AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP

Evaluation of engraftment kinetics following double unit umbilical cord blood transplantation in patients with life threatening haematological malignancy in whom stem cell transplant (SCT) offers the only prospect of cure

Abbreviated Study Title: Double unit cord blood transplantation.

ALLG BM08

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Contents

1. GENERAL

1.1. Persons Responsible

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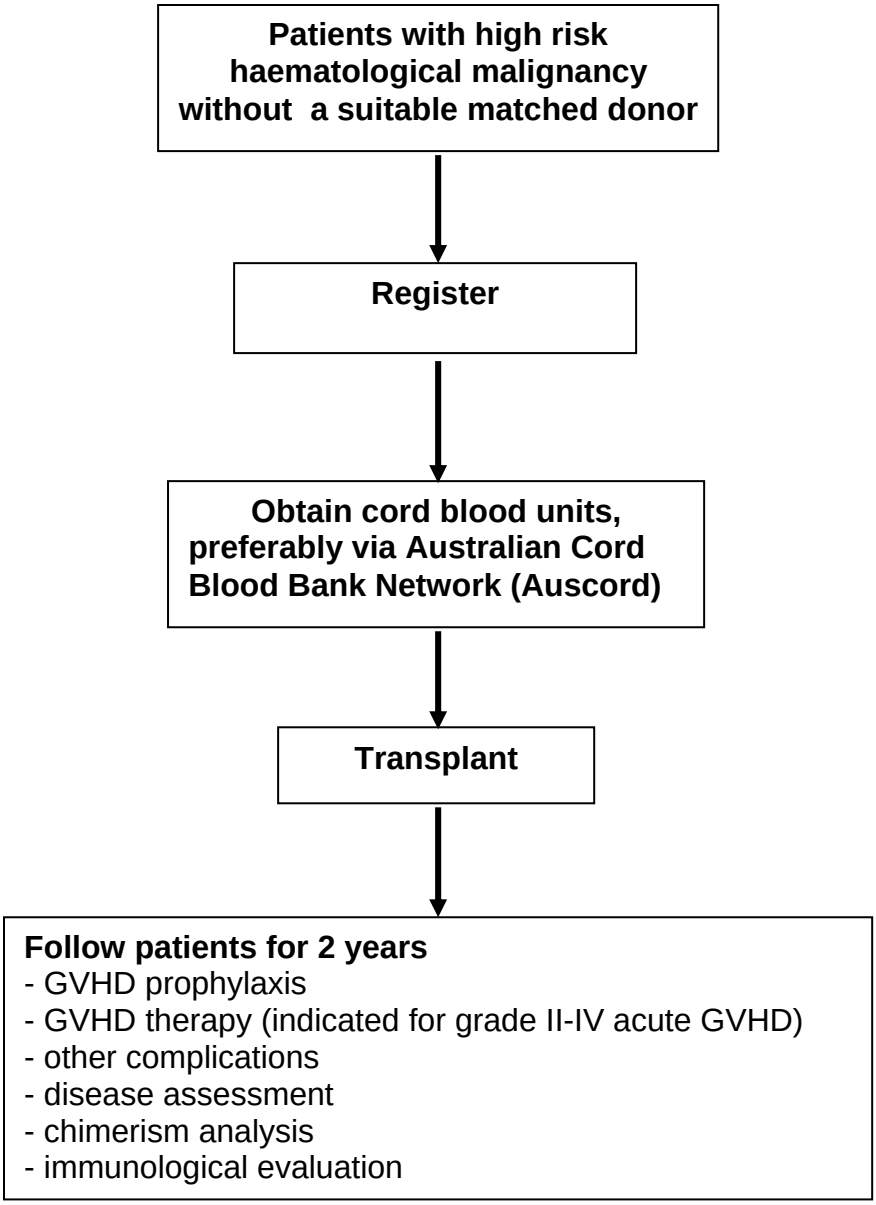
Sponsor: ALLG

Independent Data Monitoring Committee:
ALLG Safety Data Monitoring Committee

1.2. Protocol Synopsis

Study Title:	A Study of Double Unit Umbilical Cord Blood Transplantation in Adult Patients with Life Threatening Malignancy
Acronym:	Double unit cord blood transplantation
Indication:	Adult patients with haematological malignancies requiring stem cell transplantation who do not have an identified suitable donor.
Primary Objective:	Estimation of time to neutrophil engraftment of double unit unrelated cord blood transplantation in adult patients.
Secondary Objectives:	Estimation of sustained donor neutrophil and platelet engraftment at days 100 and 180 post transplant, chimerism, GVHD, toxicity and safety, disease free survival and overall survival.
Study Design:	Open-label, non-randomised, prospective study
Study Population:	Patients age 18 – 55 years inclusive with haematological malignancy requiring stem cell transplantation.
Sample Size:	20 but with provision for expansion to 30 or 40 patients, prior to interim analysis of the primary endpoint (time to neutrophil engraftment), if accrual is rapid.
Therapy:	Myeloablative conditioning with cyclophosphamide and TBI
Primary Endpoints:	Time to donor neutrophil engraftment
Secondary Endpoints:	Sustained neutrophil and platelet engraftment, toxicity, survival (OS and DFS), treatment response, transplant related mortality.
Duration of the Study:	4 years.
Sponsor:	ALLG

2. SCHEMA


Patients with high risk haematological malignancy without a suitable matched donor
Register
Obtain cord blood units, preferably via Australian Cord Blood Bank Network (Auscord)
Transplant
Follow patients for 2 years
- GVHD prophylaxis
- GVHD therapy (indicated for grade II-IV acute GVHD)
- other complications
- disease assessment
- chimerism analysis
- immunological evaluation

3. STUDY PARAMETERS

	Baseline	Conditioning and Transplant	1 month post transplant	2 mth post transplant	3 mth post transplant	6 mths post transplant	9 mths post transplant	1 year post transplant	18 mths post transplant	2 years post transplant
Patient characteristics[1]	X									
Disease assessment[2]	X		X		X	X		X		X
Cardiac function[3]	X									
Pulmonary function studies	X									
FBE[4]	X	daily	Daily until ANC $\geq$10.0 x 10^9/L for one day or $\geq$5.0 x10^9/L for 3 consecutive days, then 3 times weekly	3 times weekly	Weekly	X		X	X	X
Biochemistry[5]	X		three times weekly	weekly	Weekly	X		X	X	X
Serology[6]	X									
Assessment of infection prophylaxis and infectious episodes/febrile neutropenia		X	continuous →							
Chimerism on PB			X	X	X	X	X	X		X
GVHD assessment / documentation			X	X	X	X		X		X
Adverse event reporting and assessment of other complications			X	X	X	X	X	X	X	X
Immunological evaluation[7]										
IgG, IgA, IgM			x	x	x	x		x	x	x
immunophenotyping			x	x	x	x		x	x	x

1. Age, sex, ECOG PS, prior therapy
2. As appropriate: CT scans neck/chest/abdomen/pelvis; bone marrow biopsy; lymphocyte surface markers; serum paraprotein and Bence Jones protein
3. Cardiac function: either gated heart pool scan or echocardiography
4. FBE: haemoglobin, neutrophils, platelets
5. Biochem: liver function studies, urea, creatinine blood electrolytes
6. Hepatitis B, hepatitis C, HIV.
7. Patients with documented donor engraftment

4. TREATMENT PLAN/GVHD PROPHYLAXIS

	Day -8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Cord blood infusion	D5 -D19	D20 - D22	D23 - D25	
Conditioning, TBIS & transplant													
Option A													
Cyclophosphamide 60 mg/kg				X	X								
TBI 200 cGy bd						X	X	X	X				
Option B													
Cyclophosphamide 60 mg/kg			X	X									
TBI 165 cGy bd					X	X	X	X	X				
GVHD Prophylaxis													
Option 1													
Fludarabine	X	X	X										
Cyclosporin						X	→	→	→	→	→	→	to D100, taper if no GVHD
Mycophenolate Mofetil						X	→	→	→	→	→	→	to D30, taper if no GVHD
Option 2													
ATG					X	X	X						
Cyclosporin								X	→	→	→	→	to D100, taper if no GVHD
Methylprednisolone										1 mg/kg IV	0.5 mg/kg	0.25 mg/kg	taper to 0 from D26 - D33

5. STUDY OBJECTIVES

5.1. Primary Objective

To estimate the time to neutrophil engraftment of double unit unrelated cord blood transplantation in adult patients with high risk malignancy. Specifically, to analyse the ability of a two unit cord blood transplant with Filgrastim support to achieve timely engraftment.

5.2. Secondary Objectives

To assess time to platelet engraftment, chimerism, GVHD, toxicity and safety, disease free survival (DFS) and overall survival (OS) in these patients

6. BACKGROUND INFORMATION AND STUDY RATIONALE

The use of umbilical cord blood (CB) as a source of haemopoietic stem cells (HSC) for transplantation is increasing, with over 2000 transplants performed worldwide. The majority of these have been in the unrelated setting, being facilitated by the establishment of cord blood banks[1]. Potential advantages of using CB compared to other sources of HSC include a reduction in search time and procurement[2], a low risk of transmission of viral disease and a reduced incidence of graft versus host disease (GVHD)[3,4], a major cause of transplant related morbidity. The reduced incidence of GVHD has resulted in CB transplantation (CBT) being performed with greater degrees of human leukocyte antigen (HLA) disparity than would normally be accepted for unrelated donor (URD) bone marrow transplantation (BMT). As the stringency for HLA matching is not as strict this may result in more patients having potential donors identified. The major limiting factor to more widespread use of CB is the characteristic delay in engraftment with a median time to neutrophil engraftment of 28 days and platelet engraftment up to 90 days. This is partly due to an insufficient dose per unit and severely limits the use of CBT in adult patients. Eurocord, the international registry for BMT units performing CBT, recommend transplantation with CB only be contemplated if the infused cell dose is at least 3.7×10^7 nucleated cells (NC)/kg[5], allowing for the fact that up to 20% of the stored nucleated cells can be lost on thawing. Currently, only 2% of banked CB units would reach this criterion for a 60 kg adult.

Transplantation using CB remains an experimental procedure with long-term data on survival and relapse of underlying disease not yet available. Two recent reviews have analysed the outcomes of adult patients receiving unrelated CBT. Eurocord have reported results on 156 adults who received a median cell dose of 1.7×10^7 NC/kg from CB units containing a median 2.2×10^7 NC/kg[5]. Haematologic malignancy was the reason for transplant being performed in 108 cases. The median age of the recipients was 26 (range 15 - 53) with a median weight 60 kg (range 35 - 110). Median time to neutrophil engraftment was 32 days. Engraftment was superior in patients who received a cell dose of $>1.7 \times 10^7$ NC/kg. The incidence of grade II - IV GVHD was only 38% despite >96% of patients receiving a graft with a 1 - 3 HLA antigen mismatch. With a median follow up of 20 months actuarial survival was 27% at 1 year. In patients transplanted with good prognosis disease 1 year survival was 39%. Patients who received a cell dose of $\geq 2.0 \times 10^7$ NC/kg had a decreased 100 day mortality. Relapse rates were low but follow-up was short with the majority of deaths due to infection or GVHD. Laughlin et al reviewed the outcome of CBT in 68 adult recipients and report encouraging results[6]. The majority of patients had malignant disease and received a median cell dose of 2.1×10^7/kg (range 1.0 – 6.3) with 71% being mismatched at 2 or 3 HLA loci. With daily filgrastim support median time to neutrophil engraftment was 27 days (range 13 – 59) and platelet engraftment was 58 days (range 35 – 142). In this high risk population, grade II – IV GVHD occurred in 60% of recipients. Day

100 mortality was 51% with the predominant causes of death being infection (49%) and regimen related toxicity (43%). At 22 months overall survival was 28%.

Delayed engraftment, rather than HLA disparity, has emerged as the limiting factor to more widespread use of CB as a source of HSC. Novel approaches to enhance both the rate and degree of engraftment are needed. This delay in engraftment may simply reflect the low cell number in CB grafts but may also reflect the immaturity of CB cells or the lack of facilitating cells in the graft. Current data indicate that engraftment is related to cell dose infused, whether quantified by nucleated cell dose[4] or $CD34^+$ cell dose[7], and preliminary evidence suggests outcome is related to prompt engraftment. Techniques to increase CB cell numbers include improvements in collection techniques, ex-vivo expansion of stem cells or the use of multiple CB units.

Transplantation of 2 or more immunologically different CB units may result in immunologic rejection but encouraging preliminary results have been reported using this approach in adult patients from the University of Minnesota[8]. Twenty three adult patients, with high risk haematological malignancy, aged 13-53 with a median weight of 73 kg (range 48-120) received a HLA disparate 2 unit CBT following myeloablative conditioning. The median cryopreserved cell dose was 4.8 x 10^7/kg (range 1.6-7.0). Median time to neutrophil engraftment was 23 days (range 15-41) after G-CSF 5 µg/kg/day from day 1. All evaluable patients had sustained donor engraftment. Grade III-IV acute GVHD was seen in only 13% of patients. Projected Disease-free survival at 12 months in this high risk group of patients was 57% with infection and relapse/progressive disease being the predominant causes of death. Despite the use of two CB units, both units contributed to engraftment in a minority of patients at day 21 (24%) and even fewer at day 60 (2/19). By day 100, sustained engraftment was derived from only one unit in all patients. Given the relatively small cell dose of the predominating unit, engraftment was superior to that predicted, suggesting the second unit facilitated engraftment by an, as yet, unexplained mechanism.

Rationale for this study

Umbilical cord blood is a suitable source of haemopoietic stem cells for use in BMT. However, the finite cell dose associated with most collected units limits the usefulness of this approach in adults. Preliminary results using a double unit transplant approach in adult patients with high risk haematological disease who lack a suitable sibling or unrelated donor show that this approach is not detrimental and may even be beneficial in enhancing engraftment. This study will estimate the time to engraftment after double cord blood transplantation in adult patients with life threatening malignancies.

Hypothesis

Transplantation of two cord blood units is feasible and safe to administer.

7. STUDY PLAN

7.1. Study Design

This is a multicentre study to estimate the time to engraftment after double unit cord blood transplantation in adult patients with haemopoietic malignancies that are incurable with conventional treatment and who do not have a suitable identified donor. The intention is to enrol 20 patients over a 2 year period. If the accrual rate is faster than the expected 20 patients in 2 years,

consideration will be given to expanding the sample size to 30 or 40 patients. This decision will be made before any interim statistical analysis of the primary endpoint.

7.2. Participating Centres and Number of Patients

This protocol will be open to all centres affiliated with the ALLG. It is estimated that at least 20 patients will be recruited.

7.3. Expected Study Duration

It is expected that recruitment of patients will require approximately 2 years. Patients will be followed up for 2 years, with an anticipated study duration of approximately 4 years.

7.4. Premature Discontinuation of the Study

7.4.1 Patient withdrawal

A patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and sponsor also have the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a patient (or a patient's legally authorised guardian/representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

7.4.2 Premature discontinuation of study

The study can be terminated according to the criteria described in Section 11.6.

If the study is stopped for safety reasons, no further patients will be enrolled into the study. Patients already enrolled should be treated according to investigator discretion.

8. INCLUSION AND EXCLUSION CRITERIA

8.1. Inclusion Criteria

1. Male and female patients with high risk haematological malignancy in whom SCT offers the only prospect of cure, but do not have either a fully matched or one-antigen mismatched related donor or an identified suitable matched unrelated donor (URD). If a matched URD has been identified but the delay in obtaining marrow will result in unnecessary risk to the patient, then a double unit cord transplant could be considered. Examples of high risk malignancies would include, but not be restricted to, the following:

    - Acute myeloid leukaemia (AML) beyond 1st remission or in patients in 1st remission (CR1) with poor risk cytogenetics (monosomy chromosome 5 or 7, del(5q), abn (3q26), complex karyotype)
    - Acute lymphoblastic leukaemia beyond first remission or in patients in (CR1) with adverse risk factors [t(9;22), t(4;11), pro-B ALL (CD10neg, CD20 neg, non-T), WCC at presentation > 30,000, not in remission at d28]
    - Myelodysplastic syndrome
    - 2^o AML or refractory anaemia with excess blasts.
    - Chronic myeloid leukaemia - second chronic phase, accelerated phase or blast crisis.

- Hodgkin lymphoma – patients with primary refractory disease or who have relapsed after a previous autologous transplant.
- Non-Hodgkin's lymphoma – relapsed patients not suitable for an autologous transplant or in patients who have relapsed after a previous autologous transplant or in patients with poor risk follicular lymphoma.
- Multiple Myeloma – patients who have relapsed after a previous autologous transplant.

2. Age 18 to 55 years inclusive.

3. ECOG performance status 0-2.

4. Satisfactory major organ function
   - Cardiac function as measured by either a gated blood pool scan or echocardiogram showing left ventricular ejection fraction > 40%.
   - Pulmonary function as measured by a DLCO ≥ 50% of normal.
   - Renal function as measured by a calculated or actual creatinine clearance > 30 ml/min.
   - Hepatic function as measured by a serum bilirubin ≤ 30 mol/l and transaminases ≤ 2 x ULN.

5. Written informed consent given by recipient.

Note: It is desirable but not mandatory to collect back up autologous blood or marrow cells of adequate number (CD34+ >2 x 106/kg) to rescue the patient in the event of graft failure/prolonged pancytopenia (defined as failure to achieve an absolute neutrophil count of ≥ 0.5 x 109/L by day 42).

8.2. Exclusion Criteria

1. Patients with a suitable matched related or unrelated donor in whom marrow or peripheral blood stem cells can be procured within a satisfactory time period.
2. Patients who are positive for hepatitis B, hepatitis C or HIV.
3. Pregnant or lactating women.
4. Severe uncontrolled infection.
5. Contraindication to use of any of the study drugs, including known sensitivity to *E coli* derived preparations.

9. INDIVIDUAL COURSE OF STUDY

9.1. Patient Information

Informed consent must be obtained prior to registering a patient on the study. A draft Patient Information and Consent Form is attached as Appendix 1.

9.2. Patient Registration

To register a patient, fax the completed Registration Form to the ALLG Trial Centre on +613 9656 1420. The patient's eligibility will be checked and any queries dealt with by phone. Once eligibility is confirmed, a Confirmation of Registration Form will be faxed to the centre with a registration number.

Patients will not be registered if treatment has started, or if written consent has not been given. Information to assess compliance with the inclusion and exclusion criteria may be required for registration.

9.3. Description of Study Therapies

9.3.1 Selection of CB units

1. The two identified units must be a 4-6 HLA A, B (by serological testing) and DRB1 (by high resolution molecular testing) antigen match to the patient. The two selected units do not need to be HLA-identical to each other. Ideally, they should have no greater than 2 mismatches between each other at the A, B, and DRB1 loci but this is not an absolute requirement.
2. The combined cell dose of the 2 most appropriate units will depend upon the degree of HLA match of each unit. Units that are 5/6 or 6/6 matches must have a cryopreserved cell dose of ≥ 1.5 x 107/kg. Units that are 4/6 matches must have a cryopreserved cell dose of ≥ 2.0 x 107/kg.
3. Every attempt should be made to procure one of the identified units from the Australian Cord Blood Bank Network (Auscord). An example of a suggested letter of request is shown in Appendix 2.

9.3.2 Conditioning, TBI and transplant

Cyclophosphamide 120 mg/kg divided into 2 daily doses + fractionated TBI.
Two options for TBI are available, 1200 or 1320 cGy, depending upon institutional preference:

A. Cyclophosphamide 120 mg/kg + 1200 cGy fractionated TBI.
d-5 cyclophosphamide 60 mg/kg.
d-4 cyclophosphamide 60 mg/kg.
d-3 TBI 200 cGy bd.
d-2 TBI 200 cGy bd.
d-1 TBI 200 cGy bd.
d0 cord blood infusion.

B. Cyclophosphamide 120 mg/kg + 1320 cGy fractionated TBI.
d-6 cyclophosphamide 60 mg/kg.
d-5 cyclophosphamide 60 mg/kg.
d-4 TBI 165 cGy bd.
d-3 TBI 165 cGy bd.
d-2 TBI 165 cGy bd.
d-1 TBI 165 cGy bd.
d0 cord blood infusion.

9.3.3 GVHD prophylaxis

Two options are available, depending upon institutional preference:

A: Fludarabine, cyclosporin and mycophenolate;
1. Fludarabine 25 mg/m^2 d –8 to d –6 (total 3 doses).
2. Cyclosporin 3 mg/kg IV daily commencing on d-3 with appropriate dose titration according to therapeutic level and renal function. Continue until d +100 and then taper if GVHD has not developed.
3. Mycophenolate Mofetil 1mg/kg d -3 to d +30 inclusive. After d +30 taper if GVHD has not developed.

B: ATG, methylprednisolone and cyclosporin
1. ATG (ATGAM-horse) 30 mg/kg IV 3 doses from d -4 to d -2.
2. Cyclosporin 3 mg/kg IV daily commencing on d-1 with appropriate dose titration according to therapeutic level and renal function. Continue until d +100 and then taper if GVHD has not developed.
3. Methylprednisolone 1 mg/kg IV d +5 to d +19, 0.5 mg/kg d +20 – d+22, 0.25 mg/kg d +23 – d+25, then taper to 0 d +26 – d+33.

9.3.4 GVHD therapy

Indicated for established grade II-IV acute GVHD, preferably biopsy proven. GVHD severity will be coded according to standard criteria (Appendix 1).

1st Line: Commence methylprednisolone 2-4 mg/kg daily. If positive response, continue for 10-14 days then taper based on clinical factors. If progressive disease by day 3, or if no response by day 7, or incomplete response by day 14, 2nd line therapy needs instituting.

2nd Line therapy: according to institutional criteria.

9.3.5 Supportive care

1. Filgrastim (r-metHuG-CSF, NEUPOGEN®) 5 μg/kg SC from day +1 until ANC >10.0 $x10^9$/L for one day or >5.0 $x10^9$/L for three consecutive days.
2. Antibiotic, antiviral and antifungal prophylaxis and treatment should follow current institutional guidelines.

9.4. Parameters for the Study Objective

This study is a prospective multi-centre study that will obtain laboratory and clinical data for analysis. Clinical and laboratory data will be obtained at enrolment and then at regular points post transplant. Critical laboratory data will be obtained from the donated cord blood units.

9.4.1 Pretreatment evaluation

CB Units
1. Pre and post thaw nucleated cell count, leukocyte count and CD34+ count.
2. HLA typing (serological class 1, molecular class 2) will be obtained from the appropriate cord blood bank.

Pre transplant clinical data
1. Baseline clinical data including age, sex, details of primary disease being treated, date of diagnosis, all therapy, disease status at transplant.
2. Disease assessment: as appropriate - bone marrow biopsy, lymphocyte surface markers, serum paraprotein and Bence Jones protein, CT scan neck, chest abdomen and pelvis.
2. Complete blood count ((including liver function studies, urea, creatinine, and routine blood electrolytes) and biochemical analysis (including liver function studies, urea, creatinine, and routine blood electrolytes).
3. Assessment of cardiac function by either gated heart pool scan or echocardiography and pulmonary function studies.

9.4.2 Subsequent evaluations

Post transplant clinical data

1. Details of conditioning.

2. Details of immunosuppression including doses of cyclosporin and mycophenolate and any other second line agents used.
3. Antimicrobial, antifungal, antiviral agents and intravenous immunoglobulin administered either prophylactically or therapeutically.
   - days with empirical antimicrobial therapy.
   - details of febrile episodes
   - all positive cultures, positive histopathology, positive serology and informative imaging studies will be documented.
4. GVHD assessment
   Diagnosis and grading of acute GVHD will be made according to accepted criteria (Appendix 3).
   - date of diagnosis, histopathology and therapy with response (response vs stable vs progression)
   - assessments will be made at 1 mth post transplant, 2 months, 3 months, 6 months 1 year and 2 years. Assessments will include grading of severity and organ involvement.

5. Development of other complications such as veno-occlusive disease of liver, interstitial pneumonitis, haemorrhagic cystitis, and microangiopathic haemolytic anaemia. This will include criteria and evidence used for diagnosis, investigations performed, duration, and management. Assessments will be made at 1 mth post transplant, 2 months, 3 months, 6 months, 9 mths, 1 year, 18 months and 2 years.

   Non-haematological toxicity will be graded according to the NCI CTCAE criteria, version 3 (See Appendix 4).

6. Disease assessment will take place at 1 month post transplant, 3 months, 6 months, 1 year and 2 years, and at other timepoints as clinically indicated. Evaluations to be carried out will be determined by the underlying disease and will include as appropriate: bone marrow biopsy, lymphocyte surface markers, serum paraprotein and Bence Jones protein, CT scan neck, chest abdomen and pelvis.

7. Date of relapse, date of death, and cause of death where relevant.

<u>Post transplant laboratory data</u>

1. Haematological data daily until haemopoietic recovery (ANC $\geq$10.0 x10^9/L for one day or $\geq$5.0 x10^9/L for three consecutive days). Thereafter, haematological data to be collected three times weekly until 2 months post transplant, then weekly until 3 months then at 6 months, 1 year, 18 months and 2 years. Blood product support will be documented.

2. Biochemical analysis (including liver function studies, urea, creatinine, and routine blood electrolytes) three times a week until 1 month post transplant and then weekly until 3 months, then at 6 months, 1 year, 18 months and 2 years.

3. Chimerism analysis on peripheral blood samples at 1 month post transplant, 2 months, 3 months, 6 months, 1 year and 2 years. Chimerism will be assessed using DNA fingerprinting (VNTR analysis) on T cell and myeloid subsets using flow sorting.

4. Immunologic evaluation will be carried out on patients with documented donor engraftment at 1 month post-transplantation, 2 months, 3 months, 6 months, 1 year, 18 months and 2 years. Assessment will include immunoglobulin levels (IgG, IgA and IgM)

and immunophenotyping studies to define T, B and natural killer cell numbers and subsets ($CD3^+$, $CD3^+/CD4^+$, $CD3^+/CD8^+$, $CD19^+$, $CD3^-/CD16^+/CD56^+$).

10. ADVERSE EVENTS

10.1. Definitions

An *adverse event* is any new, undesirable medical experience or change of an existing condition which occurs during or after treatment. Adverse events that are possibly, probably or definitely protocol treatment-related should be recorded on the appropriate case report form and graded according to NCI CTCAE Version 3 (see Appendix 4)

A *serious adverse event* is any untoward medical occurrence that suggests a significant hazard or side effect. This includes, but may not be limited to, any event that (at any dose):

- results in death
- is life-threatening (places the patient at immediate risk of death)
- requires or prolongs inpatient hospitalisation
- is disabling or incapacitating
- is a congenital anomaly/birth defect

Important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

10.2. Reporting serious adverse events

10.2.1 All events

All adverse events that occur between the first study-related procedure and 26 weeks after cord blood transplant will be reported.

All serious adverse events (including filgrastim related events) must be reported within 24 hours of the investigator becoming aware of the event. Fax the SAE form and the SAE report cover sheet to:

ALLG Trial Centre
Peter MacCallum Cancer Centre
St Andrews Place, East Melbourne, Vic 3002

Fax: +613 9656 1420

10.2.2 Filgrastim related events

All serious adverse events judged related to filgrastim must also be sent or faxed as follows:

- TGA within 15 calendar days of discovery or notification of the event using the ADRAC 'blue card' which can be downloaded from: http://www.health.gov.au/tga/adr/bluecard.pdf.

  The Secretary, ADRAC
  Reply Paid 100
  Woden ACT 2606

Fax: (02) 6232 8392

- Amgen Australia within 1 working day to:

  Clinical Safety
  Amgen Australia Pty Ltd
  Level 1, 801 Glenferrie Road
  Hawthorn VIC 3122
  Fax: (03) 9818 5123
  Ph: (03) 9854 9800

All serious and medically significant adverse events considered related to filgrastim by the investigator will be followed until resolved or considered stable. The following attributes must be assigned: description; dates of onset and resolution; severity; assessment of relatedness filgrastim and action taken.

10.2.3 General

The investigator should notify the Institutional Ethics Committee of serious adverse events occurring at the site, in accordance with local procedures.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occur, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Any pregnancy occurring during this study should be immediately reported to Clinical Safety, Amgen Australia.

11. STATISTICAL ASPECTS

11.1. Trial design

This is a single-arm, multi-centre study to evaluate the efficacy and toxicity of double unit cord blood transplants in adult patients with haemopoietic malignancies that are incurable with conventional treatment and who do not have a suitable identified donor. Efficacy will be assessed by estimation of the cumulative incidence of donor engraftment and toxicity will be assessed by the monitoring of adverse events and the estimation of treatment-related mortality.

11.2. Definitions of study endpoints

The primary endpoint is the ***time to neutrophil engraftment*** which is measured from the day of transplant until the earlier of the first day on which the absolute neutrophil count $\geq 1.0 \times 10^9$/L or the first occasion for which two consecutive readings of absolute neutrophil count $\geq 0.5 \times 10^9$/L.

The secondary endpoints are:

Time to platelet engraftment measured from the day of transplant until the first of three successive days on which the unsupported platelet count $\geq 20 \times 10^9$/L. A platelet count will be regarded as unsupported if there have been no platelet transfusions in the 48 hours prior to the collection of the blood sample.

Incidence of sustained donor neutrophil engraftment at days 100 and 180 post transplant - sustained neutrophil engraftment is defined as absolute neutrophil counts $\geq 1.0 \times 10^9$/L continuously for the previous 4 weeks without G-CSF support.

Incidence of sustained donor platelet engraftment at days 100 and 180 post transplant – sustained platelet engraftment is defined as platelet counts $\geq 20 \times 10^9$/L continuously for the previous 4 weeks without platelet transfusions.

Donor chimerism at days 28, 56, 100, 180, 270 and 356 will be reported as mixture percentages (p) from the two donors (D_1 and D_2) and the recipient R (i.e. $p_{D_1} + p_{D_2} + p_R = 100\%$).

DNA for chimerism studies will be prepared using standard methods. DNA will be amplified using the AmpFISTR Profile Plus kit for PCR. This simultaneously amplifies nine short tandem repeat loci. For institutions that do not use this method, samples can be sent to the IMVS, Adelaide, for analysis.

Incidence of severe (grades III or IV) acute GVHD (in the first 100 days following transplant) and ***occurrences of chronic GVHD*** (after day 100 and at days 180 and 365 post-transplant). These will be assessed using a modified version of the Glucksberg scale (Appendix 3)..

Occurrences of adverse events (NCI CTCAE v3.0) in the first 100 days following transplant.

Transplant related mortality defined as death due to conditioning-related toxicity, including Veno-Occlusive Disease (VOD) and interstitial pneumonitis, failure of engraftment, GVHD and infection, during the first 100 days following transplantation.

Overall survival (OS) will be measured from the date of transplant until the date of death from any cause.

Disease-free survival (DFS) will be measured from the date of transplant until the earlier of the date that relapse occurs or the date of death from any cause. The date on which relapse occurs, for each type of malignancy, is the first date on which a post-transplant sample or scan exhibits the following:

AML and ALL. The peripheral blood counts fall below the criteria for CR (Hb <100 g/L, ANC < 1.5 x 10^9/L, platelets < 100 x 10^9/L). Ideally a bone marrow biopsy should be performed. If BM blasts are >5% with marrow cellularity > 20% relapse can be said to have occurred.

CML. Molecular relapse, defined as the reappearance of detectable bcr-abl transcript by RQ-PCR, or cytogenetic relapse, defined as reappearance of Philadelphia chromosome positive metaphases in the BM, or, haematological relapse, defined as peripheral blood evidence of leukaemia relapse (anaemia, leukocytosis, thrombocytosis or thrombocytopenia).

NHL and Hodgkin Disease. The reappearance of adenopathy on CT scan or recurrence of BM involvement.

Myeloma. The reappearance of a serum paraprotein or in the case of light chain disease, a rise in serum free light chains or reappearance of Bence Jones protein.

A study close-out (censor) date will be used in the analysis of OS and DFS. For OS this will be taken to be the earliest of the dates of last contact of patients who are still alive and being followed-up. For DFS, this will be taken to be the earliest of the dates of last disease assessment for live patients who are not known to have relapsed and are still being followed-up.

11.3. Statistical methods

All patients will be registered prior to their transplant. The primary group of patients to be analysed will be the eligible patients who undergo a transplant. Details will be provided of any ineligible registered patients and any registered patients who did not receive a transplant.

Baseline characteristics (at registration) and characteristics of the patients at transplantation, and their double units of cord blood, will be summarized using descriptive statistics.

The distributions of time to neutrophil engraftment and time to platelet engraftment will be estimated using both the Kaplan-Meier (product-limit) method and the cumulative incidence function for engraftment – the former treats death before engraftment as a censoring event while the latter treats it as a competing risk. Estimates from both methods will be presented in the form of cumulative incidence curves with associated point-wise 95% confidence intervals.

The incidences of sustained donor neutrophil engraftment and also sustained donor platelet engraftment at day 100, and also day 180, will be calculated using the number of transplanted patients as the denominator and exact methods for the multinomial distribution will be used to calculate 95% confidence intervals for these incidences or rates. Separately for each engraftment endpoint, transplanted patients will (at 100 or 180 days) be classified into one of six distinct groups: sustained engraftment (SE), SE lost but patient is alive, no SE achieved but patient is alive, patient has died without loss of SE, SE lost and patient has died, and, no SE achieved and patient has died.

Donor chimerism at days 28, 56, 100, 180, 270 and 365 will be reported for each of these time points in the form of summary statistics (minimum, lower quartile, median, upper quartile and maximum) for the sum of the donor percentages,

$$p_{D_1} + p_{D_2}$$

and for the ratio of the absolute value of the difference in the donor percentages to the sum of the donor percentages,

$$\left| p_{D_1} - p_{D_2} \right| / (p_{D_1} + p_{D_2})$$

where for each sample at each time, the sum of the donor percentages and the recipient percentage is 100, i.e.,

$$p_{D_1} + p_{D_2} + p_R = 100\%$$

The sum of the donor percentages can vary from zero (no donor chimerism) to 100% (complete donor chimerism) and the ratio of the absolute difference to the sum can vary from zero (no predominance of one donor) to one (complete predominance of one donor) but it is undefined (0/0) when there is no donor chimerism. If appropriate, individual profiles, through time, of both the sum and the ratio will be presented graphically and summarised with median and quartile smoothers to elucidate any trends.

Estimates of the incidence of severe (grade III or IV) acute GVHD will be calculated using both the Kaplan-Meier (product-limit) method and the cumulative incidence function – the former treats death before the occurrence of severe acute GVHD as a censoring event while the latter treats it as a competing risk. Estimates from both methods will be presented in the form of cumulative incidence curves with associated point-wise 95% confidence intervals.

Occurrences of chronic GVHD will be tabulated and the occurrences of adverse events, in the first 100 days following transplant, will be cross-tabulated by worst grade and type of event.

The incidence of treatment related mortality by day 100 post-transplant will be calculated using the number of transplanted patients as the denominator and exact methods for the multinomial distribution will be used to calculate 95% confidence intervals for this incidence or rate. Transplanted patients will at 100 days be classified into one of three distinct groups: alive, treatment-related death, and death from other causes.

Both OS and DFS will be estimated using the Kaplan-Meier (product-limit) method and point-wise 95% confidence intervals will be calculated using Greenwood's formula and the logistic transformation.

11.4. Sample size and precision

The sample size for this trial is 20 patients and this has been chosen for pragmatic reasons. If no patients die or are lost-to-follow-up before "donor engraftment", the maximum standard error for the cumulative incidence (expressed as a percentage) of neutrophil engraftment is ± 11.2%. If the accrual rate is faster than the expected 20 patients in 2 years, consideration will be given to expanding the sample size to 30 or 40 patients. This decision will be made before the interim statistical analysis of the primary endpoint (see below) commences. With 30 or 40 patients, the maximum standard errors for the cumulative incidence of neutrophil engraftment are ± 9.1% and ± 7.9% respectively.

11.5. Trial duration

It is expected that the accrual of 20 patients will take approximately 2 years. If the accrual rate is faster than this, consideration will be given to expanding the sample size to 30 or 40 patients. Patients will be followed up for a minimum of 2 years so the anticipated duration of the trial is approximately 4 years. Final statistical analyses and publication of the final report will take place after each surviving patient has been followed up for a minimum of 2 years. Publication of interim statistical analyses of the primary endpoint (time to neutrophil engraftment), time to platelet engraftment and donor chimerism at days 28, 56 and 100 will be considered when all surviving patients have had their day 100 assessments.

11.6. Trial modification

Consideration will be given to expanding the sample size from 20 to 30 or 40 patients if it takes less than 2 years to accrue 20 patients. The decision to expand the sample size will be made before the commencement of the interim analysis of the primary endpoint.

Consideration will be given to stopping the study if there is evidence of failure of neutrophil engraftment by day 28. In this context, neutrophil engraftment is considered to have occurred on the earlier of the first day on which the absolute neutrophil count $\geq 1.0 \times 10^9$/L or the first occasion for which two consecutive readings of absolute neutrophil count $\geq 0.5 \times 10^9$/L. If neither of these thresholds is reached on, or before, day 28 post-transplant, failure of neutrophil engraftment will be deemed to have occurred. A failure rate of approximately 20% at day 28 is expected with single donor cord blood transplants and it is anticipated that the dual donor transplant failure rate will not exceed this. Thus consideration will be given to terminating the trial if there are 5 or more failures for neutrophil engraftment by day 28 in the first 10 patients registered on the trial. With this guideline, the probability that consideration will be given to early stopping is ≤ 0.05 when the true failure rate $< 22.3\%$ and ≥ 0.80 when the true failure rate $> 58.1\%$.

Consideration will also be given to early stopping or modification of the trial if new information becomes available on the unequivocal superiority of alternative treatment or if fewer than 5 patients are registered per annum.

12. DOCUMENTATION

Trial documentation must be kept in a secure location and be available for inspection as required. This includes

- ethics approval documents including approval letter, approved consent form, TGA notification, correspondence regarding any protocol amendments
- ALLG documentation including commitment statement (or subsequent document), financial statement (or subsequent document)
- trial specific documents including patient registration log, signature log, fax cover sheets (patient registration, SAE reporting)
- patient documentation, including CRFs and supporting documents (reports, imaging etc)

13. CRFs

CRFs will be designed by the ALLG Trial Centre and provided electronically to participating centres. Baseline CRFs should be completed and returned as soon as possible after patient registration. Other CRFs should be sent in progressively during protocol treatment and follow up.

14. DRUG SUPPLIES

Amgen Australia will provide NEUPOGEN® (filgrastim) for patients in this study for whom reimbursement is not available through the S100 scheme. All other medications will be purchased through the hospital pharmacy.

15. ETHICAL REGULATIONS

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)] and the Declaration of Helsinki (1996). The study may not start without written independent ethics committee approval and the written informed consent of the patient.

This study will require an investigator-sponsored notification under the Clinical Trial Notification scheme with the Therapeutic Goods Administration.

16. PUBLICATION

Any formal presentation and publication of results from this trial will be considered as a joint publication by the investigators and ALLG. Authorship will be determined by mutual agreement. Investigators participating in multicentre studies agree not to present data gathered from one centre or a small group of centres before the full publication, unless formally agreed to by all other investigators.

17. LITERATURE

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APPENDIX 1: Sample Patient Information and Consent

PLAIN LANGUAGE STATEMENT

A Study of Double Unit Umbilical Cord Blood Transplantation in Patients with Life Threatening Malignancy

WHAT IS THE PURPOSE OF THE STUDY

Adults with leukaemia, lymphoma, or myeloma that have not responded to standard chemotherapy or relapsed after initial treatment have a low chance of long term survival using available conventional therapy. Based on available data, we consider that allogeneic (using a donor other than the patient) stem cell transplantation (SCT) offers you a better chance of achieving a prolonged remission than would likely be obtained with the use of standard chemotherapy or other treatment strategies. It is for this reason that SCT is being offered to you as further treatment for your disease. As you do not have a suitably matched family donor and searching of marrow donor registries has not found a suitable matched unrelated donor, donor cells from two unrelated cord blood units are to be used.

Over one thousand transplants using umbilical cord blood (UCB) have been reported in the literature. UCB is increasingly being used as a source of stem cells for transplantation. Cord blood has a number of potential benefits over allogeneic bone marrow, including a reduction in the time required for searching, a reduced rate of graft versus host disease (GVHD), and a lower rate of transmission of herpes virus infections. GVHD is a major cause of complications following allogeneic SCT and is directly related to the degree of matching between the donor and recipient. As the incidence of GVHD is lower using cord blood there is a lower requirement for stringent matching which results in a greater chance of finding an appropriate match.

The major drawback in the use of cord blood for transplantation is the delay in the recovery of blood counts (engraftment). This delay is a direct result of the low cell counts in the cord blood units and results in an increased risk of infectious or haemorrhagic complications. Speed of engraftment is enhanced in patients who are transplanted with a cord unit that has a high nucleated cell count (NCC), being greater than 3.7×10^7 cells per kilogram body weight of the patient. At present only about 2% of all cord blood units stored in worldwide cord blood banks would be of sufficient size for a transplant in a 60 kg adult. If the cell dose is less than 2×10^7/kg, then current recommendations are not to proceed with a cord transplant as the risk of non-engraftment is high. In some cases, where an unrelated marrow donor is not found, cord blood transplant may be the only option available to the patient. In an attempt to increase the cell yield, and therefore potentially allowing more adult patients the opportunity to receive a SCT, combining two cord units may be of benefit.

WHAT WILL HAPPEN WHEN YOU ARE ENROLLED INTO THE STUDY?

If you consent to this treatment, you will be admitted as an inpatient to the Royal Adelaide Hospital based on bed availability. Next you will begin a series of steps which will prepare your body to accept the cord blood transplant, which will involve treatment with radiotherapy for 3-4 days. You will receive chemotherapy with a drug known as cyclophosphamide for 2 days. Chemotherapy used in the transplant may impair fertility or cause sterility. Consequently, all patients will be referred to a fertility specialist for consideration of treatment to preserve fertility. Your bone marrow transplant physician will discuss with you the methods used, and any implications that fertility preserving treatments may have for the timing of the transplant.

The day you receive your cord blood transplant is designated day 0. The appropriate cord blood units will have been identified and transported to Adelaide prior to your admission to hospital. On the day of the transplant, the cord blood is thawed and then given to you as an intravenous infusion.

Following transplantation, you will receive standard supportive care. Your course will be closely monitored for any transplant complications such as infections, graft versus host disease, graft failure, interstitial pneumonia or recurrence of disease.

ARE THERE ANY RISKS?

Chemotherapy and Radiotherapy:

Your doctor will explain in detail the chemotherapy drugs to be used in your case and any side-effects you may experience. The main side effect of the chemotherapy is bone marrow depression, which decreases the red and white blood cells and platelets and leads to increased risks of infection and bleeding. Until your transplanted cord blood begins to grow, you remain at high risk for developing serious bleeding and infections. The problems arising from decreased red blood cells and platelets can be corrected at least in part by the use of transfusions. Infections can be treated with antibiotics. If you received this dose of chemotherapy and radiotherapy and did not receive a transplant, your own marrow might not regrow sufficiently to produce enough blood cells to sustain life before a life-threatening complication occurs. Chemotherapy and radiotherapy in the doses given usually cause mucositis (inflammation of the lining of the mouth and intestinal tract). This usually leads to soreness of the mouth which can be severe and require strong pain killers to control. Less often mucositis of the intestines can cause diarrhoea and abdominal pains. Mucositis is usually most severe for the first 2 weeks after the transplant and usually settles down after that. Complete loss of hair occurs quite soon after the infusion although hair generally grows back 4 to 6 months after the transplant.

Cyclophosphamide:

Cyclophosphamide will cause lowering of the blood counts and temporary hair loss; it can also cause inflammation of the bladder, which is prevented by co-administration of a drug called MESNA.

A potential concern, particularly in patients receiving a cord blood transplant cells, is failure of the transplanted stem cells to grow or be rejected. For unrelated cord blood transplants, the risk of failure of engraftment is approximately 10%. If graft failure due to rejection, viral infection, or other aetiology occurs, we would attempt to provide you with a second, or booster, transplant. This second transplant would normally be from marrow or blood harvested and frozen from you before the transplant. If your graft fails in spite of these measures, the consequences would probably be lethal except in the unlikely event that your own marrow recovers despite the high dose of chemotherapy.

Graft-versus-host disease is a disease in which the cells of the transplanted cord blood react against your own body organs and tissue. There are both acute and chronic forms of this complication. Graft versus- host disease may never appear, may be mild and transient, or may lead to severe complications. Graft-versus-host disease can cause skin rash, diarrhoea, or inflammation and injury to the liver (hepatitis). It may be severe enough to cause death in up to 20 - 30% of patients receiving allogeneic transplants from unrelated donors. The risk of GVHD in unrelated cord blood transplant is less than 40%. The risk will vary depending on the degree of mismatching. Whether there is an added risk of GVHD by using two cord transplants is unknown. Cyclosporin and mycophenolate will be used to prevent or minimise GVHD. Your doctor will discuss with you treatment approaches for management of established graft-versus-host disease.
Cyclosporin can cause tremor, kidney and liver abnormalities, loss of appetite, nausea, vomiting, fluid retention, high blood pressure and a burning sensation in the hands and feet. It can also cause headaches, convulsions and skin rashes. These effects are usually reversible with dose reduction or cessation of the drug.
Mycophenolate can cause nausea, vomiting, abdominal discomfort, diarrhoea and a lowering of the white blood cell count.
ATG may cause adverse reactions after the first dose, which are usually reversible including fever, chills, rigors, nausea and rash.
Methylprednisolone may cause fluid retention, increased appetite, high blood pressure, high blood sugar levels and mood changes.

Chronic GVHD may also occur in some patients undergoing stem cell transplantation.

The leukaemia/lymphoma/myeloma may recur at a later date even if the transplant is successful. This risk is lower than your chance of relapse or death from disease without a transplant.

You may develop a second type of cancer that is different from your primary malignancy following chemotherapy for your transplant. This has occurred very rarely in transplant patients. It is difficult to quantify the actual risks or types of second malignancies which might potentially occur, because we do not yet have long term follow-up, e.g. >10-20 years, with patients who have been successfully transplanted.

There are risks from transfusions of all blood products. These risks may include fluid overload, serious allergic reactions, and infections such as viral hepatitis B or C, cytomegalovirus infection, and AIDS. All blood products which you receive will be screened against such transmissible diseases according to standard blood bank guidelines, in order to reduce the risks of viral transmission to as great a degree possible within the limits of currently available technology. You will receive cytomegalovirus negative
blood products at all times if you test negative for this virus pre-transplant, unless an emergency arises in which only cytomegalovirus positive blood products are available.

Full and complete restoration of immunological function may require as long as 1-2 years following successful cord blood engraftment. During this time there is an increased susceptibility to infection. You will be prescribed certain medications to reduce your risk of those infections for which such preventive treatment has been found to be effective. Preventive treatment is not always 100% effective, and development of these or other opportunistic infections may necessitate additional tests and treatment, some of which may even necessitate readmission to the hospital after your transplant. Some of these
infections can even lead to fatal outcomes, examples of which would include life-threatening pneumonia, liver disease, and/or loss of your transplanted marrow graft.

Overall, there is approximately a 20 - 30% risk of early mortality from all potential early complications, associated with allogeneic transplantation in this institution. As transplantation with 2 cord blood units is an experimental procedure we cannot predict the mortality risk but would not expect it to be lower because of the nature of allogeneic transplantation.

ARE THERE ANY ALTERNATIVES?
If you do not wish to participate in this treatment program, your doctors will discuss alternative therapies with you. These could include: chemotherapy alone, radiotherapy; autologous transplantation, or no further therapy.

METHOD OF RESEARCH
The data collected from this study will be used to evaluate the success of this approach by evaluating engraftment, toxicity, GVHD, rate of relapse and overall survival.

ETHICAL ISSUES

The use of cord for transplantation has already demonstrated that cord blood can successfully engraft and function. Dual cord blood transplant is being undertaken in a setting where there are no other options or the options.

PREGNANCY AND LACTATION

For patients in the reproductive age group, the ability to have children in the future will be reduced as the result of chemotherapy. However, it is also important for you to avoid having babies during and within 12 months from your last chemotherapy because of the risk of giving birth to babies with malformations. Breast-feeding is also not advisable because of the possible excretion of chemotherapy into the milk from the mother who is receiving chemotherapy.

PARTICIPATION IS VOLUNTARY
It is important that you understand that your participation in this study must be voluntary. This is the case with all research projects in the hospital. If you do not wish to take part, you are under no obligation to do so. At any time you have the right to ask questions and if you decide to take part, but later change your mind, you are free to withdraw from this project at any stage without compromising your medical care at this treatment centre in any way. You will be informed if any additional information is discovered which might affect your willingness to participate**.** In addition, your doctor may withdraw you from this study. Reasons for such withdrawal may include that it is felt that it is in your best interest, you have not been following procedures, or for administrative reasons.

CONFIDENTIALITY
All information obtained from your participation in this study is confidential. The results of this study may be published but your name or your identity will not be revealed without your permission. During required reviews, study monitors or representatives from regulatory authorities may have access to medical records which contain your identity. Direct access to your original medical records will be for verification of clinical procedures and/or data, without violating your confidentiality and will not be made publicly available. Signing of the consent form means you give such access. Your name will not be used on any study documents; instead a code, a number or your initials will identify you. Information may also be shared with relevant registries. However, no information by which you can be identified will be released or published.

Before deciding whether or not to take part, you may wish to discuss the matter with a relative or friend or your local doctor - you should feel free to do so. In addition, if you would like more

information about the study, or if there are any other matters which concern you, either now or in the future, do not hesitate to ask one of the doctors treating you. People that you can ask include Dr Lewis (telephone 8222 3328) and, after hours, the Duty Haematologist can be contacted through the Royal Adelaide Hospital switchboard on 8222 4000. If you wish to discuss aspects of the study with
someone not directly involved you may also contact the Chairman, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

....
(SIGNATURE) (WITNESS)
....
(DATE) (DATE)

Haematology and Bone Marrow Transplant Unit
Royal Adelaide Hospital
PATIENT CONSENT FORM

TITLE*: A Study of Double Unit Umbilical Cord Blood Transplantation in Adult Patients with Life Threatening Malignancy*

PRINCIPAL INVESTIGATOR: Dr Ian Lewis

I. I, the undersigned.....hereby consent to my involvement in the research project entitled - " A Study of Double Unit Umbilical Cord Blood Transplantation in Adult Patients with Life Threatening Malignancy".
II. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.
III. The detail of the procedure proposed has also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed, and an indication of any discomfort which may be expected.
IV. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.
V. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.
VI. I understand that I should not become pregnant during the course of this trial. In the event of a pregnancy occurring, I agree to notify the investigator as soon as is practically possible.
VII. I am informed that no information regarding any medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.
VIII. I understand that my involvement in the project will not affect my relationship with my medical advisers in their management of my health. I also understand that I am free to withdraw from the project at any stage.
IX. I understand that I will be given a signed copy of this patient information sheet and consent form. I am not giving up my legal rights by signing this consent form.

Signed:..... This day / /

Before me:..... This day / /

Approved by Human Ethics Committee, Royal Adelaide Hospital:

APPENDIX 2: Sample request letter

Ms Fatimah Scott, BMT Coordinator
Department of Health and Aging
Blood and Organ Donation Task Force.
MDP 2, GPO Box 9848
CANBERRA ACT 2601

(insert date)

Dear Ms Scott

Re: **Application for assistance under the Cord Blood Transplant Program**
Name:
Date of birth:
Address:
Medicare number:
Hospital number:
Consultant Haematologist:
Consultant contact numbers: Telephone Fax

(insert name) was diagnosed with *(insert diagnosis)* in *(when).* He/She has since undergone several treatment programs including *(eg PBSCT and achieved complete remission/ relapsed in such and such and after further treatment has achieved a 2nd remission/etc.)* The planned course of treatment now is for a bone marrow transplant, which is his/her only chance of achieving a cure.

An extensive search of *(person's)* family has failed to identify a compatible donor, as has a search of the Australian Bone Marrow Donor Registry as well as an extensive search of international registries. However, a search of international cord blood registries has identified a compatible cord blood unit.

We hereby apply for financial assistance under the Cord Blood Transplant Program to cover the cost of obtaining the donor unit from overseas.

I trust that this information is adequate for your assessment. If any further information is required please do not hesitate to contact me on (*insert phone number*).

Yours sincerely

APPENDIX 3: GVHD grading scale

Clinical classification of acute GVHD (Glucksberg)

Stage	Skin	Liver	Gastrointestinal
0	No rash	Bilirubin < 34 µmol/L	Diarrhoea < 500 ml/day
1	Maculopapular rash on <25% of body surface	Bilirubin 34-50 µmol/L	Diarrhoea 500-1000 ml/day
2	Maculopapular rash on 25-50 % of body surface	Bilirubin 51-102 µmol/L	Diarrhoea 1000-1500 ml/day
3	Generalised erythroderma	Bilirubin 103-255 µmol/L	Diarrhoea >1500 ml/day
4	Generalised erythroderma with formation of bullae and desquamation	Bilirubin >255 µmol/L	Severe abdominal pain with or without ileus

Grading of acute GVHD

Overall grade		Stage	
	Skin	**Liver**	**Gut**
I (mild)	1 or 2	0	0
II (moderate)	1-3	1	1
III (severe)	2 or 3	2 or 3	2 or 3
IV (life-threatening)	2-4	2-4	2-4

adapted from Glucksberg, H. et al, Transplantation 18:295 (1974)
modified according to Armitage, JO. N. Engl. J. Med. 330:827-838 (1994)

Clinical classification of chronic GVHD

Limited chronic GVHD	Extensive chronic GVHD
Either or both: 1 Localised skin involvement 2 Hepatic dysfunction due to chronic GVHD	Either: 1 Generalised skin involvement; or 2 Localised skin involvement and/or hepatic dysfunction due to chronic GVHD, plus: a) Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis; or b) Involvement of eye: Schirmer's test with less than 5 mm wetting; or c) Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy; or d) Involvement of any other target organ

adapted from Shulman, HM. et al, Am J Med 69:204 (1980)

APPENDIX 4: Common Terminology Criteria for Adverse Events

In the present study, toxicities will be recorded according to the **Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.**
At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html
Investigators who do not have access to Internet can contact the ALLG Trial Centre to receive a copy of this document.