** Mild tightness of arms and legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL.	**2** Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL.	**3** Contracture with significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)

Photographic Range of Motion (P-ROM Score)



Global severity scoring for Chronic GvHD will be according to NIH scoring

Mild	1 or 2 organs involved with no more than score 1 *plus* Lung score 0
Moderate	3 or more organs involved with no more than score 1 ***OR*** At least 1 organ (not lung) with a score of 2 ***OR*** Lung score of 1
Severe	At least 1 organ with a score of 3 ***OR*** Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix 6 PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	10/04/2019	-	-	
2.0	27/03/2020	1.0	6.2.1 – Inclusion Criteria	Clarification of complete response included for specific haematological cancers
			8.3 – CD62L^{-} Tem Dose Levels	Number of cells to be infused is weight dependent
			17 - Statistics	
			8.5 8.6 9.6	Added sections on follow-up post-DLT period, after graft failure, progression/relapse and assessments during long term follow up
			12 – Safety Reporting	Clarification of reporting processes
			16.1 – End of Trial	All patients will be followed up until end of trial is declared