Blood and Marrow Transplantation Program
Masonic Cancer Center
University of Minnesota

Haploidentical Donor T-cell Replete Allogeneic Hematopoietic Cell Transplant following Reducing Intensity Conditioning for Patients with Selected High Risk Non-Malignant Disease

MT2017-30
CPRC # 2017LS101

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Revision History

Revision #	Version Date	Detail of Changes	Consent change? (Y/N)
	09/26/2017	Original to CPRC	
	11/08/2017	Response to CRPC minor stipulations providing consistency in objectives throughout and clarifying conditioning chemotherapy dose modifications	NA
	11/20/2017	Section 3.5.2 edited for clarity. Removed Dr. Weston Miller from the Investigator list.	No
1	02/28/2018	Synopsis and section 1 – edited transplant objectives for consistency Section 6.2, 6.3, 6.4 and 6.5.3 updated standard of care medication orders (to current BMT standard practice Section 7.1 combined labs into “basic metabolic panel” Section 7.2 Added research lab: ATG levels Section 10.2.3 removed “autologous recovery by 100 days” from stopping rules and fixed typographical error Appendix 1, clarified ATG dosing chart is also for ALD patients	Yes
1A	03/30/2018	Edited endpoints for consistency per CPRC request	No
1B	04/16/2018	Layout of table 6.2 edited for clarity	No
1C	06/19/2018	Corrected dosing error in table 6.2	No
2	09/28/2018	Updated section 6.2.1.5 for females who elect ovarian transposition	Yes
3	03/15/2019	Eligibility: Expanded upper age eligibility to 55 years of age, in order to make treatment available to older adults with non-malignant diseases who may benefit from a reduced intensity PTCy approach; removed performance IQ from ALD diagnosis Section 6.1 and 10.2.3 – the back up stem cell harvest can be either marrow or PBSC	Yes

		Section 9.2 updated CPRC risk determination	
4	5/14/2019	Throughout document clarified that the Haploidentical stem cells may be from either a related or an unrelated donor.	No
5	01/15/2020	Section 4.2 Revised to allow for either PBSC or Bone Marrow as the stem cell source, per physician preference Updated Section 8.2, AE Reporting with IRB's new Ethos system Removed Appendix IX, eligibility checklist, per current CTO SOP. Eligibility checklists will be only kept in Oncore.	No

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Synopsis

Haploidentical Donor T-cell Replete Allogeneic Hematopoietic Cell Transplant following Reduced Intensity Conditioning for Patients with Selected High Risk Non-Malignant Disease
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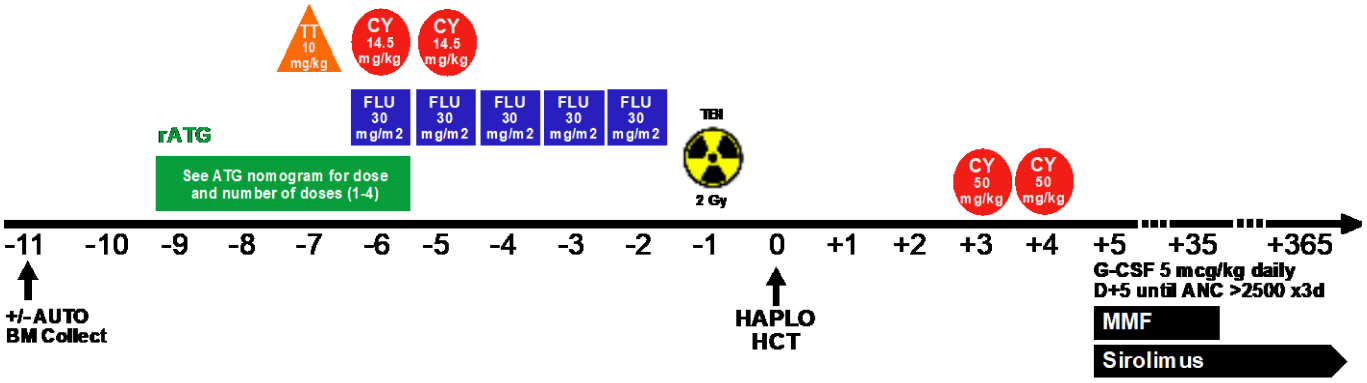
Design:	Open label, interventional, phase II trial
Objectives:	To establish safety as measured by sustained hematopoietic engraftment and efficacy as measured by 1 year overall survival
Key Inclusion Criteria:	• Diagnosis of sickle cell disease (SCD), thalassemia, other high risk hematologic disorder, cerebral adrenoleukodystrophy (cALD) or other inherited metabolic disorders • Meets the disease specific criteria (detailed in section 2) • 0 to 55 years of age • Available haploidentical related or unrelated donor
Treatment Plan:	Reduced intensity conditioning (RIC) with rabbit ATG, fludarabine, cyclophosphamide, thiotepa and low dose (2 Gy) total body irradiation followed by T-cell replete, unmanipulated, haploidentical related or unrelated donor stem cell transplant (HaploHCT) and post-transplant cyclophosphamide (PTCy)
Primary Endpoint:	• Incidence of neutrophil recovery by day +42
Secondary Endpoints:	• Probability of overall survival at 1 year • Incidence of primary graft failure (neutropenic and non-neutropenic) by day +42
Transplant Endpoints:	• Incidence of secondary graft failure (neutropenic and non-neutropenic) by day +180 • Incidence of acute graft-versus-host disease (GVHD) at 100 days • Incidence of chronic GVHD at 1 year • Incidence of transplant-related mortality at 100 days, 180 days, and 1 year following transplant
Exploratory Endpoints:	• Sorted lymphocyte chimerism at days 21, 42, 84, 100, 180, 1 and 2 years • Description of immunological recovery by assessment of lymphocyte subsets and immune globulin levels at days 21, 42, 84, 100, 180, 1 and 2 years • Impact of residual ATG on day -1 on neutrophil recovery, graft failure, and T cell chimerism.
Accrual Objective:	20 patients over 5 years.

Schema

HaploHCT for high risk non-malignant diseases



1.0 Hypothesis and Objectives

This is a Phase II study for the use of T-cell replete reduced intensity conditioning (RIC) haploidentical donor allogeneic hematopoietic cell transplantation (HaploHCT) for individuals with high-risk non-malignant diseases who lack a suitable HLA-matched sibling donor.

1.1 Hypothesis

1.1.1 Reduced intensity conditioned (RIC) HaploHCT will be safe and will provide acceptable rates of neutrophil engraftment in the setting of alternative-donor HCT.

1.2 Objective

1.2.1 To establish the safety as measured by sustained hematopoietic engraftment and efficacy as measured by 1 year overall survival of RIC followed by HaploHCT for patients with selected high-risk non-malignant disorders

1.3 Primary Endpoint

1.3.1 Incidence of neutrophil recovery at day +42

1.4 Secondary Endpoints

1.4.1 Incidence of overall survival at 1 year

1.4.2 Incidence of primary graft failure (neutropenic and non-neutropenic)

1.5 Transplant Endpoints

1.5.1 Incidence of secondary graft failure (neutropenic and non-neutropenic)

1.5.2 Incidence of acute graft-versus-host disease (GVHD) at 100 days

1.5.3 Incidence of chronic GVHD at 1 year

1.5.4 Incidence of transplant-related mortality at 100 days, 180 days, and 1 year following transplant.

1.6 Exploratory Endpoints

1.6.1 Degree of mixed T cell chimerism
1.6.2 Description of immunological recovery
1.6.3 Impact of day -1 residual serum ATG on neutrophil recovery, graft failure, and T cell chimerism

2.0 Background and Rationale

2.1 HaploHCT:

Haploidentical donor allogeneic hematopoietic cell transplantation (HaploHCT) provides unique benefits over other alternative donor (AD) stem cell sources, including allowance for less stringent HLA-match, rapid availability of stem cells, and option for future boost of cells if needed. Previously prohibitive rates of acute graft-versus-host disease (GVHD) with haploidentical matched donors have in recent years been overcome by the introduction of post-transplant cyclophosphamide (PTCy) on days +3 and +4 following HaploHCT. PTCy selectively eliminates alloreactive over homeostatically proliferating donor T cells, effectively reducing acute GVHD rates to that of matched unrelated donor HCT and allowing for adequate donor T cell preservation for engraftment and peripheral expansion for early protection against virus reactivation or infection[1-3]. Given recent improvements in outcomes for HaploHCT with PTCy, this HCT approach has been made available to more populations of patients[4].

High-risk non-malignant diseases (NMD) often lack unaffected HLA-matched sibling donors (MSD) and must rely upon AD options for HCT. For many such disorders, we have yet to determine the best combination of conditioning and stem cell source to achieve reliable rates of engraftment, disease-free and overall survival. Identification of an appropriate stem cell donor is a barrier for many patients. For example, for sickle cell disease (SCD), 76% lack a MSD[5]. A recent publication[6] reported probabilities of 20% for identifying an 8/8 HLA-matched unrelated donor (MUD), 84% for 7/8-HLA matched MUD, and 90% for a 5-6/6 HLA-matched UCB unit. In other NMD population, such as high risk cerebral adrenoleukodystrophy (cALD), expediency is critical to interrupt the destructive disease process. The time needed to identify and collect stem cells from an unrelated bone marrow or peripheral blood stem cell donor is prohibitive. HaploHCT provides a rapidly available donor option for the majority of patients lacking a MSD.

We seek to provide a reduced toxicity conditioning HaploHCT treatment option for these NMD patients lacking a MSD and often lacking a quickly available appropriate AD stem cell source.

2.1.1. HaploHCT in NMD

While the majority of experience with HaploHCT using PTCy is in treatment of leukemia, a body of literature can be compiled describing outcomes of this HCT strategy in NMD such as hemoglobinopathies, primary immunodeficiencies, and severe aplastic anemia. As reviewed in Table 1, conditioning regimens have been variable but largely reduced intensity or reduced toxicity with intensive patient immunosuppression to minimize graft failure (GF). GVHD prophylaxis typically includes a calcineurin inhibitor or mTOR inhibitor and mycophenylate mofetil (MMF) in addition to PTCy.

High-risk hemoglobinopathies are the most reported on NMD group to undergo HaploHCT with PTCy. From Johns Hopkins University, Bolanos-Meade et al.[7] reported results in 14 adult patients with sickle cell disease (SCD) receiving unmanipulated bone marrow (BM) from haploidentical donors following conditioning with fludarabine (Flu) 30 mg/m2/d x 5 days, cyclophosphamide (Cy) 14.5 mg/kg/d x 2 days, anti-thymocyte globulin (ATG) 0.5 mg/kg x1 day and 2 mg/kg x 2 days, and a single fraction of low dose 2 Gy total body irradiation (TBI). GVHD prophylaxis included PTCy 50 mg/kg/d on days +3 and +4, MMF starting on day +4 and tacrolimus or sirolimus starting on day +5. Median neutrophil and platelet engraftment were both day +24. All patients had count recovery (no aplasia), though rates of graft failure were high at 43%, with one patient with no detectible donor DNA and 5 with complete loss of donor chimerism over time, for a total of 6 episodes of GF in the 14 haploidentical donor transplant recipients. However, all 17 patients were alive at a median follow-up of 711 days (range 244-1981) with 11 ultimately attaining disease-free survival (DFS).

Over the course of enrollment, several alterations were made to the study, including addition of ATG after the initial 2 patients to improve engraftment, replacement of tacrolimus with sirolimus after the initial 10 patients to decrease the incidence of posterior reversible encephalopathy syndrome (PRES), and granulocyte-colony stimulating factor (GCSF) priming of bone marrow from the donors for the final 3 patients to improve engraftment. PRES occurred in 30% of patients receiving tacrolimus and 0 of 7 patients treated with sirolimus. GCSF mobilization increased the cell dose at

transplant from a median of 4.35 x 10^8 TNC/kg recipient weight, 5.24 x 10^6 CD34+ cells/kg recipient weight, and 3.61 x 10^7 CD3+ cells/kg recipient weight without GCSF to 1.14 x 10^9 TNC/kg recipient weight, 6.02 x 10^6

Table 1. HaploHCT with PTCy for NMD

Reference *Institution*	Patients	Conditioning	GVHD prophy	1 yr OS (%)	1 yr DFS (%)	1° GF rate (%)	Gr 2+ aGVHD (%)	cGVHD (%)	Comments
Sickle cell disease									
Bolanos- Meade J, et al., 2012[7] *Johns Hopkins, US*	14	Flu 150 mg/m^2 Cy 29 mg/kg rATG 4.5 mg/kg TBI 200 cGy	PTCy Siro MMF	100	57	43	0	0	Changes during trial: To decrease PRES: Changed tacro to siro Added GCSF to prime BM To decrease GF: Added ATG
De La Fuente J, et al., 2015[8] *Great Ormond, UK*	16	Flu 150 mg/m^2 Cy 29 mg/kg rATG 4.5 mg/kg TT 10 mg/kg TBI 200 cGy	PTCy Siro MMF	94	94	0	13	6	1 death (MAS→2ry GF→2nd HCT→VOD)
Dhedin N, et al., 2016[9] *Paris, France, London, UK, Vanderbillt, TN, US*	5 7 22	Flu 150 mg/m^2 Cy 29 mg/kg rATG 4.5 mg/kg TBI 200 cGy Above + TT 10 mg/kg Above + Pre-HCT IST: 3 mon Aza 3 mg/kg/d + HU 30 mg/kg/d TT 10 mg/kg	PTCy Siro MMF	 100 86.4	 100 81.8	20 0 0	 29	 0	+50% 2ry GF →triggered stopping rule +9% 2ry GF Acute + chronic GVHD 18.2%
Wiebking, et al., 2017[10] *Munich, Germany*	3	CAMPATH 0.4 mg/kg Flu 150 mg/m^2 Treo 42 g/m^2 TT 10 mg/kg Cy 29 mg/kg	PTCy Tacro MMF	100	100	0	0	0	
Thalassemia									
Anurathapan U, et al., 2016[11] *Thailand*	31	Pre-HCT IST: Two 5d cycles of Flu 40 mg/m^2/d + Dexa 25 mg/m^2/d + HU Flu 210 mg/m^2 Bu 650 mg/m^2 (no target AUC) rATG 4.5 mg/kg	PTCy Tacro or Siro	95	94	6	29	16	VOD 16%
DOCK8 deficiency									
Shah N, et al., 2017[12] *NIH, US*	7	Flu 150 mg/m^2 Bu (cumulative AUC 11,600) Cy 29 mg/kg TBI 200 cGy	PTCy Tacro MMF	86	86	0	57 (all gr, max gr3 in 1)	0	1 death (d+165 worsening of pre-existing pulmonary fibrosis, possible COP)
Severe aplastic anemia									
Clay J, et al., 2014[13] *King's College,UK*	4 SAA 4 primary GF following 1st HCT	Flu 150 mg/m^2 Cy 29 mg/kg TBI 200 cGy	PTCy Tacro MMF	75	75	25	13	0	2 patients with DSA developed 1° GF and died of sepsis
Esteves I, et al., 2015[14] *Brazil*	16 SAA	Flu 150 mg/m^2 Cy 28 mg/kg TBI 200-600 cGy	PTCy Tacro or CSA MMF	67	67	0	13 (2/15 alive at d+30)	23 (3/13 alive at d+100)	5 deaths from infection, 1 before engraftment 2ry GF in 2
Jaiswal SR, et al., 2015[15] *New Delhi, India*	10 SAA	Flu 150 mg/m^2 Cy 30 mg/kg Mel 120 mg/m^2 hATG 45 mg/kg	PTCy CSA +/- siro MMF	60	60	0	13	13	4 deaths: ARDS (2), HLH (1), aGVHD (1)
DeZern, et al., 2017[16] *Johns Hopkins, US*	13 SAA	Flu 150 mg/m^2 Cy 29 mg/kg rATG 4.5 mg/kg TBI 200 cGy	PTCy Tacro MMF	100	100	0	15	8	9 / 13 with evidence of clonality pre-HCT, 0/13 post-HCT 15% with delayed engraftment (later than d+42) No 2ry GF
Wiskott-Aldrich syndrome									

Kreetapirom P, et al., 2017[17] ***Thailand***	1	Flu 210 mg/m^2 Bu 320 mg/m^2 (no target AUC) rATG 4.5 mg/kg	PTCy CSA MMF	Yes	Yes	No	Gr 1	0	CMV reactivation, bronchiolitis obliterans
Mixed NMD									
Klein OR, et al., 2016[18] ***Johns Hopkins, US***	IPEX (1) XIAP (1) CGD (1) GT (1)	CAMPATH, Flu, Cy, Mel, TBI CAMPATH, Flu, Mel, TBI CAMPATH, Flu, Mel, TBI CAMPATH, Flu, TBI	PTCy Tacro MMF	100	100	0	0	0	XIAP patient developed VOD IPEX patient developed late 2ry GF (>2 years post-HCT), required a 2nd haploHCT

Prophy, prophylaxis; yr, year; OS, overall survival; PFS, progression free survival; GF, graft failure; Gr, grade; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; Flu, fludarabine; Cy, cyclophosphamide; rATG, rabbit anti-thymocyte globulin; TBI, total body irradiation; PTCy, post-transplant cyclophosphamide; siro, sirolimus; MMF, mycophenylate mofetil; tacro, tacrolimus; PRES, posterior reversible encephalopathy syndrome; GCSF, granulocyte-colony stimulating factor; BM, bone marrow; TT, thiotepa; MAS, macrophage activation syndrome; HCT, hematopoietic cell transplantation; VOD, veno-occlusive disease; treo, treosulfan; IST, immunosuppressive therapy; dexa, dexamethasone; HU, hydroxyurea; Bu, Busulfan; AUC, area under the curve; COP, cryptogenic organizing pneumonia; SAA, severe aplastic anemia; DSA, donor specific antibodies; CSA, cyclosporine; hATG, horse anti-thymocyte globulin; ARDS, acute respiratory distress syndrome; HLH, hemophagocytic lymphohistiocytosis; IPEX, immune dysregulation, polyendocrinopathy, X-linked syndrome; XIAP, X-linked inhibitor of apoptosis; CGD, chronic granulomatous disease; GT, Glanzmann's thrombasthenia; Mel, melphalan; haploHCT, haploidentical donor hematopoietic cell transplantation

CD34+ cells/kg recipient weight, and 1.09 x 10^8 CD3+ cells/kg recipients weight with GCSF. No haploidentical BM recipients developed acute or chronic GVHD. Three infections were noted including 1 CMV reactivation (no disease development), one case of EBV viremia (responded to a single dose of rituximab), and one patients with RSV upper respiratory tract infection as well as tuberculosis identified from a bronchoscopy specimen (patients recovered). In summary, the first report of 14 SCD patients undergoing HaploHCT with PTCy revealed this approach to be feasible with excellent survival and GVHD risk, low rates of infectious complications, but high rates of graft failure.

De La Fuente et al.[8] described promising preliminary data on 16 pediatric recipients (13 SCD, 3 Thalassemia) of HaploHCT. Transplant conditioning included those agents above in the Johns Hopkins protocol (Flu 150 mg/m2, Cy 29 mg/kg, TBI 2 Gy, and ATG 4.5 mg/kg), but differed by the addition of thiotepa (TT) 10 mg/kg. Patients received GCSF primed BM. GVHD prophylaxis was unchanged, including PTCy 50 mg/kg on days +3 and 4, MMF, and sirolimus. All engrafted, though one patient developed secondary graft failure attributed to macrophage activation syndrome, underwent an autologous HCT for rescue, developing veno-occlusive disease (VOD) after the 2nd conditioning regimen and ultimately died. Neutrophil engraftment was achieved at a median of 17 days, platelet engraftment at 32 days. Acute GVHD (grade >/= 2) was observed in 2 patients (1 skin, 1 gut) and chronic GVHD in 1 patient. Median time to sirolimus discontinuation was 124 days as patients demonstrated excellent donor chimerism (un-separated donor peripheral blood chimerism of >/=95% in 93.3% and CD3+ donor chimerism >/= 95% in 73.3% of patients at day +28).

An alternative approach to improve upon the Johns Hopkins / Bolanos-Meade[7] outcomes included enhanced pre-conditioning immunosuppression as described by Anurathapan, et al[11]. Thirty-one severe thalassemia patients (median age of 10 years) received 2 courses of pre-transplant immunosuppression consisting of Flu 40 mg/m^2/day and dexamethasone 25 mg/m^2/day x 5 days (cycles started at day-68 and day -40 pre-transplant). The conditioning phase of therapy included Flu 210 mg/m2, busulfan (Bu) 130 mg/m2, and ATG 3.5 mg/kg. Patients received GCSF mobilized peripheral blood stem cell grafts. GVHD prophylaxis included PTCy 50 mg/kg on days +3 and 4, 60 days of MMF and 6-12 months of either tacrolimus or sirolimus. No complications were identified during the pre-transplant immune suppression. Primary graft failure was low at 6% with median neutrophil recovery on day +14. One-year overall survival was 95% with disease-free survival of 94%.

Dhedin et al.[9] recently expanded upon De la Fuente[8]. In a systematic approach to HaploHCT, Dhedin et al. transplanted the first 5 SCD patients using the Johns Hopkins approach, however with 3 of 5 patients demonstrating graft failure, they transitioned to a 2nd strategy, where thiotepa 10 mg/kg was added to the conditioning regimen (the De la Fuente approach). Of 7 patients treated with Flu, Cy, ATG, TT, and TBI 2 Gy, all engrafted (median time to neutrophil recovery 25 days), 2 had viral reactivation, 2 had >grade 2 acute GVHD, but no chronic GVHD. Subsequently, similar to the Anurathapan approach, pre-transplant immunosuppression was intensified by the addition of 3 months of azathioprine, hydroxyurea, and hypertransfusion pre-transplant. All 22 patients transplanted by this final strategy engrafted (median time to neutrophil recovery of 17 days) though two (9%) had secondary graft failure and three died of infectious complications/MAS. GVHD rates were low (cumulative incidence of acute and chronic GVHD of 18.2%). Overall survival in this latter group declined to 86.4% and event-free survival 81.8%.

Combined, the above experience in HaploHCT for hemogobinopathies outlines the need for higher intensity conditioning than the Johns Hopkins approach to achieve reliable donor engraftment in NMD patient population who have not previously been exposed to myelo- or immunosuppressive therapies (as compared to patients with malignancies) but highlights the potentially lethal infectious risks of excess immune suppression.

2.1.2 MSD-HCT and non-Haplo AD-HCT for NMD

2.1.2.1 Outcomes in the literature

For most diseases amenable to treatment with HCT, including NMD, an unaffected MSD is the standard against which AD-HCT is compared. Using the example of SCD, modern outcomes on large cohorts MSD-HCT following MAC show overall survival ranging from 91-100%, event-free survival from 82-91%, and graft failure at or less than 8%[19-24]. Earlier trials informed need for strong immunoablation (patients heavily transfused and alloimmunized placing them at high risk of graft failure) and targeted supportive care (against neurologic complications) to achieve such remarkable results. There is very little published data on the use of AD-HCT (unrelated donor, URD or umbilical cord blood, UCB) in SCD or other high-risk hemoglobinopathies. Using MAC, MUD BMT for 27 adult thalassemia patients in Italy yielded an overall survival (OS) of 79% with graft failure rate of 13%[25]. However, the chance of finding a MUD in the registry depends on the patient's ethnicity and is as low as 19% in African Americans and 27% in Southeast Asians[26].

Another important finding of early trials of MSD-HCT for SCD was resolution of symptoms with stable mixed donor chimerism[27, 28]. This suggested that less intensive RIC regimens may be adequate for cure of this devastating disorder[29]. Unfortunately, there have not been consistent positive results from RIC in hemoglobinopathies, regardless of donor source. Jacobsohn et al.[30] reported in 2004 on 13 patients with NMD undergoing RIC with a regimen of Flu, Bu, and ATG. Of these 13, 3 were transplanted for SCD (2 MSD, 1 MUD) and 1 for thalassemia (MUD). Of these 4 patients, 2 died (one of chronic GVHD, one of infection) and 2 lived, though with graft failure and persistent SCD. Similarly, Horan et al. 2005[31] reported on 4 patients (3 SCD, 1 thalassemia) receiving conditioning with fludarabine, ATG, and low dose total body irradiation. Unfortunately, 3 of 4 had graft failure with withdrawal of immunosuppression, with one dying following a 2nd alloHCT and one experiencing a subsequent stroke. Only one promising report of RIC [Flu, Bu, ATG, total lymphocyte irradiation (TLI)] in hemoglobinopathies was published by Krishnamurti, et al. 2008,[32] showing 100% OS of 7 patients with stable donor engraftment and DFS in 6 of 7. Two national trials for RIC URD HCT in patients with severe SCD are underway: the SCURT trial (NCT00745420) and the STRIDE trial (NCT01565616). The probability of finding an adequately matched UCB unit for HCT is better than finding an HLA-matched URD, but the rates of graft failure are higher with this source.

In fact, the SCURT trial closed enrollment on the UCBT arm due to the high incidence of GF (5/8 patients)[33].

2.1.2.2 Outcomes at the University of Minnesota

Our experience at the University of Minnesota mirrors the findings in the literature, with excellent outcomes for MAC + MSD but need for improvement for RIC + AD regimens. We conducted 5 consecutive trials from 1996 to 2015, including 36 pediatric and young adult patients undergoing HCT for high risk red blood cell disorders including SCD, thalassemia, and Diamond-Blackfan Anemia) These trials included two different MAC regimens (n=11, Bu, Cy, ATG and Flu, Bu) and two different RIC regimens (n=25), Flu, Cy, CAMPATH,TBI and Flu, Bu, ATG, TLI). In general, MAC was used for patients with MSD and RIC for those with AD. While 1 year DFS following 1st HCT was respectable for MSD receiving MAC including busulfan, cyclophosphamide, and ATG at 88%, DFS for AD-HCT with RIC was disappointing at 56%.

2.2 Proposed approach

The objectives of our study are to use haploidentical donors to expand stem cell graft options for high-risk non-malignant diseases such as RBC disorder patients with often limited or no donor options and provide an expeditious pathway to alloHCT and for cALD patients requiring urgent intervention to halt the disease process. Excellent outcomes with MSD regimens preclude enrollment in this HaploHCT trial for those patients with a suitable MSD. Further, with the Johns Hopkins HaploHCT conditioning regimen (fludarabine 150 mg/m^2, cyclophosphamide 29 mg/kg, and TBI 2 Gy) as a baseline, we plan to reduce rates of GF by intensifying conditioning with the addition of thiotepa, maintain recipient lymphodepletion with serotherapy (rabbit ATG with precision dosing based on weight and absolute lymphocyte count[34]), and infuse unmanipulated haploidentical donor stem cells followed by PTCy 50 mg/kg on days +3 and +4 for GVHD prophylaxis along with a combination of MMF and sirolimus.

Supportive care will be specific to the patient's diagnosis. For high risk RBC disorder patients, we will use hydroxyurea and hypertranfusion to maintain a hgb >10 for the month prior to admission for alloHCT to reduce recipient bone marrow activity/inflammation. Immediately prior to admission, a simple or exchange transfusion may be indicated for sickle cell disease patients to achieve a HgbS <30%. Once conditioning starts, we will maintain hgb >9 g/dL, platelets >50,000/mm^3, Magnesium >1.5 mEq/L, provide anti-seizure

prophylaxis with keppra while on immunosuppression, and tight blood pressure control to avoid neurologic complications such as PRES or cerebrovascular accident.

For cALD patients, supportive care will include use of anti-oxidant / anti-inflammatory medications from day -10 (prior to initiation of conditioning) until day +100 (N-acetylcysteine, celecoxib, Vitamin E, and alpha lipoic acid). In addition, through conditioning and until sirolimus is discontinued, cALD patients will be maintained on Keppra for seizure prophylaxis. Concurrent treatment for pre-existing or suspected adrenal insufficiency will be provided, including maintenance hydrocortisone dosing and stress-dosing when indicated.

2.3 Study Outcomes

The primary objective of this study is to demonstrate safety as measured by timely neutrophil engraftment (by day +42) and secondary objective to demonstrate efficacy as measured by 1 year overall survival for RIC HaploHCT with PTCy for selected high risk non-malignant diseases.

3.0 Patient Selection

3.1 Eligible Diseases

3.1.1 Sickle Cell Disease (SCD)

- If diagnosis of SCD must meet one or more of the following disease characteristics:
    - Stroke, CNS hemorrhage or a neurologic event lasting longer than 24 hours, or abnormal cerebral MRI or cerebral arteriogram or MRI angiographic study and impaired neuropsychological testing
    - Acute chest syndrome with a history of recurrent hospitalizations or exchange transfusions
    - Recurrent vaso-occlusive pain 3 or more episodes per year for 3 years or more years or recurrent priapism,
    - Impaired neuropsychological function and abnormal cerebral MRI scan
    - Stage I or II sickle lung disease,

- Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate [GFR] 30-50% of the predicted normal value)
- Bilateral proliferative retinopathy and major visual impairment in at least one eye
- Osteonecrosis of multiple joints with documented destructive changes
- Requirement for chronic transfusions
- RBC alloimmunization

3.1.2 Transfusion Dependent Alpha- or Beta-Thalassemia

3.1.3 Other Non-Malignant Hematologic Disorders

Transfusion dependent or involve other potential life-threatening cytopenias, including but not limited to Paroxysmal Nocturnal Hemoglobinuria, Glanzmann's Thrombasthenia, Severe Congenital Neutropenia and Shwachman-Diamond Syndrome

3.1.4 cALD

- Diagnosis of ALD by abnormal plasma very long chain fatty acid (VLCFA) profile or *ABCD1* gene mutation
- Cerebral disease on MRI
- Absence of a Major Functional Disability (cortical blindness, loss of communication, wheelchair dependence) on the ALD Neurologic Function Scale

3.1.5 Other inherited metabolic disorders

Any other inherited metabolic disorder for which alloHCT is indicated and for whom, in the opinion of the treating physician, the patient's best treatment option is with a haploidentical donor following non-myeloablatve conditioning.

3.2 Age, Performance Status, Consent

Age: 0-55 years

Performance Status: Karnofsky ≥ 70%, Lansky play score ≥ 70

Consent: voluntary written consent (adult or parental/guardian)

3.3 Adequate Organ Function

Renal: Creatinine <2.0 mg/dl for adults or glomerular filtration rate > 50 ml/min for children

Hepatic: Bilirubin and ALT <3 times the upper limit of institutional normal

Cardiac: Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 40%.

3.4 Exclusion Criteria

- Availability of a suitable HLA-matched related donor
- Uncontrolled infection
- Pregnant or breastfeeding
- HIV positive

3.5 Donor Selection

3.5.1 Donors regardless of match and selection criteria must:

- Not be affected by the same disease making the patient eligible for alloHCT. Disease carriers may be permitted depending on the clinical situation.
- Meet donor criteria as outlined in University of Minnesota protocol MT2012-14C: Procedure Guidelines for Related Hematopoietic Stem Cell Donors; or NMDP requirements for unrelated donors.

3.5.2 Match-specific Criteria:

HLA mismatched or haploidentical related or unrelated donors: The donor and recipient must be haploidentical at a minimum of one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1.

Donor-specific anti-HLA antibody testing requirement: Testing for antibodies targeting donor specific HLA antigens at HLA-A, B, C, DRB1, DQ and DP will be completed as per institutional standards.

When more than one donor is available, the donor with the lowest number of HLA allele mismatches will be chosen, unless there is an HLA cross-match incompatibility or a medical reason to select otherwise, in which case donor selection is the responsibility of the PI. In cases where there is more than one donor with the least degree of mismatch, donors will be selected based on the most favorable combination of the factors below.

Donor selection criteria in decreasing order of priority:

1. Absence of donor-specific HLA antibodies is preferred [negative flow cytometric cross-match assay or the mean fluorescence intensity (MFI) of any anti-donor HLA antibody by solid phase immunoassay <1000]. If donor-specific anti-HLA antibodies cannot be avoided, the risks will be discussed with the patient and consenting parent/guardian and options including debulking or deferring transplant will be considered.
2. The lowest number of mismatches in the host-versus-graft direction is prioritized to minimize graft rejection.
3. If more than one donor with the same degree of HLA match, absent or equivalent donor-specific anti-HLA antibodies, and equivalent host-versus-graft allele mismatches, the following prioritization will be used:
   a. Homozygous normal donor is preferable to heterozygote (carrier)
   b. ABO-compatible donor is preferable to ABO-incompatible donor
   c. CMV status
      1) For a CMV seronegative patient, prefer a CMV seronegative donor
      2) For a CMV seropositive patient, prefer a CMV seropositive donor
   d. Younger donor is preferable to older, avoiding those >55 years of age if possible
   e. Male donor preferred over nulliparous female donor over multiparous female donor

4.0 Donor Stem Cell Mobilization and Acquisition

Per physician preference, either peripheral blood stem cells or bone marrow may be utilized as a stem cell source.

4.1 Bone Marrow

Haploidentical related donor BM will be collected according to current institutional guidelines (University of Minnesota protocol MT2012-14C: Procedure Guidelines for Related Hematopoietic Stem Cell Donors). Unrelated donors will be collected per NMDP SOPs.

A minimum of 2 x 10^8 total nucleated cells/kg recipient weight will be collected with a goal of 8-16 x 10^8 total nucleated cells/kg recipient weight.

Bone marrow will be red cell depleted in cases of ABO incompatibility.

4.2 Peripheral Blood

PBSC will be collected and processed per institutional guidelines (University of Minnesota protocol MT2012-14C: Procedure Guidelines for Related Hematopoietic Stem Cell Donors). Unrelated donors will be collected per NMDP SOPs.

A minimum of 4 x 10^6 CD34+/kg unprocessed cells will be collected with a goal of 7-10 x 10^6 CD34+/kg unprocessed cells.

5.0 Registration in OnCore

Registration will occur after the patient/parent/guardian has signed the subject consent and eligibility is confirmed. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is under attachments within the study in OnCore.

6.0 Treatment Plan

Dose and/or schedule modifications based on weight (i.e. for pediatric patients), clinical issues or current institutional practice are permitted at the discretion of the treating physician in collaboration with BMT pharmacists. All drugs will be prepared and administered per institutional guidelines, with the drugs, doses and scheduled modified as clinically indicated.

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc).

6.1 Autologous stem cell collection

We plan to pre-emptively collect autologous bone marrow or G-CSF mobilized peripheral blood from the initial 5 patients enrolled on this protocol to rescue any cases of aplastic graft failure. Should no episodes of aplastic

graft failure occur, subsequent autologous stem cell collection will take place on an individualized patient basis.

For autologous bone marrow collection, the patient will be admitted on day -12 and will be hydrated overnight and transfused as needed to achieve hgb >9-10, platelet count >50,000, and INR/PTT ≤1.5 x ULN. The following day (day -11), the patient will undergo a bone marrow harvest and Hickman line placement (if needed). Collected bone marrow (goal of 2 x 10^8 TNC/kg) will be counted, processed and cryopreserved. GCSF will not be used for mobilization in hemoglobinopathy patients given risk of leukocytosis triggering a veno-occlusive crisis.

Alternatively, non-hemoglobinopathy patients may undergo leukapheresis to obtain peripheral blood stem cells after GCSF mobilization. Leukapheresis (for the collection of PBSCs) will be performed per institutional standard with adaptations for small children as outlined below. In patients without an appropriate double-lumen leukapheresis-grade catheter in place, this may be accomplished through a percutaneously placed temporary leukapheresis-grade catheter or two large bore peripheral IVs, which is/are then removed following completion of the leukapheresis.

Patients will be primed with filgrastim (Neupogen, G-CSF) 10 mg/kg/QAM for 5 days before planned leukapheresis. Peripheral CD34 enumeration should be undertaken on the morning of the 4th day of filgrastim before pheresis catheter placement. If the peripheral CD34 count is >/= 10 x 10^6/L (and/or viable CD34% >/= 1% of viable CD45%) pheresis cathether placement can proceed (if needed) with leukopheresis the following day. Following each leukapheresis, the cells will be processed and cryopreserved per institutional standards. Prior to cryopreservation, an aliquot of each collection will be analyzed for cell count and immunophenotype. The target for the leukapheresis will be 6 x 10^6 viable CD34+ cells/kg, with acceptable range of 2 -10 x 10^6 CD34+ cells/kg. This may require up to two days of leukapheresis.

For patients smaller than 10 kg, the leukapheresis procedure established for adults will be modified. During the procedure, a set volume of blood is contained in the tubing and apparatus. For larger children and adults, this represents less than 10% of their total blood volume and is usually well tolerated. However, in very small children, the extracorporeal blood volume may be >10% of their total blood volume and this may cause clinically

significant hypovolemia. For patients for whom the extracorporeal blood volume is >10% of their total blood volume, the machine will be primed with irradiated packed red blood cells.

Leukapheresis can be safely accomplished in the outpatient setting for patients >22 kg. Smaller children will be admitted to the inpatient unit following pheresis catheter placement for leukopheresis.

6.2 HaploHCT Regimen

Day	Drug	Dose and route	Refer to section:
-9 to -6 (variable # of days)	Rabbit ATG* (Thymoglobulin®)	IV over 6 hours with pre-meds Continue methylprednisolone per taper through day -2. Specific dose and number of days per ATG nomogram	6.3.1.1 Appendix I
-7	Thiotepa	5 mg/kg IV Q12H x 2 doses	6.3.1.2
-6	Cyclophosphamide	14.5 mg/kg IV over 2 hours	6.3.1.3
	MESNA	14.5 mg/kg IV via continuous infusion	
	Fludarabine	30 mg/m^2 IV over 1 hour (if <10 kg, 1 mg/kg)	6.3.1.4
-5	Cyclophosphamide	14.5 mg/kg IV over 2 hours	6.3.1.3
	MESNA	14.5 mg/kg IV via continuous infusion	
	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-4	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-3	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-2	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-1	TBI**	2 Gy as a single dose	6.3.1.5
0	Stem cell infusion		6.4
+3	Cyclophosphamide	50 mg/kg IV over 2 hours	6.5.1
	MESNA	50 mg/kg IV via continuous infusion	
+4	Cyclophosphamide	50 mg/kg IV over 2 hours	6.5.1
	MESNA	50 mg/kg IV via continuous infusion	

* Rabbit ATG dosing (daily dose and number of days) will be determined according to the ATG dosing nomogram (Appendix I) as described below in section 6.2.2.
**See alternate study calendar in section 6.2.1.5 for females who elect Ovarian transposition

6.2.1 Conditioning regimen

6.2.1.1 Rabbit ATG (Thymoglobulin®)

Rabbit ATG mg/kg IV will be administered via central venous catheter as follows:

- Pre-medicate 30 minutes prior to ATG infusion with methylprednisolone 1 mg/kg IV, acetaminophen 15 mg/kg dose (max dose = 650 mg) enterally and diphenhydramine 1 mg/kg/dose (max dose = 50 mg) enterally or IV.
- Infuse ATG daily at 9 am through a 0.22 micrometer filter over 6 hours.
- Hypersensitivity orders per standard guidelines during ATG administration.
- ATG dose and number of doses as per ATG nomogram (Appendix I). First dose to be given on day -9.

6.2.1.2 Thiotepa

Thiotepa 5 mg/kg IV Q12H x 2 doses to be administered via central venous catheter over 2 hours per institutional guidelines.

6.2.1.3 Cyclophosphamide

Cyclophosphamide 14.5 mg/kg IV will be administered over 2 hours on days -6 and -5. Cyclophosphamide dosing is calculated based on actual body weight (ABW). Refer to cyclophosphamide institutional standards regarding dosing for obese patients.
Alterations to dosing should be discussed with the BMT pharmacist.

Uroprotection with mesna and hyperhydration per cyclophosphamide institutional guidelines. Potassium supplementation in fluids to be adjusted based on patient need and serial serum potassium measurements.

6.2.1.4 Fludarabine

Fludarabine 30 mg/m^2 IV will be administered over 1 hour on days -6 to -2. For children <10 kg, use a weight based fludarabine dose of 1 mg/kg. If the adjusted creatinine clearance is < 70 ml/min, dose-reduce Fludarabine by 20%. Alterations to dosing should be discussed with the BMT pharmacist.

6.2.1.5 Total body irradiation (TBI)

Total body irradiation of 2 Gy will be administered in a single fraction on day -1.

The total body irradiation will be delivered with right and left lateral fields, with the patient supine on a specially designed couch.

Based on measurements of transverse thicknesses, aluminum compensators will be used to ensure that the dose homogeneity across the field is within 10% of the prescribed dose. Usually head/neck, leg and lung compensators are used (although based on calculated mid-mediastinal doses, lung compensators are often not needed).

Total body irradiation will be delivered with a linear accelerator using 6, 18, 24 MV X-rays. The energy used will be based on the calculated dose to the midline at points up and down the patient's torso. The lowest energy that gives 90-100% of the prescription point dose will be used.

A beam "spoiler" will be used to ensure a full skin dose.

Half value layer lung and kidney blocks will not be utilized.

Ovarian transposition/radiation shielding and testicular radiation shielding will be considered for appropriate candidates.

Men who request testicular shielding will also be treated with AP and PA total body radiation beams prescribed at midline at midpelvis and treated with 6MV photons at a dose rate of 10-19 cGy /minute instead of the rt/lt lateral beams. Lung compensators will be used to keep the lung dose within 10% of prescription. A beam spoiler will be used.

Females who elect to have Ovarian transposition/radiation shielding will be treated according to the study calendar below:

Day	Drug	Dose and route	Refer to section:
-10	TBI	2 Gy as a single dose	6.3.1.5
-9 to -6 (variable # of days)	Rabbit ATG* (Thymoglobulin®)	IV over 6 hours with pre-meds Continue methylprednisolone per taper through day -2. Specific dose and number of days per ATG nomogram	6.3.1.1 Appendix I

Day	Drug	Dose and route	Refer to section:
-7	Thiotepa	5 mg/kg IV Q12H x 2 doses	6.3.1.2
-6	Cyclophosphamide	14.5 mg/kg IV over 2 hours	6.3.1.3
	MESNA	14.5 mg/kg IV via continuous infusion	
	Fludarabine	30 mg/m^2 IV over 1 hour (if <10 kg, 1.17 mg/kg)	6.3.1.4
-5	Cyclophosphamide	14.5 mg/kg IV over 2 hours	6.3.1.3
	MESNA	14.5 mg/kg IV via continuous infusion	
	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-4	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-3	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-2	Fludarabine	30 mg/m^2 IV over 1 hour	6.3.1.4
-1	Rest		
0	Stem cell infusion		6.4
+3	Cyclophosphamide	50 mg/kg IV over 2 hours	6.5.1
	MESNA	50 mg/kg IV via continuous infusion	
+4	Cyclophosphamide	50 mg/kg IV over 2 hours	6.5.1
	MESNA	50 mg/kg IV via continuous infusion	

* Rabbit ATG dosing (daily dose and number of days) will be determined according to the ATG dosing nomogram (Appendix I) as described below in section 6.2.2.

Females who undergo ovarian transposition will be treated with AP and PA total body radiation beams prescribed at midline at midpelvis and treated with 6MV photons at a dose rate of 10-19 cGy /minute instead of the rt/lt lateral beams. Lung compensators will be used to keep the lung dose within 10% of prescription. The transposed ovary will be blocked with 5HVL cerrebend blocks. Ovarian location will be determined by ultrasound and marked at the time of transposition. A beam spoiler will be used. On day -8 the oophorpexy will be reversed.

Refer to Appendix II for risks associated with this treatment plan.

6.3 Haploidentical Allogeneic Stem Cell Infusion (day 0)

On day 0 the stem cells will be infused per cell source specific institutional guidelines.

Recommended Pre-medication: acetaminophen 15 mg/kg (maximum 650 mg) PO and diphenhydramine 0.5 mg/kg (maximum 25 mg) PO/IV.

Vital signs will be checked before and after the infusion, and one hour post infusion per University Of Minnesota transplant guidelines. More frequent vital signs may be required depending on reactions to the product infusion.

Refer to Appendix VI for risks associated with transplant.

6.4 GVHD Prophylaxis/Immunosuppression

6.4.1 Post-transplant Cyclophosphamide:

Cyclophosphamide 50 mg/kg IV will be administered over 1 hour on days +3 and +4. Cyclophosphamide dosing is calculated based on actual body weight (ABD) . Refer to cyclophosphamide institutional standards regarding dosing for obese patients. Alterations to dosing should be discussed with the BMT pharmacist. Uroprotection with mesna and hyperhydration per cyclophosphamide institutional guidelines.

Refer to Appendix III for risks associated with cyclophosphamide and mesna.

6.4.1 Sirolimus:

Patients will receive sirolimus therapy beginning on day +5. Dosing of sirolimus will be per the University of Minnesota Pediatric BMT Program guidelines. The target trough sirolimus level will be 10-15 ng/mL for the first 4 months post-HCT and 10 ng/mL from 4-12 months post-HCT.

Empiric dose adjustments when administered concurrently with anti-fungal –azoles should be considered.

The timing of the sirolimus taper will be at the discretion of the treating physician, but in general begins at d+365. Patients with <50% CD3+ donor chimerism at 1 year post-transplant should be considered for prolonged sirolimus use with a target trough of 5-10 ng/mL.

Refer to Appendix III for risks associated with sirolimus.

6.4.2 Mycophenylate Mofetil (MMF):

Patients will receive mycophenylate mofetil (MMF) therapy beginning on day +5. Dosing of MMF will be 1 gram three times daily (total daily dose 3 grams/day) if the recipient is >50 kg, or 15 mg/kg/dose three times daily if the recipient is ≤50 kg. The same dosage is used orally or intravenously. Consider dose modification if renal and/or hepatic impairment (GFR<25 mL/minute corrected). Consider consulting the pediatric BMT pharmacist when changing MMF doses or routes of administration.

MMF pharmacokinetics are not required, but may be obtained when clinically indicated. Consult with the pediatric BMT pharmacist for AUC interpretations and dose adjustments when necessary.

Stop MMF at Day +35 or 7 days after engraftment achieved (ANC>500 x 10^6 neutrophils/L x 3 days), whichever is later. If sufficient GVHD is observed to require systemic therapy, MMF should be continued for 7 days after GVHD is controlled (e.g. resolution of skin rash, vomiting, and diarrhea).

Refer to Appendix III for risks associated with MMF.

6.5 Supportive Care

Supportive care will be provided per University Of Minnesota institutional guidelines for transplant patients including any supportive care research protocols.

All patients will receive standard supportive transfusion care according to transfusion committee guidelines or as modified based on clinical parameters.

Acute and chronic GVHD will be staged and treated using current University of Minnesota BMT program GVHD protocols.

Antimicrobial prophylaxis directed towards bacteria, fungi and viruses will be per University of Minnesota current institutional guidelines for transplant patients.

Refer to Appendix IV for side effects associated with supportive care medications.

Specific Supportive Care as follows:

6.5.1 All patients

6.5.1.1 Radiation Shielding

Consider ovarian transposition and radiation shielding or testicular radiation shielding. This should be discussed and interested patients should meet with radiation oncology and/or gynecology to discuss prior to transplant.

6.5.1.2 Seizure Prophylaxis

Patients will receive Levetiracetam (Keppra) for seizure prophylaxis starting at initiation of conditioning (day -9) and continuing until discontinuation of sirolimus.

6.5.1.3 GCSF

On day +5 or once ANC declines below 1000 x 10^9/L (whichever occurs later), patients will start G-CSF support at 5 mcg/kg/dose (IV/SQ) daily until ANC ≥ 2500/mm^3 for 2 consecutive days. Once a patient has met these criteria, the ANC will be monitored and G-CSF re-dosed if the ANC falls to <1000 x 10^9/L.

6.5.2 Hemoglobinopathy patients

6.5.2.1 Pre-Transplant Therapy

- **Hydroxyurea** – Beginning at least 1 months prior to transplant (preferably 2-3 months) until admitted for conditioning.

  Hydroxyurea (HU) 30 mg/kg enterally. If subjects are already taking HU for their underlying disease, they will continue their regular home dose until admission to the hospital for conditioning.

- **Hypertransfusion (SCD only)** - Packed RBC transfusions will be increased to achieve a goal hemoglobin of 10 g/dL for one month prior to transplant.

- **Exchange Transfusion (SCD only)** - For patients not on a chronic transfusion protocol and having a hemoglobin S

level >30%, a partial exchange transfusion will be performed with a goal of reducing the hemoglobin S level to 30% or lower prior to the beginning of conditioning.

6.5.2.2 Transfusion guidelines (SCD only):

- **Anemia** - Transfusion of packed red blood cells will be administered as needed to maintain a hemoglobin of 9-10 gm/dL through day 100.
- **Thrombocytopenia** - Transfusion of platelets will be administered to maintain the platelet count >50,000.

6.5.3 cALD patients

- **N-acetylcysteine (NAC)** - Beginning on day -10 and continuing through day +100.

  NAC 70 mg/kg/dose IV, every 6 hours (while inpatient) and 3 times daily (once outpatient). While inpatient, patients will receive NAC on a target schedule of 02:00, 08:00, 14:00 and 20:00 and drug will be administered over 15-30 minutes. While outpatient, patients will receive NAC "TID" and infusion rates may vary.

- **Celecoxib -** Beginning on day -10 and continuing through day +100.

  Dosed by patient weight:
  >25 kg: Celecoxib 100 mg PO twice daily
  ≥ 10 kg and ≤ 25 kg: Celecoxib 50 mg PO twice daily

  Note: Recommended hold/dose adjustment parameters: serum creatinine > 2.5 x baseline; ALT or AST > 3x ULN; hemorrhage; uncontrolled hypertension.

- **Vitamin E -** Beginning on day -10 and continuing through day +100.

  Vitamin E 450 IU PO daily

- **Alpha Lipoic Acid -** Beginning on day -10 and continuing through day +100.

  Alpha Lipoic Acid 200 mg PO twice daily.

Refer to Appendix V for risks associated with this supportive care plan.

6.6 Autologous Stem Cell Rescue

Infusion of autologous stem cells will be considered by the treating physician and protocol PI for any of the following indications:

- Lack of neutrophil engraftment by day +42 in the absence of serious infectious complications
- Lack of neutrophil engraftment by day +35 concurrent with serious infectious complication

The autologous stem cells will be stored for two years, then, either discarded, or, if the patient "opts-in" to specimen storage, may be de-identified and used in future research.

6.7 Follow-Up

Patients will be followed for 2 years post-transplant according to the current University of Minnesota BMT follow-up as outlined in section 6.

Follow-up after 2 years will be per the University of Minnesota standard hematopoietic stem cell transplantation protocol for long-term follow-up.

7.0 Clinical Evaluations

All clinical evaluations are standard of care and will be done according to current institutional guidelines and disease specific guidelines. Post-transplant and some pre-transplant monitoring may be tailored for each patient's clinical case.

Scheduled evaluations after screening and until engraftment may be performed +/- 3 days from the targeted date; assessments performed after engraftment and through day 100 may be done +/-7 days of the targeted date. After day 100 assessments may be done +/- 30 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

7.1 Patients

	Pre-transplant work-up	Days in Reference to the transplant		
		Day 1 to engraftment	Follow-up Days 31-100	6 months, 1 and 2 years
MD/NC to ensure that Hydroxyurea is started at least one month prior to transplant for RBC disorder patients	X			
Informed consent	X			
Medical history	X	daily	weekly	X
Physical exam	X	daily	weekly	X
Radiation Therapy consult (discuss testicular or ovarian shielding as appropriate)	X			
Performance status	X		X(100)	X
Height/Weight	X			
GVHD evaluation		daily	weekly	X
Toxicity Assessment		daily	weekly	X
Gynecology Consult (Females only if interested in ovarian transposition and radiation shielding)	X			
Neuropsychological testing	X*			1, 2 yrs (also at 6 mo for cALD)
Laboratory				
CBC, diff	X	daily	weekly	X
Platelet	X	daily	weekly	X
PT/PTT	X	As clinically indicated		
Ferritin	X		X (100)	X
Ferriscan and/or Liver Biopsy	As clinically indicated			
ABO, Coombs	X			
Red cell antibody studies, Red cell Antigen typing (phenotype) (RBC disorder patients)	X			
Reticulocyte count	X		X (100)	X
Basic metabolic panel	X	daily	weekly	X
Urinalysis and NM GFR	X			
Adenovirus, EBV and CMV DNA PCR	X	weekly	weekly	X
Free T4 and TSH	X		X (100)	X
LH, FSH, Anti-mullerian hormone (AMH) and Estradiol levels for females $\geq$10 yr; LH, FSH and testosterone levels for males $\geq$11 yr	X			X
Urine or serum pregnancy test	X			
Semen analysis and storage (if desired)	X			
Lymphocyte subsets (extended profile including B and NK populations)		Day 21	Days 42, 84, 100	X

	Pre-transplant work-up	Days in Reference to the transplant		
		Day 1 to engraftment	Follow-up Days 31-100	6 months, 1 and 2 years
Immune globulin levels (IgG, A, M, E)		Day 21	Days 42, 84, 100	X
Bone marrow biopsy/aspirate	As clinically indicated			
Donor chimerism -- BM	As clinically indicated			
Sorted lineage donor chimerism per clinical standard- PB	X	Day 21	Days 42, 84, 100	X
Donor chimerism (CD71+)– PB (send out to UCSF) for RBC disorder patients	X	Day 28	Days 60, 100	X
Procedures				
EKG	X	As clinically indicated	As clinically indicated	X
MUGA or echo	X	As clinically indicated	X (100)	X
Chest x-ray	X			
PFT's	X			X
Sickle Cell Disease Only				
Exchange Transfusion (ask MD if indicated, see section 6.5 for details)	X			
Cerebral MRI and MRA	X	As clinically indicated		
Hemoglobin S level	X		X (100)	X
Hematology consult for exchange transfusion prior to transplant (ask MD if indicated)	X			
Neurology Evaluation (e.g. If history of stroke or abnormal MRI)	as clinically indicated			
Thalassemia Only				
Hemoglobin electrophoresis	X		X (100)	X

* For cALD, previous neuropsychological testing may be used for pre-transplant baseline evaluation

7.2 Research Labs

ATG (Thymoglobulin) PK Sampling - a blood sample will be obtained to characterize individual Thymoglobulin PK parameters. Thymoglobulin concentrations as well as anti-Thymoglobulin antibodies will be determined.

	Day -1
PK sample – 1.0 mL EDTA tube	X

The study CRA will pick up the sample and deliver to the Translational Therapy lab (TTL). TTL will batch ship the sample to Utrecht University Lab in the Netherlands.

Centrifuge the tube immediately after collection, at 3-5°C for 15 minutes at 3500 rpms to separate the plasma.

Immediately following centrifugation, transfer the supernatant to a pre-chilled 0.5 mL Microtube Screw Cap vial (approx. 0.33 mL of plasma). Freeze at approx. -80 C until shipment.

Tube labels will have the protocol number and sample name pre-printed. The following information on the label must be filled in by the site using the appropriate source documents for completion:

- Date sample was drawn
- Time the sample was drawn (24:00 hour clock)
- Patient number

The label should be placed vertically on the tube (not horizontally) so all of the information can be read.

7.3 Donor Screening

Marrow or peripheral blood donors will undergo screening evaluations based on the current recommendations and procedures of the University of Minnesota and National Marrow Donor Program.

8.0 Adverse Event Monitoring and Reporting

8.1 Event Documentation

Transplant related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database. Events requiring prompt reporting to the University of Minnesota Institutional Review Board (IRB), early stopping rule events, and protocol deviations will be documented in OnCore.

8.2 Adverse Event Reporting

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy to:
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in	Within 5 business days of event discovery	RNI	ETHOS system	SAE Coordinator mcc-saes@umn.edu

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy to:
	harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh				
Masonic Cancer Center SAE Coordinator	Events that impact the early study stopping rules.	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu	

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

9.0 Study Data Collection and Monitoring

9.1 Data Collection

This study will track SAE's, stopping rule events, and clinical deviations using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms.

All transplant related outcomes and complications will be recorded in the Blood and Marrow Transplantation (BMT) database.

9.2 Data and Safety Monitoring

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp

For the purposes of data and safety monitoring, this phase II study is classified as high risk. Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress quarterly

- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 8.2 to the Masonic Cancer Center's SAE Coordinator and the University of Minnesota IRB.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

9.3 Study Related Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

9.4 Record Retention

The investigator will retain study records for at 6 years after the study file is closed with the IRB.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

10.0 Statistical Considerations

This is a treatment Phase II study for the use of T-cell replete reduced intensity conditioning (RIC) haploidentical donor allogeneic hematopoietic cell transplantation (HaploHCT) for individuals with high-risk non-malignant diseases who lack a suitable HLA-matched sibling donor.

10.1 Primary, Secondary and Transplanted-Related Endpoints

The primary objective of this phase II trial is to estimate the rate of donor neutrophil engraftment by day +42, defined as ANC > 500 ($0.5x10^9$/L) for three consecutive measurements.

Secondary endpoints include:

- Incidence of overall survival at 1 year
- Incidence of primary graft failure defined as failure to reach ANC>500 prior to day +42 with >50% donor myeloid cells

Transplant related endpoints include:

- Incidence of secondary graft failure at 6 months, 1 and 2 years, defined at any time after day +42, as either
  - Graft failure with autologous recovery (non-neutropenic). Based on underlying disease, but may include consideration of Hgb S percentage exceeding that of the donor and ongoing transfusion dependence)
  - Aplastic graft failure (neutropenic), with bone marrow cellularity <10% and ongoing transfusion dependence
- Incidence of acute graft-versus-host disease (GVHD) at 100 days
- Incidence of chronic GVHD at 1 year
- Incidence of transplant-related mortality at 100 days, 180 days, and 1 year following transplant

Exploratory endpoints include:

- Sorted lymphocyte chimerism at days 21, 42, 84, 100, 180, 1 and 2 years
- Description of immunological recovery (lymphocyte subsets and immune globulin levels) at days 21, 42, 84, 100, 180, 1 and 2 years
- Impact of day -1 residual serum ATG on neutrophil recovery, graft failure, and T cell chimerism.

All endpoint data will be recorded in the University of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

10.2 Data Collection and Statistical Plan

10.2.1 Statistical Analysis

Cumulative incidence will be used to estimate incidence of engraftment, graft failure, treating late death (>day +21) as a competing risk (Lin, 1997). Kaplan-Meier curves will be used to estimate disease-free and overall survival (Kaplan & Meier, 1958). Hall-Wellner confidence bands will be obtained for both disease-free and overall survival estimates. Chimerism will be described with medians, ranges, interquartile ranges (IQR) and respective box plots. Immunological recovery will be descriptive over time in a similar fashion. The association of ATG with neutrophil recovery and graft failure may be measured with Fine and Gray regression or a simple Chi-square test. Its association with chimerism at specified time-points will be assessed by the general-Wilcoxon test but may be more descriptive in format using simple box-plots.

10.2.2 Sample Size

The overall sample size of 20 patients is based on Simon's optimal two-stage design assuming a type-I error of 5% and 80% power. The null hypothesis or the rate considered unworthy of further investigation is ≤ 50% engraftment. The alternative hypothesis or the rate considered worthy of further investigation is ≥80%.

After enrollment of 7 patients, the trial will be terminated if 4 or fewer achieve neutrophil recovery. If we reach the second stage, the study will go on to enroll an additional 13 patients for a total sample size of 20 patients. If 14 or more patients engraft out of 20 patients, the regimen will be considered worthy of further study. We expect to accrue 4-5 patients per year. Therefore, we anticipate completion of enrollment within 4-5 years.

10.2.3 Safety Monitoring and Stopping Rules

Aplastic graft failure defined as lack neutrophil engraftment, treatment-related mortality by day 100 and Grade III-IV acute GHVD by day 100 will be monitored using early stopping rules. Stopping rules were developed based on adaptation of the Pocock stopping boundaries (Pocock, 1977). In the event that a stopping boundary is crossed, study accrual will halt, the IRB and study committee will be notified and the study plan will be reviewed.

1) Aplastic graft failure by day +42

The goal is to construct a boundary based on excessive failure by day 42 such that the probability of early stopping is at most 10% if the expected rate is equal to 10% and our sample size is 20. With these stipulations, the study will be stopped if there is failure in 2 out of 2 patients, 3 out of 8 patients, 4 out of 14 patients or 5 at any time. If the actual probability of failure is 30%, the probability of reaching the boundary will be 80%.

If no aplastic graft failure is identified in the initial five RBC disorder or initial five cALD disorder patients, pre-Haplo HCT autologous stem cell collection can be discontinued.

2) Treatment-related mortality by day +100

The goal is to construct a boundary based on excessive mortality by day 100 such that the probability of early stopping is at most 10% if the expected rate is equal to 20% and our sample size is 20. With these stipulations, the study will be stopped if there is mortality in 3 out of 4 patients, 4 out of 7 patients, 5 out of 10 patients, 6 out of 13 patients, 7 out of 17 patients or 8 at any time. If the actual probability of failure is 40%, the probability of reaching the boundary will be 68%.

3) Grade III-IV Acute GVHD by day +100

The goal is to construct a boundary based on excessive GVHD by day 100 such that the probability of early stopping is at most 10% if the expected rate is equal to 20% and our sample size is 20. With these stipulations, the study will be stopped if there is GVHD in 3 out of 4 patients, 4 out of 7 patients, 5 out of 10 patients, 6 out of 13 patients, 7 out of 17 patients or 8 at any time. If the actual probability of failure is 40%, the probability of reaching the boundary will be 68%.

Note. We understand that the inclusion of stopping rules may slightly reduce the overall power of the trial.

11.0 Conduct of the Study

11.1 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

11.2 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. In the case of minor patients, the parent/guardian will be required to sign and date the parental consent form and the minor, if 8 years or older will be presented with a minor information sheet.

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Appendix I - Rabbit ATG (Thymoglobulin) dosing for ALD and RBC disorder patients

Patient Weight (kg)@	Absolute Lymphocyte Count#	Cumulative dose (mg/kg)&	Number of doses	Daily dose (mg/kg)
5	0.1	10	4	2.5
5	0.5	10	4	2.5
5	1	10	4	2.5
5	2	10	4	2.5
5	3	10	4	2.5
5	4	10	4	2.5
7.5	0.1	8	4	2.0
7.5	0.5	9	4	2.3
7.5	1	10	4	2.5
7.5	2	10	4	2.5
7.5	3	10	4	2.5
7.5	4	10	4	2.5
10	0.1	7	4	1.8
10	0.5	8	4	2.0
10	1	9	4	2.3
10	2	10	4	2.5
10	3	10	4	2.5
10	4	10	4	2.5
15	0.1	6	3	2.0
15	0.5	6	4	1.5
15	1	7	4	1.8
15	2	8	4	2.0
15	3	10	4	2.5
15	4	10	4	2.5
20	0.1	5	2	2.5
20	0.5	5	3	1.7
20	1	6	3	2.0
20	2	8	4	2.0
20	3	10	4	2.5
20	4	10	4	2.5
25	0.1	4	2	2.0
25	0.5	5	2	2.5
25	1	5	3	1.7
25	2	6	3	2.0
25	3	9	4	2.3
25	4	10	4	2.5
30	0.1	4	2	2.0
30	0.5	4.5	2	2.3
30	1	5	2	2.5
30	2	6	3	2.0

Patient Weight (kg)[@]	Absolute Lymphocyte Count[#]	Cumulative dose (mg/kg)[&]	Number of doses	Daily dose (mg/kg)
30	3	8	4	2.0
30	4	10	4	2.5
35	0.1	3.5	2	1.8
35	0.5	4	2	2.0
35	1	5	2	2.5
35	2	6	3	2.0
35	3	7.5	3	2.5
35	4	10	4	2.5
40	0.1	3	2	1.5
40	0.5	3.5	2	1.8
40	1	4	2	2.0
40	2	5	2	2.5
40	3	6	3	2.0
40	4	10	4	2.5
50	0.1	3	2	1.5
50	0.5	3	2	1.5
50	1	4	2	2.0
50	2	5	2	2.5
50	3	6	3	2.0
50	4	8	4	2.0
60	0.1	2.5	2	1.3
60	0.5	3	2	1.5
60	1	3	2	1.5
60	2	4	2	2.0
60	3	5	2	2.5
60	4	7.5	3	2.5
70	0.1	2.5	1	2.5
70	0.5	2.5	2	1.3
70	1	3	2	1.5
70	2	4	2	2.0
70	3	5	2	2.5
70	4	6	3	2.0
80	0.1	2	1	2.0
80	0.5	2.5	1	2.5
80	1	3	2	1.5
80	2	4	2	2.0
80	3	5	2	2.5
80	4	6	3	2.0

[@]Recipient's weight in kilograms; [#]Absolute lymphocyte count ($x10^3$/uL) determined from the CBC diff obtained prior to first ATG dose on day -10 or -9; [&]Cumulative dose is an estimate; actual dose is determined by last two columns, number of doses x daily dose. For patients whose weights and/or ALC between those shown in the nomogram, round to the closest value (rounding up if at midpoint).

Appendix II – Treatment Related Risks: Conditioning Chemotherapy

Fludarabine		
Common	**Less Common**	**Rare**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Cyclophosphamide		
Common	**Less Common**	**Rare**
• low white blood cell count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term infertility (inability to have children) in women and men	• low platelet count (mild) with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if pregnancy occurs while taking cyclophosphamide	• heart problems with high doses, with chest pain, shortness of breath, or swollen feet • severe allergic reactions • skin rash • scarring of bladder • kidney damage (renal tubular necrosis) which can lead to kidney failure • heart damage, with trouble getting your breath, swelling of feet, rapid weight gain • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug • death from infection, bleeding, heart failure, allergic reaction, or other causes

Mesna is administered before, during and after the cyclophosphamide to protect against bladder damage.

Mesna		
Common	**Less Common**	**Rare, but may be serious**
• bad taste when taken by mouth (may recommend taking it with a strong-flavored beverage) • nausea or vomiting	• mild diarrhea • headache • loss of appetite • flu-like symptoms (fever, flushing, dizziness)	• fast heartbeat • low blood pressure • allergic reaction (may include shortness of breath, wheezing, swelling in the mouth or throat,

Mesna		
Common	**Less Common**	**Rare, but may be serious**
	• cold symptoms (sore throat, runny nose) • feeling tired or sleepy	hives, itching, flushing, or fever)

Thiotepa		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • nausea • vomiting • loss of appetite • temporary or permanent sterility (inability to have children)	• tiredness (fatigue) • anemia (low red blood cell count) • dizziness • headache • fever • pain where the drug was injected • hair loss, thinning or brittle hair (including hair on the face or body)	• blurred vision • confusion • allergic reaction with itching, hives (welts), swelling in throat, wheezing, dizziness, or shortness of breath • second type of cancer • death from infection, bleeding, or other cause

Rabbit ATG (Thymoglobulin®)		
Common	**Less Common**	**Rare**
• fever • chills • leukopenia • pain • headache • abdominal pain • diarrhea • hypertension • nausea • thrombocytopenia • peripheral edema • dyspnea • asthenia • hyperkalemia • tachycardia	• malaise • dizziness	• severe allergic reaction (anaphylaxis)

Total Body Irradiation		
Common	**Less Common**	**Rare**
• nausea and vomiting • diarrhea • cataracts • sterility (inability to have children) • endocrinopathies (hormone imbalance due to damage to the endocrine gland) • stunted growth in children • intestinal cramps • mucositis (mouth sores)	• parotitis (swelling and inflammation of the parotid gland) • interstitial pneumonitis (explained below in the damage to vital organs section) • generalized mild reddening of the skin • veno-occlusive disease (VOD - explained below in the damage to vital organs section)	• dysphagia (difficulty swallowing) • deformities of the backbone (vertebrae) • nephropathy (numbness or tingling in hands and/or feet) • risk of 2nd malignancy years later (when given along with chemotherapy)

Appendix III – Treatment Related Risks: GVHD Prophylaxis/Immune Suppression

Risks of post-transplant cyclophosphamide and mesna are as above in Appendix II.

Mycophenolate Mofetil (MMF)	
Common	**Rare, but may be serious**
• constipation • stomach pain or swelling • nausea • vomiting • difficulty falling asleep or staying asleep • pain, especially in the back, muscles, or joints • uncontrollable shaking of a part of the body • headache • rash	• diarrhea • swelling of the hands, arms, feet, ankles, or lower legs • difficulty breathing • chest pain • fast heartbeat • dizziness • fainting • lack of energy • pale skin • black and tarry stools • red blood in stools • bloody vomit • vomit that looks like coffee grounds • yellowing of the skin or eyes

Sirolimus		
Common	**Less Common**	**Rare**
• Headache • Hypertension • Nausea • Diarrhea • immuno-suppression • fever • constipation • Tremor • renal dysfunction • elevated creatinine/BUN, anemia • pain (abdominal, back, pain) • hyperlipidemia • hypercholesterolemia • hypertrigylceridemia, hyperglycemia • peripheral edema • weight gain • arthralgia • Acne	• Chest pain • Insomnia • Dyspepsia • Vomiting • Dyspnea • Elevated LFTs (with elevated sirolimus levels) • Stomatitis • urinary tract infections • URIs • mild thrombocytopenia • leukopenia • hyper/hypokalemia • hypophosphatemia • rash, hives, pruritis, • delayed wound healing or dehiscence • hypomagnesaemia • proteinuria	• Hypotension • Asthma • increased cough • flu like syndrome • tachycardia • anorexia • hypersensitivity reactions (exfoliative dermatitis, angioedema) • Opportunistic infections • pleural and pericardial effusions • non-infectious pneumonitis or bronchiolitis-obliterans organizing pneumonia and pulmonary fibrosis • thrombosis • myalgias • increased risk of CNI-induced HUS/TTP/TMA) • Chronic renal dysfunction • renal tubular necrosis • CHF • Ascites • arthrosis • bone necrosis • osteoporosis • Lymphoproliferative disorders • skin malignancies

Appendix IV – Treatment Related Risks: Supportive Care

G-CSF		
Common	**Less Common**	**Rare**
• none	• bone and muscle pain • abnormal blood tests which suggest that the drug is affecting the liver	• fast heartbeat • low blood pressure • allergic reaction (may include shortness of breath, wheezing, swelling in the mouth or throat, hives, itching, flushing, or fever) •

Hydroxyurea		
Common	**Less Common**	**Rare**
• Cough or hoarseness • fever or chills • lower back or side pain • painful or difficult urination	• Black, tarry stools • blackening of the fingernails and toenails • blood in the urine or stools • pinpoint red spots on the skin • sores in the mouth and on the lips • unusual bleeding or bruising	• Confusion • convulsions (seizures) • difficulty with urination • dizziness • headache • joint pain • seeing, hearing, or feeling things that are not there • swelling of the feet or lower legs

Appendix V - Risks of the Anti-Oxidant/Anti-Inflammatory Regimens

Levetiractem (Keppra) is used to prevent seizures during times of increased risk. Keppra will be started on from day -9, with the start of conditioning, until sirolimus is discontinued. Risks of Keppra include hallucinations; fever, chills, body aches, flu symptoms; weakness, lack of coordination; increasing or worsening seizures; and nausea, stomach pain, loss of appetite, itching, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes). Less serious side effects include dizziness, spinning sensation; drowsiness; feeling irritable; headache; runny nose, sore throat; or neck pain.

N-acetylcysteine can cause nausea, vomiting, and diarrhea or constipation. Rarely, it can cause rashes, fever, headache, drowsiness, low blood pressure, and liver problems.
When inhaled, it can also cause swelling in the mouth, runny nose, drowsiness, clamminess, and chest tightness.
N-acetyl cysteine has an unpleasant odor that may make it hard to take.

Celecoxib:		
Common	**Less Common**	**Rare**
• cough • fever • rash • sneezing • sore throat	• vomiting • heartburn • nausea • diarrhea • stomach pain • wheezing • headache • tiredness (fatigue), weakness • increased sensitivity of skin to sunlight (higher risk of sunburn) • loss of appetite • liver function test changes • bloating or swelling, especially of the legs and feet* • peptic (stomach) ulcers • bleeding from the stomach or intestines • abnormal blood tests which suggest that the drug is affecting the liver	• decreased hearing • vision changes • double vision • hepatitis (liver inflammation) • liver damage, which may cause yellow skin or eyes (jaundice) • rash and itching • high blood pressure • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) and tiredness • urinary tract infection • kidney damage (usually gets better after medicine is stopped) • kidney failure • blood in urine • stroke (higher risk with long term use) • heart attack (higher risk with long term use) • anxiety • severe allergic reaction with trouble breathing, raised itchy

Celecoxib:		
Common	**Less Common**	**Rare**
		welts on the skin, or swelling of the face, mouth, or throat • heart attack or stroke

Vitamin E may cause allergic skin reactions (inflammation or itching), blurred vision, changes in cholesterol levels, changes in insulin resistance, diarrhea, dizziness, fatigue, flu-like symptoms, headache, heart conditions, increased risk of death, increased risk of fainting or falls, increased risk of heart failure, increased risk of high blood pressure in pregnancy, increased risk of stroke, increased risk of tuberculosis, kidney dysfunction, nausea, severe response to infection (in preterm babies), sexual dysfunction, stomach pain, vision loss, and weakness.

Alpha Lipoic Acid is generally safe, but may cause a rash or lower blood sugar. People at risk for thiamine deficiency should take a thiamine supplement.

Appendix VI – Transplant Related Risks

Hematopoietic Cell Transplantation – regardless of stem cell source
With the cell infusion

- nausea and vomiting
- possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)

As result of transplant

- Slow recovery of blood counts
- Graft failure
- Graft-Versus-Host Disease (GVHD)
- Other complications including:
  - Damage to the vital organs
  - Serious infections
  - Relapse of disease or a new blood cancer
  - Risk to the unborn

Additional Risks associated with the using a Haploidentical Donor
Based on previous experience at this instutition and others there is lower transplant related mortality (TRM), a greater chance of disease relapse but similar overall survival when compared with other transplants using a related or unrelated matched donor.

Appendix VII - Performance Status

Karnofsky Performance Status Scale (≥ 16 years)

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Lansky Score (children < 16 years)

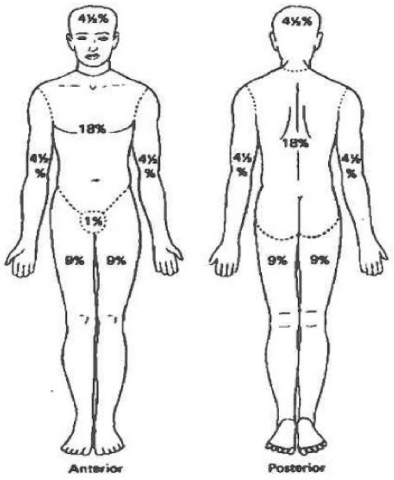
Lansky Score	Performance Status
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Appendix VIII –GVHD Scoring

Acute GVHD. Organ stage and overall grade will be assessed and recorded at designated research visits as per the guidelines below.

GUIDE FOR GVHD STAGING

ORGAN	CLINICAL STAGE
SKIN	1 = Rash <25% BSA 2 = Rash 25-50% BSA 3 = Generalized erythroderma 4 = Generalized erythroderma with bullous formation or desquamation
LOWER GI	ADULT / PEDS 0 = <500 (<280ml/m^2) 1 = 500-1000 (281-555ml/m^2) 2 = 1000-1500 (556-833ml/m^2) 3 = >1500 (>834ml/m^2) 4 = Severe abdomen pain with or without ileus, or stool with frank blood
Liver	1 = Bili 2.1-3.0 2 = Bili 3.1-6.0 3 = Bili 6.1-15.0 4 = Bili >15.1
UPPER GI	0 = No prolonged nausea or vomiting 1 = Persistent nausea, vomiting or anorexia



GVDH Grading

Overall Grade	Organ Stage			
	Skin	Liver	Lower GI	Upper GI
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	
IV	4	-	4	