Clinical trial results:
Transplantation of umbilical cord blood (UCB) from unrelated donors (URD) in patients with haematological diseases using a reduced intensity conditioning regimen.

Summary

EudraCT number	2004-003845-41
Trial protocol	GB
Global end of trial date	01 April 2020

Results information

Result version number	v1 (current)
This version publication date	17 November 2021
First version publication date	17 November 2021

Trial information

Trial identification

Sponsor protocol code	UCL/07/131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00959231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	CRUK and UCL Cancer Trials Centre, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	CRUK and UCL Cancer Trials Centre, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase II study for patients with haematological malignancies to validate the safety and efficacy of umbilical cord blood transplantation using a reduced intensity preparative regimen in patients with disorders of the blood using the approach developed by the University of Minnesota.

Protection of trial subjects:

Patients underwent screening evaluations to confirm eligibility for the trial, these included: medical history, full blood count, biochemistry tests (liver and renal function), bone marrow, infection screening, imaging, cardiac function assessment and assessement by a radiation oncologist. Patients were counselled about these potential side effects prior to starting treatment. They were monitored closely for toxicity and the protocol listed details on supportive medication, dose modifications etc. In case side effects did occur out of clinic hours, all trial subjects were given patient cards with contact details of the local haematology team that they could access at any time for advice. Due to the potential effect of the trial treatment on pregnancy, the trial subjects had consented to use barrier methods of contraception during treatment for a year afterwards. All patients were assessed for toxicity and monitored regularly for adverse events.

Background therapy:

All patients will receive prophylaxis for GVHD with 2 drugs both beginning at day -3. These included:
- Ciclosporin (CsA) therapy (schedule according to local policy) beginning on day -3 maintaining a trough level of 200-400 µg/L
- Mycophenolate mofetil (MMF) 1g three times daily (tds)

G-CSF (Lenograstim) 5 µg/kg (IV/SC)(prepared according to local policy) was also given daily from day +7 until ANC > 2.5x109/l for 2 consecutive days.

The following medications and support therapies are examples of supportive care that were permitted as outlined in the protocol:
- Transfusions for anaemia, thrombocytopenia
- Broad spectrum antibiotics and GCSF
- Parenteral nutrition
- Antibiotic, antifungal and antiviral prophylaxis
- Allopurinol to prevent tumour lysis syndrome

The protocol contained guidance for the Investigator on the above supportive medication and dose modifications.

Evidence for comparator:

Not applicable - no comparator used

Actual start date of recruitment	17 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 60 patients were recruited.2 patients withdrew consent & were not included in the analysis.The 1st patient was registered 17 Dec 2009 & the last patient was registered on 20 Feb 2014. Patients were registered from 16 UK centres. Using the censored deaths method, the median follow-up time was 47 months (95% CI: 37-50).

Pre-assignment

Screening details:

All inclusion criteria & none of the exclusions had to be met. Patients were ≤ 70 yrs,high risk, with advanced/poorly responding haematological disease with published evidence that RIC haematopoietic stem cell transplantation was likely to be effective,with no alternative therapy likely to achieve cure/significantly prolong disease-free survival.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Safety & Efficacy Population

Arm description:

60 patients were enrolled into the RIC UCBT trial. 2 patients withdrew from the trial and were not included in the analysis. Patients received a reduced intensity conditioning regimen comprising of fludarabine 40mg/m2/day day -6 to -2 (total 200mg/m2), cyclophosphamide 50mg/kg day -6 and total body irradiation 200cGy day -1. The umbilical cord blood units transplanted were selected on the basis of ≥4/6 HLA A, B DRB1 matched with the recipient. The cell dose and donor-recipient HLA disparity were used to determine an acceptable single or dual unit graft.

Arm type	Safety & Efficacy
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day -6: Cyclophosphamide 50 mg/kg IV over 2 hours. To be prepared according to the manufacturer’s recommendations and run as an infusion over 2 hours.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day -6 to Day -2: 40 mg/m2 IV over 1 hour. To be prepared and administered according to the manufacturer’s recommendations.

Number of subjects in period 1[1]	Safety & Efficacy Population
Started	58
Completed	58

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2 patients withdrew from the trial and were not included in the analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
These were the 58 evaluable patients out of the 60 patients recruited into the study as 2 patients withdrew consent from trial participation and were removed from all analyses.	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	58	58	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	48	48	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous			
The median age in years of the evaluable participants.			
Units: years			
median	52		
full range (min-max)	20 to 68	-	
Gender categorical			
The gender (male or female) of the evaluable participants.			
Units: Subjects			
Female	23	23	
Male	35	35	
Blood Group			
The blood group of evaluable participants			
Units: Subjects			
O Blood Group	24	24	
A Blood Group	25	25	
B Blood Group	6	6	
AB Blood Group	3	3	
Ethnicity			
The Ethnic group of evaluable participants			
Units: Subjects			
White	40	40	
Asian or Asian British	10	10	
Mixed Race	4	4	
Black or Black British	3	3	
Chinese	1	1	
Performance Status			

The performance status of evaluable participants			
Units: Subjects			
70%	2	2	
80%	5	5	
90%	27	27	
100%	24	24	
Primary Diagnosis			
The primary cancer diagnosis of the evaluable participants.			
Units: Subjects			
Acute Myeloid Leukaemia (AML)	27	27	
Acute Lymphoblastic Leukaemia (ALL)	7	7	
Non-Hodgkin (Follicular lymphoma, B-cell lymphoma)	7	7	
Myelodysplasia Syndrome (MDS)	7	7	
Other Leukaemias (CMML, T-PLL, NK cell)	3	3	
Hodgkin Lymphoma	3	3	
Acute Undifferentiated Leukaemia	1	1	
Chronic Myeloid Leukaemia (CML)	1	1	
Multiple Myeloma	1	1	
Primary myelofibrosis transformed to AML	1	1	
Disease Status at Registration			
The participant's disease status at the time of Registration			
Units: Subjects			
Complete Response (CR)	46	46	
Partial Response (PR)	8	8	
Progression/Relapse	2	2	
Accelerated phase	1	1	
Unknown	1	1	
Co-morbidity Index			
The co-morbidity index of participants at Registration			
Units: Subjects			
"0"	28	28	
"1"	12	12	
"2"	8	8	
"3+"	9	9	
Not Reported	1	1	
Lines of Prior Treatmnet			
The number of lines participats received prior to participating in the study			
Units: Subjects			
0 lines	1	1	
1 line	17	17	
2 lines	26	26	
3 + lines	14	14	

End points

End points reporting groups

Reporting group title	Safety & Efficacy Population

Reporting group description:

60 patients were enrolled into the RIC UCBT trial. 2 patients withdrew from the trial and were not included in the analysis. Patients received a reduced intensity conditioning regimen comprising of fludarabine 40mg/m2/day day -6 to -2 (total 200mg/m2), cyclophosphamide 50mg/kg day -6 and total body irradiation 200cGy day -1. The umbilical cord blood units transplanted were selected on the basis of ≥4/6 HLA A, B DRB1 matched with the recipient. The cell dose and donor-recipient HLA disparity were used to determine an acceptable single or dual unit graft.

Primary: Non-relapse mortality at day 100

End point title	Non-relapse mortality at day 100[1]

End point description:

Non-relapse mortality at 100 days post-transplant was defined as the time from infusion to death not due to relapse. Patients who relapsed were censored at the date of relapse and patients who did not relapse and did not die were censored at the date of last follow-up.
Statistical analysis method: Kaplan Meier method

End point type	Primary

End point timeframe:

From the day of transplant to Day 100 post transplant.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics - Rates calculated using Kaplan Meier method

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58[2]			
Units: percent				
number (confidence interval 95%)				
Non-relapse mortality at 100 day post transplant %	4 (1 to 13)			

Notes:

[2] - 58 evaluable patients

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was the time from infusion until a patient died from any cause. Patient who did not die were censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

From infusion until death from any cause.

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58[3]			
Units: percent				
number (confidence interval 95%)				
The overall survival (%) at 3 months	97 (87 to 99)			
The overall survival (%) at 1 year	70 (57 to 80)			
The overall survival (%) at 2 years	59 (45 to 71)			

Notes:

[3] - 58 evaluable patients

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival

End point title	Relapse-free survival

End point description:

Relapse-free survival was the time from infusion until a patient relapsed or died, whichever occured first. Patient who did not relapse and did not die were censored at the date of last follow-up. Rates calculated using Kaplan Meier method

End point type	Secondary

End point timeframe:

From infusion until a relapse or death, whiever occurs first.

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: percent				
number (confidence interval 95%)				
Relapse-free survival (%) at 3 months	90 (79 to 95)			
Relapse-free survival (%) at 1 year	60 (46 to 71)			
Relapse-free survival (%) at 2 year	52 (39 to 64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to relapse

End point title	Time to relapse

End point description:

Time to relapse was calculated as duration from unit 1 date of infusion to date of relapse. Patients who did not relapse were censored at the date of last follow-up or date of death. Descriptive statistics calculated using Kaplan Meier method.

End point type	Secondary

End point timeframe:

From infusion until relapse.

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Percentage				
number (confidence interval 95%)				
1 year relapse rate (%)	31 (21 to 45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chimerism kinetics over time

End point title	Chimerism kinetics over time

End point description:

Lineage-specific chimerism studies (PBMC, B-cells, T-cells & Granulocytes) were performed on 5-10ml EDTA peripheral blood sample on days 7, 14, 21, 28, 35, 60 and 100, at 6 months, 1 year and 2 years to determine the relative contribution of donor and recipient to overall haematopoiesis.
Primary engraftment was defined as neutrophil recovery associated with detectable donor chimerism within the first month after transplantation. Sustained donor engraftment was defined as ongoing neutrophil recovery and donor haematopoiesis beyond day 42. Complete donor chimerism was defined as marrow reconstitution of at least 90% donor origin.
Descriptive statistics only.

End point type	Secondary

End point timeframe:

day 7, 14, 21, 28, 35, 60 and 100, at 6 months, 1 year and 2 years post transplant.

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: patients				
Complete single unit dominance	39			
Sustained donor-donor mixed chimerism	3			
Sustained donor-recipient mixed chimerism	5			
Dominance reversion	1			

Primary graft failure	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Haematopoietic recovery

End point title	Haematopoietic recovery

End point description:

Haematopoietic recovery was defined as a) time to 1st of 3 consecutive days with ANC > 0.5 x 109/L after first post-transplant nadir b) time to platelets > 20 x 10^9/L (first of 3 consecutive days) with no platelet transfusions in the 7 preceding days and c) time to RBC independence (Hb > 9gms and no transfusions for 15 days).
Descriptive statistics only.

End point type	Secondary

End point timeframe:

See description

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: patients				
Neutrophil recovery by day 42	52			
Platelet recovery by day 100	49			
Red cell recovery by day 100	40			
Primary graft failure	5			
Secondary graft failure	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of acute and chronic GVHD

End point title	Incidence of acute and chronic GVHD

End point description:

Incidence of acute GVHD (Day 100) and chronic GVHD (1 year).
Patients were staged for acute GVHD daily up until engraftment and discharge and thereafter weekly until day 100 post-transplant. Patients were assigned an overall acute GVHD score based on extent of skin rash, volume of diarrhoea and maximum bilirubin level. Incidence of grades II-IV and grades III-IV GVHD by day 100 was monitored.
Patients were assessed for chronic GVHD on day 180 and at 1 year post-transplant.
Statistical analysis method: Kaplan Meier method

End point type	Secondary

End point timeframe:

Acute GVHD- from infusion unitl day 100 post transplant.
Chronic GVHD - from infusion until 1 year post transolant.

End point values	Safety & Efficacy Population			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: patients				
Number of patients with grade II-IV acute GVHD	19			
Number of patients with grade III-IV acute GVHD	14			
Number of patients with limited chronic GVHD	12			
Number of patients with extensive chronic GVHD	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of informed consent to 42 days post-transplant (or after this date if the site investigator felt the event was related to the trial treatment).

Adverse event reporting additional description:

All adverse events that occured between informed consent and 42 days post-transplant must have been recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) were also reported to UCL CTC using the trial specific SAE Report.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	ALL evaluable patients

Reporting group description:

60 patients were recruited into the study. 2 patients withdrew consent from trial participation and were removed from all analyses. All other patients (total of 58) were evaluable. All 58 patients received the conditioning regimen and GVHD prophylaxis according to protocol. 56 patients received a double CBU graft and 2 patients a single unit.

Serious adverse events	ALL evaluable patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 58 (25.86%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	3		
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial hemorrhage			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paresthesia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Blood urea increased			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			

subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal- other- had to stop ciclosporin			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection NOS			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection- upper respiratory tract			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ALL evaluable patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		

Hypotension			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	9		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	32 / 58 (55.17%)		
occurrences (all)	32		
Fever			
subjects affected / exposed	42 / 58 (72.41%)		
occurrences (all)	42		
Flu like symptoms			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Localized edema			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Non-cardiac chest pain			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	11		
Dyspnea			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		

Epistaxis subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Sore throat subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8		
Other investigations subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Creatinine increased subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5		
Weight loss subjects affected / exposed occurrences (all)	11 / 58 (18.97%) 11		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5		
Nervous system disorders Depression subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5		
Insomnia subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Dizziness subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8		

Headache			
subjects affected / exposed	16 / 58 (27.59%)		
occurrences (all)	16		
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	37 / 58 (63.79%)		
occurrences (all)	37		
Neutrophil count decreased			
subjects affected / exposed	43 / 58 (74.14%)		
occurrences (all)	43		
Platelet count decreased			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	12		
White blood cell decreased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Febrile Neutropenia			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Eye disorders			
Blurred vision			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Dry eye			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	8		

Diarrhea			
subjects affected / exposed	38 / 58 (65.52%)		
occurrences (all)	38		
Nausea			
subjects affected / exposed	37 / 58 (63.79%)		
occurrences (all)	37		
Vomiting			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	15		
Constipation			
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	13		
Dry mouth			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Mucositis (NS)			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Mucositis oral			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Rash (NS)			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	8		
Rash maculo-papular			
subjects affected / exposed	17 / 58 (29.31%)		
occurrences (all)	17		
Rash	Additional description: Cord Blood Infusion-associated complication		
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Alopecia			

subjects affected / exposed	14 / 58 (24.14%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Hematuria			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Other Renal and urinary disorders			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Chest wall pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Infections and infestations			
Lung Infection			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Other Infections and infestations			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Upper respiratory infection			

subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Bacterial Coagulase-negative staphylococcus	Additional description: Type of Infection reported		
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	13		
Bacterial Haemophilus influenzae	Additional description: Type of infection reported		
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Other bacterial infection	Additional description: Type of infection reported		
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	18		
Bacterial Other gram negative	Additional description: Type of infection reported		
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	13		
Bacterial Other gram positive	Additional description: Type of infection reported		
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	13		
Fungal Candida sp	Additional description: Type of infection reported		
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	8		
Other fungal infection	Additional description: Type of infection reported		
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Viral Adenovirus	Additional description: Type of infection reported		
subjects affected / exposed	14 / 58 (24.14%)		
occurrences (all)	14		
Viral CMV	Additional description: Type of infection reported		
subjects affected / exposed	22 / 58 (37.93%)		
occurrences (all)	22		
Viral EBV	Additional description: Type of infection reported		
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	9		
Viral Other respiratory virus	Additional description: Type of infection reported		
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		

Other viral infection	Additional description: Type of infection reported		
subjects affected / exposed	21 / 58 (36.21%)		
occurrences (all)	21		
Viral RSV	Additional description: Type of infection reported		
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Viral VZV	Additional description: Type of infection reported		
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Papulopustular rash			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	18		
Hypokalemia			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		
Hypomagnesemia			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2009	Protocol, PIS (11-15, 16+, parents), consent form CF and dispensing labels. Main changes: Protocol: Update pre-registration investigations, Addition of informed consent section, Change of blood samples required for study, Instruction to send adult blood sample samples to the Anthony Nolan Trust and paediatric samples to NHSBT, Insertion of ANT contact details, Expansion of data collection section to clarify central monitoring processes, Inclusion of an on-site monitoring section, Updated graft failure urgent event reporting procedure, Updated acute GVHD urgent event reporting procedure, Changes and clarifications of reporting mechanism for AEs and SAEs, Inclusion of information about expected AEs for IMPs in paediatric patients, Updated table of events which do not require reporting as SAEs, Addition of 'Death' to list of events requiring urgent reporting, Addition of Infection reporting instruction, Insertion of criteria for assessment of chronic GVHD, Insertion of cord blood selection mechanism. PIS: PIS 11-15yr version 2.0: Inclusion of the following sentences 'You may also need to have another bone marrow test 28 days after your transplant. Your doctor will discuss this with you.' PIS 16y+ version 3.1: Change of 'Lymphoma Trials Office' to 'Haematology Trials Group' & 'Cancer Trails Unit' to 'Cancer Trials Centre'. Inclusion of the following sentence 'You may also need another bone marrow test at 28 days after transplantation. Your consultant will discuss this with you.' PIS parents version 3.1:Change of 'Lymphoma Trials Office' to 'Haematology Trials Group',Inclusion of the following sentence 'Your child may also need another bone mamarrow test 28 days after transplantation.' CF: typographical error correction. Dispensing labels: removal of redundant/duplicated informtion,add storage info,assign space to record calculated total dose,expiry date & date of
04 December 2009	Patient information sheet: 11-15yr version 2.2 – nov09 Clarification of the number and timing of biopsy samples Patient information sheet: 16y+ version 3.3 – nov09 Clarification of the number and timing of biopsy samples Patient information sheet: parents version 3.3 – nov09 Clarification of the number and timing of biopsy samples

31 December 2009	Main changes Protocol: Section 6.2.1: Deletion of the sentence 'Double units must also be ≥4/6 matched to each other.' Section 8.4: Addition of the following sentence 'In patients in whom the infused dose of DMSO will not exceed 1g/kg UCB grafts should be thawed and infused immediately. However, where this is not possible, steps to maintain cell viability are permissible according to local practice.' Section 11: Addition of the sentence 'On-site monitoring and reporting will continue as described from recruitment until 2 years post-transplant, whereupon followup reporting should continue annually until death. If a patient fails to attend a clinic or cannot be followed up at site, efforts should be made to contact the patient's GP to assess their condition. Any patients 'lost to follow-up' and who subsequently die will be 'flagged' using the NHS Information Centre.' Appendix 4: deletion of the line 'Sites must contact the central radiotherapy co-investigator before exceeding a dose rate of 30cGy/minute.' Patient information sheet: 11-15yr version 2.2 – 27nov09: Amendment to allow unused material from samples collected for central analysis to be stored at the central laboratories for potential future analyses. Patient information sheet: 16y+ version 3.3 – 27nov09: Amendment to allow unused material from samples collected for central analysis to be stored at the central laboratories for potential future analyses. Patient information sheet: parents version 3.3 – 27nov09: Amendment to allow unused material from samples collected for central analysis to be stored at the central laboratories for potential future analyses.
28 May 2010	Main changes: Protocol Section 3: Deletion of the objective 'To assess immune reconstitution at 1, 2, 3, 6, 12 and 24 months after transplant as measured by quantitative recovery of B, T and NK cells (flow cytometry), qualitative recovery of T cells (TREC and spectratyping), in vivo functional T cell responses (EBV and CMV tetramers) and quantitative immunoglobulins.' Section 10.1: Removal of the central immune reconstitution analysis to be performed as part of the RIC UCBT trial. Insertion of the following sentence 'Sites are strongly advised to open (and register RIC UCBT patients onto) the Anthony Nolan Trust/NHSBT Immune REconstitution Study (IRES): a nationwide study to examine immune reconstitution in cord blood transplant patients.' Patient information sheet: 11-15yr version 3.0 – mar10: Amendment to remove the collection of samples to be sent for central analysis as there will no longer be central analysis of samples for immune reconstitution analysis as part of this trial. Patient information sheet: 16y+ version 4.0 – mar10: Amendment to remove the collection of samples to be sent for central analysis as there will no longer be central analysis of samples for immune reconstitution analysis as part of this trial. Patient information sheet: parents version 4.0 – mar10: Amendment to remove the collection of samples to be sent for central analysis as there will no longer be central analysis of samples for immune reconstitution analysis as part of this trial. A 'pregnant partner information sheet and informed consent form' to follow up the outcome of any pregnancies occuring in female-partners of male-participants was also added.

10 January 2011	Dispensing labels for cyclophosphamide and fludarabine: permission was requested to retract these labels as there was no requirement for their submission. IMP labels for cyclophosphamide and fludarabine: Paragraph 26 of Annex 13 of the "EU Guidelines to Good Manufacturing Practice" sets out the information that should be included on labels "... unless its absence can be justified". We proposed not to apply IMP labelling to fludaradine or cyclophosphamide for the following reason: Both fludaradine & cyclophosphamide were taken from general hospital stocks on a per patient basis, with a very short time elapsing between dispensing and reconstitution. This procedure was carried out only in pharmacies by qualified personnel. Adding an IMP label for a very short time does not seem to add anything to protect the subjects involved in the trial that is not already satisfied by the normal pharmacy accountability and labelling procedures. However, as further processing involved reconstitution of the fludaradine and cyclophosphamide in IV bags , we required sites to affix a dispensing label to the IV bag and they were provided with minimum wording for this label. This wording ensured protection of the patient, and traceability to enable identification of the product and trial and to facilitate proper use of the IMP.
16 December 2011	Main changes: Protocol Section 1: Study synopsis updated to reflect that the maximum age limit was increased to 70 years of age and deletion of requirement for units to match each other in double cord transplants. Section 6.1: Clarification that chest radiographs & radiotherapy planning CTs were optional, as per local practice. Section 6.3.2: Inclusion criteria section updated to reflect that the upper age limit was increased to 70 years of age in those patients that had a co-morbidity index of 0 - 1. Section 6.3.3: Additional statement that patients aged 60-70 years must had a co-morbidity index of 0-1. Section 6.4: Change of exclusion criteria from '5-6/6 HLA-A, B, DRB1' to 'a suitably matched' sibling donor. Section 6.4: Exclusion criteria updated to indicate that patient's aged 60-70 with a co-morbidity index of >1 were excluded. Section 9.3: Chimerism analysis section updated to clarify that whole PBMC samples should be analysed in addition to the B-cell, T-cell & granulocyte fractions. Section 22: References updated to include additional references for expected adverse events added to protocol appendix 6. Appendix 6: updated to show only AEs expectedness for the trial treatment rather than expectedness for the individual IMPs. Expectedness for individual IMPs was taken directly from SPCs at UCL CTC to ensure that data was always current.

18 September 2013	Main changes: Protocol: changes to bring it in line with the Sponsor's protocol template & to reflect changes to the trial monitoring plan following an update to the risk assessment for the trial in Dec2012. Reference Safety Information: appendix 6 which listed AEs expected for the treatment regimen was updated in response to discussions at the MHRA statutory GCP inspection of the UCL CTC in Jan2013. Previously, appendix 6 included AEs expected for combination conditioning chemotherapy (FluCy), radiotherapy (TBI) and infused cells as a whole. This gave rise to concerns regarding a potential for under-reporting of SUSARs if AEs that were expected for the cells but not the drugs were classified as expected in line with the protocol appendix. The RIC UCBT CI considered it was not possible to separate out the AEs expected for the 'TBI-chemotherapy conditioning regimen' into separate lists for TBI and chemotherapy. The published literature addressed toxicities associated with 'TBI-chemo conditioning' as a whole, and all conditioning was given within the 7 days prior to transplant, therefore making it extremely difficult to undertake seperate causal assessments for individual chemotherapy agents, or for the chemotherapy conditioning regimen separately to radiotherapy. However, the CI considered it appropriate to seperate AEs expected for transplanted cell infusions from the expected AE list. Therefore for RIC-UCBT these were listed separately in appendix 6 and in section 13 of the protocol, and the expected AEs for transplanted cells were identified as exempt from SAE reporting. Details of complications of the stem cell infusion were collected as Urgent Events, to ensure the safety of the cell source continued to be assessed and recorded in the trial. SAEs not included in tthe list of AEs as expected for 'TBI-chemotherapy conditioning' ontinued to be assessed. using SmPCs for the individual IMPs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Non-serious AEs: 'occurrences all number' cannot be provided as only highest grade experienced by patients was collected on CRF; Subjects affected number is entered instead Serious AEs & non-serious AEs are listed under non-serious adverse events

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34700343