Masonic Cancer Center, University of Minnesota
Blood and Marrow Transplantation Program

Reduced Intensity Conditioning (RIC) and Transplantation of HLA-Haploidentical Related Hematopoietic Cells (Haplo-HCT) For Patients With Hematologic Malignancies

MT2016-15

CPRC # 2016LS092

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Confidential

Revision History

Revision Number	Version Date	Revision Summary	Consent Change?
	06/22/2016	original to CPRC	
	12/07/2016	Updated Eligibility section 4.1.5 to include LAR	No
	02/17/2017	Throughout protocol clarified upper age eligibility criteria	No
	05/02/2017	• Throughout protocol, clarified that PBSC may be used if haplo donor is not a suitable candidate for marrow harvest • Corrected typo on page 12 & 13	Yes (corrected typo on adult consent)
	07/18/2017	• Edited wording on 5/2/17 clarification, per CPRC request	No
	03/12/2018	• Changed PI to Dr. Brunstein; fixed typo to removed day 28 bone marrow biopsy	Yes
	09/18/2018	• Added Dr. Najla El Jurdi to study committee • Revised treatment plans based on age and co-morbidity scores. Arm B closed. Arms C and D added. • Moved standard clinical procedures to (new) appendix IV • Updated standard of care activity table, and moved post engraftment follow up to (new) appendix V • Revised statistics to account for closure of Arm B, and for new Arms C & D • Minor edits for clarity	Yes
	05/15/2019	• Section 7.1, 7.2, 7.3, Appendix IV: clarified the timing of infusion and post-transplant cyclophosphamide, tacrolimus and MMF in the event a donor undergoes more than one apheresis collection. • Dr. El Jurdi takes over as principal investigator	Yes (corrected typo on consents)
	01/21/2021	• Removed eligibility checklists • Eligibility – HIV+ patients will be permitted if patient has undetectable viral load; removed comorbidity index threshold for older individuals; allow for PBSC donor source • Minor edits of typographical errors	Yes
	09/09/2021	• Synopsis, Sections 3, 12.3 and 12.4 increased accrual goal in Arm D due to faster than expected enrollment • Edits to the synopsis and eligibility criteria to ensure both sections matched • Section 11.2 updated link to DSMP	Yes

	11/10/2021	• Minor eligibility clarification in Synopsis, schema, eligibility: patients who had previous allogeneic transplant, autologous transplant or cellular therapy are only eligible for Arm D	No
	03/11/2024	• PI change	Yes

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Study Synopsis

Reduced Intensity Conditioning (RIC) and Transplantation of HLA-Haploidentical Related Hematopoietic Cells (Haplo-HCT) For Patients with Hematologic Malignancies

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Study Design: This is a two stage phase II trial of HLA-haploidentical related hematopoietic cells transplant (Haplo-HCT) using a reduced intensity conditioning (cyclophosphamide, fludarabine, melphalan, total body irradiation) with modifications based on factors including age and comorbidities. Bone marrow is the donor graft source.

This study is designed to estimate disease-free survival (DFS) at 1 year post-transplant. Since the goal is to estimate the DFS at a long-term time-point (1 year post-transplant), the design has a planned interim analysis without suspension of accrual for futility when 15 subjects have been enrolled on arms A, C and D.

Primary Objective Probability of 1 year disease-free survival (DFS)

Secondary Objectives:

- Incidence of day 100 grade II-IV and grade III-IV acute graft versus-host-disease (GVHD)
- Probability of 6 month, 1 and 2 year treatment related mortality (TRM)
- Probability of 1 and 2 year relapse incidence
- Incidence of serious fungal and viral infections at day 100 and 1 year post-HCT

Transplant Related Objectives:

- Incidence of neutrophil recovery by day +30
- Incidence of platelet recovery by day +60
- Donor cell engraftment (chimerism) at day +21, +60, +100, +180 and + 365
- Incidence of 1 and 2 year chronic GVHD
- Probability of 1 and 2 year GVHD and relapse-free survival (GRFS)
- Probability of 2 year DFS
- Probability of 1 and 2 year overall survival (OS)

Treatment Plan

Arm A: haplo-HCT in patients with HCT-CI ≤2* <55 years old:

- Fludarabine (Flu) 30 mg/m^2 IV Days -6, -5, -4, -3, -2
- Cyclophosphamide (Cy) 30 mg/kg IV Day -6
- Melphalan (Mel) 100 mg/m^2 IV Days -5
- Total body irradiation (TBI) 200cGy Days -2, -1
- Day 0 Infuse non-T-cell depleted donor bone marrow stem cells

CLOSED: Arm B: haplo-HCT in patients ≥55 years old (or younger with HCT-CI ≥3*):

- Fludarabine (Flu) 30 mg/m^2 IV Days -6, -5, -4, -3, -2
- Cyclophosphamide (Cy) 30 mg/kg IV Day -6
- Melphalan (Mel) 70 mg/m^2 IV Days -5
- TBI 200cGy Days -2, -1
- Day 0 Infuse non-T-cell depleted donor bone marrow stem cells

* HCT-CI calculator: http://www.qxmd.com/calculate-online/hematology/hct-ci

Arm C: haplo-HCT in patients with HCT-CI ≤2* aged ≥55 and < 65 years old:

- Fludarabine (Flu) 30 mg/m^2 IV Days -6, -5, -4, -3, -2
- Cyclophosphamide (Cy) 30 mg/kg IV Day -6

- Melphalan (Mel) 70 mg/m^2 IV Days -5
- TBI 200cGy Days -2, -1
- Day 0 Infuse non-T-cell depleted donor bone marrow stem cells

* HCT-CI calculator: http://www.qxmd.com/calculate-online/hematology/hct-ci

Arm D: haplo-HCT in patients ≥65 and ≤75 years old OR any age group with HCT-CI ≥3* OR patients who had previous allogeneic transplant, autologous transplant or cellular therapy:

- -Fludarabine 30 mg/m2 IV Days -6, -5, -4, -3, -2
- -Cyclophosphamide 30 mg/kg IV Day -6
- -TBI 200cGy Days -2, -1

* HCT-CI calculator: http://www.qxmd.com/calculate-online/hematology/hct-ci

GVHD Prophylaxis (all patients):

- Cyclophosphamide (Cy) 50 mg/kg IV Days +3, +4
- Tacrolimus (Tac) IV or PO beginning Day +5 (or sirolimus, if intolerant)
- Mycophenolate mofetil (MMF) beginning Day +5

Eligible Diseases:

- Acute leukemia in complete remission, myelodysplastic syndrome, myeloproliferative neoplasm or chronic myelogenous leukemia with <5% blasts in bone marrow by morphology;
- Chemotherapy sensitive: chronic lymphocytic leukemia/small lymphocytic lymphoma; follicular lymphoma; marginal zone lymphoma; mantle cell lymphoma; diffuse large B-cell lymphoma; Hodgkin's lymphoma, Burkitt's lymphoma; T-cell lymphoma, natural killer cell malignancies and multiple myeloma eligible for an allogeneic transplantation

Selected patients may be eligible in post-chemotherapy and radioimmunoconjugate- induced aplasia

Selected patients in CR, but with positive immunophenotypic (flow cytometry) or molecular evidence of minimal residual disease (MRD) may be eligible if recent chemotherapy has not resulted in MRD negative status.

Age, PS and Graft Requirements:

- ≤ 75 years of age
- Karnofsky performance status of ≥70% or Lansky play score ≥ 70%
- A related haploidentical bone marrow/PBSC donor with up to 2 or 3 HLA locus-mismatches
- The donor and recipient must be HLA identical for at least one haplotype (using high resolution DNA based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1.

Other Inclusion Criteria:

- Adequate liver and renal function
- Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 40%
- $DLCO_{corr}$ > 40% predicted, and absence of O_2 requirements
- > 6 months after prior autologous transplant (if applicable)
- Patients who are HIV+ must have undetectable viral load. All HIV+ patients must be evaluated by Infectious Disease (ID) and a HIV management plan establish prior to transplantation

Exclusion Criteria:

- ≤ 75 years with an available 5-6/6 HLA-A, B, DRB1 matched sibling donor
- Pregnancy or breastfeeding
- Current active and uncontrolled serious infection
- Acute leukemia in morphologic relapse/persistent disease defined as > 5% blasts in normocellular bone marrow OR any % blasts if blasts have unique morphologic markers (e.g. Auer rods).
- CML in blast crisis
- Large cell lymphoma, mantle cell lymphoma and Hodgkin disease that is progressive on salvage therapy. Stable non-bulky disease is acceptable.
- Active central nervous system malignancy
- Less than 3 months since prior myeloablative transplant (if applicable); less than 6 months since prior autologous transplant (if applicable)
- Evidence of progressive disease by imaging modalities or biopsy - persistent PET activity, though possibly related to lymphoma, is not an exclusion criterion in the absence of CT changes indicating progression.

Donor Requirements

Donor Selection:

- Donors must be HLA-haploidentical relatives of the patient, defined as having a shared HLA haplotype between donor and patient at HLA-A, -B, -C, and -DRB1.
- Eligible donors (14-70 years old) include biological children, siblings or half siblings, or parents, able and willing to undergo bone marrow harvesting or PBSC collection.
- For donors <18 years, the maximum recipient weight (actual body weight) should not exceed 1.25 times the donor weight (actual body weight)[1] In addition, bone marrow product volume should be limited to 20 ml/kg donor weight for donors <18 years.

Donor Prioritization Schema:

In the event that two or more eligible donors are identified, the following order of priority is suggested:

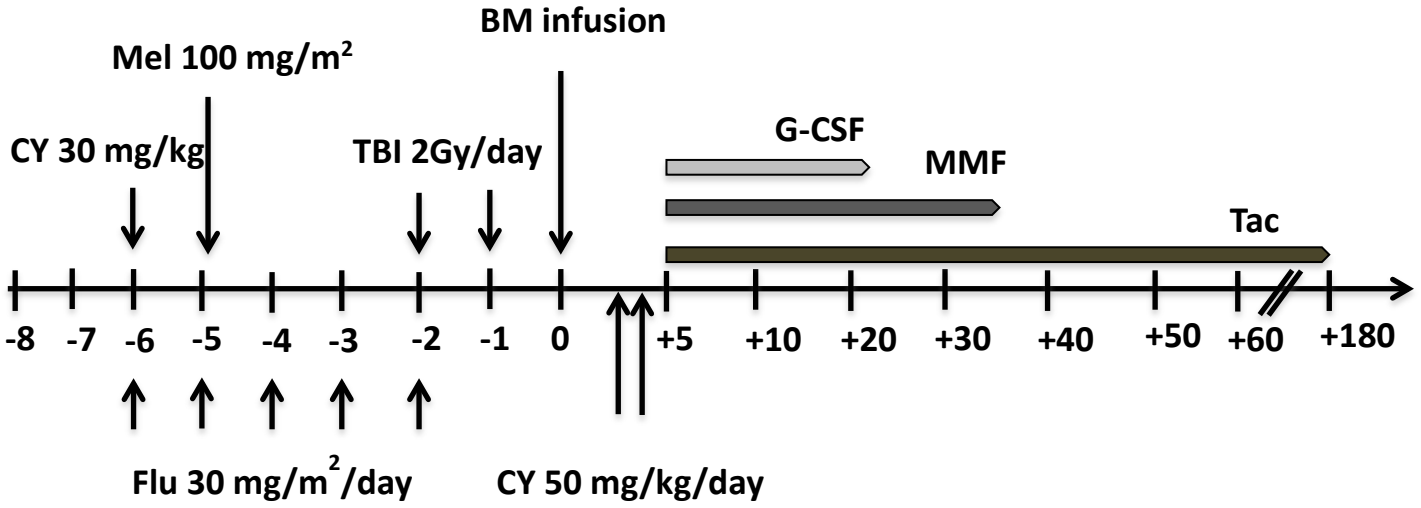
- Medically fit to donate
- Absence of recipient donor-specific anti-HLA antibodies (DSA)
- Donor age 18-40 years is prioritized over donor age < 18, then > 40, with donors <70 preferred. If multiple 18-40 year old donors are available, the youngest donor is prioritized.
- Lack of major ABO incompatibility
- For cytomegalovirus (CMV) seronegative recipients, a CMV seronegative donor
- Lack of minor ABO incompatibility
- Male donor or non-parous female preference for male patients.

Enrollment:

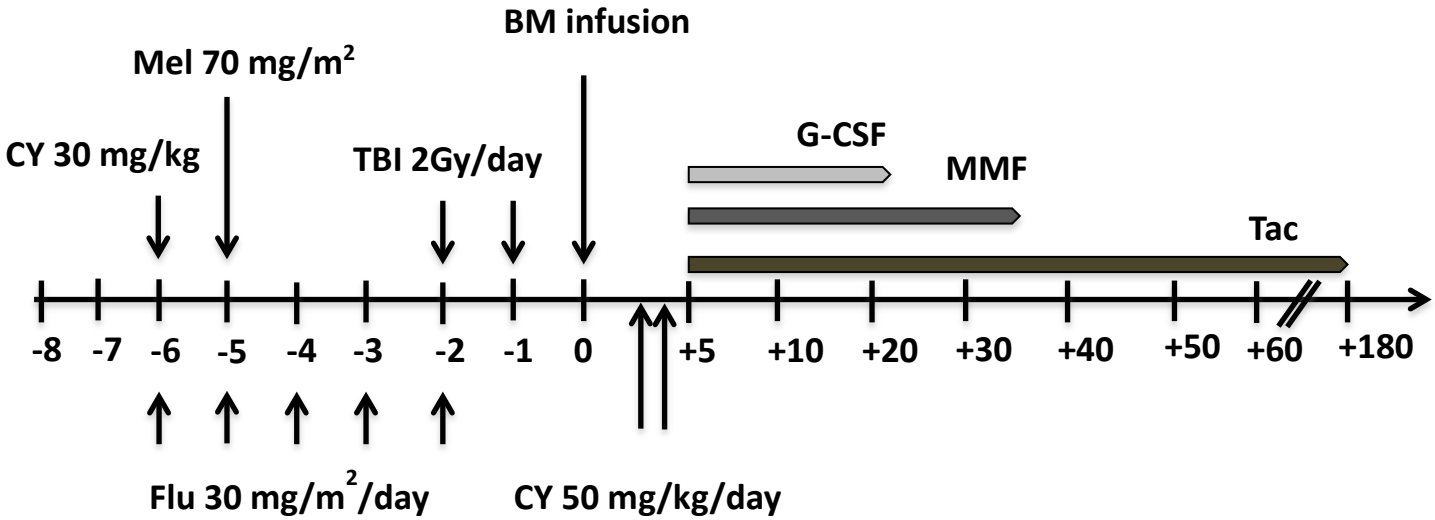
The accrual goal : 94 patients (28 patients separately for arms A and C; and 38 patients in Arm D)

Schema

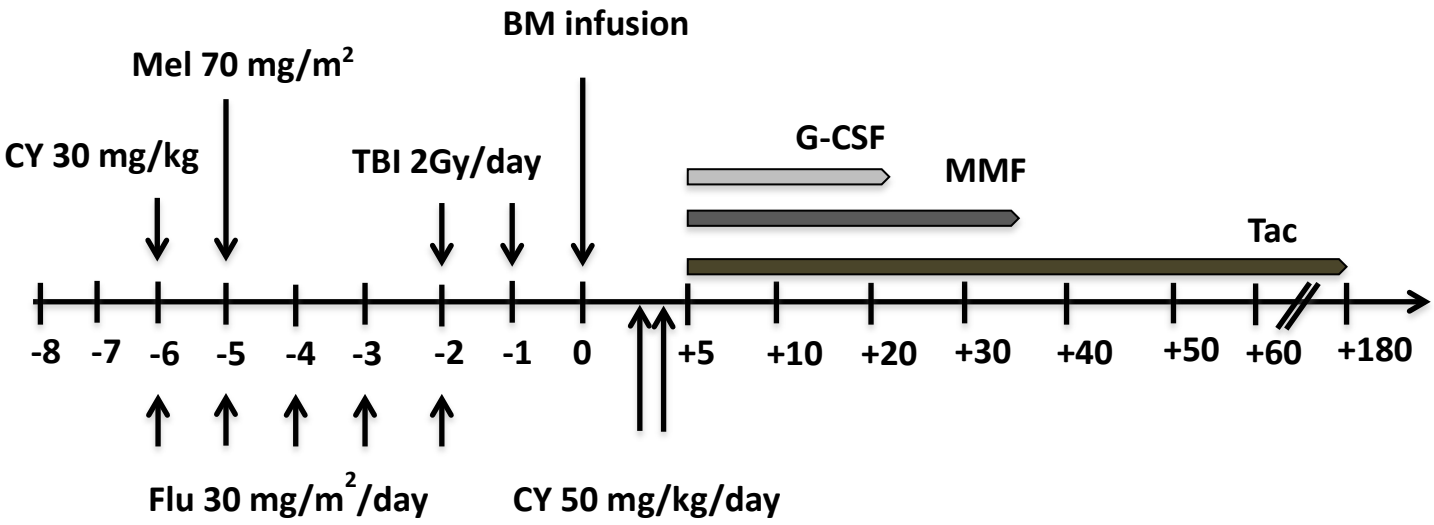
ARM A: reduced-intensity conditioning and transplantation of HLA-haploidentical related donor stem cells for patients <55 years old with HCT Comorbidity Index* (HCT-CI) ≤2



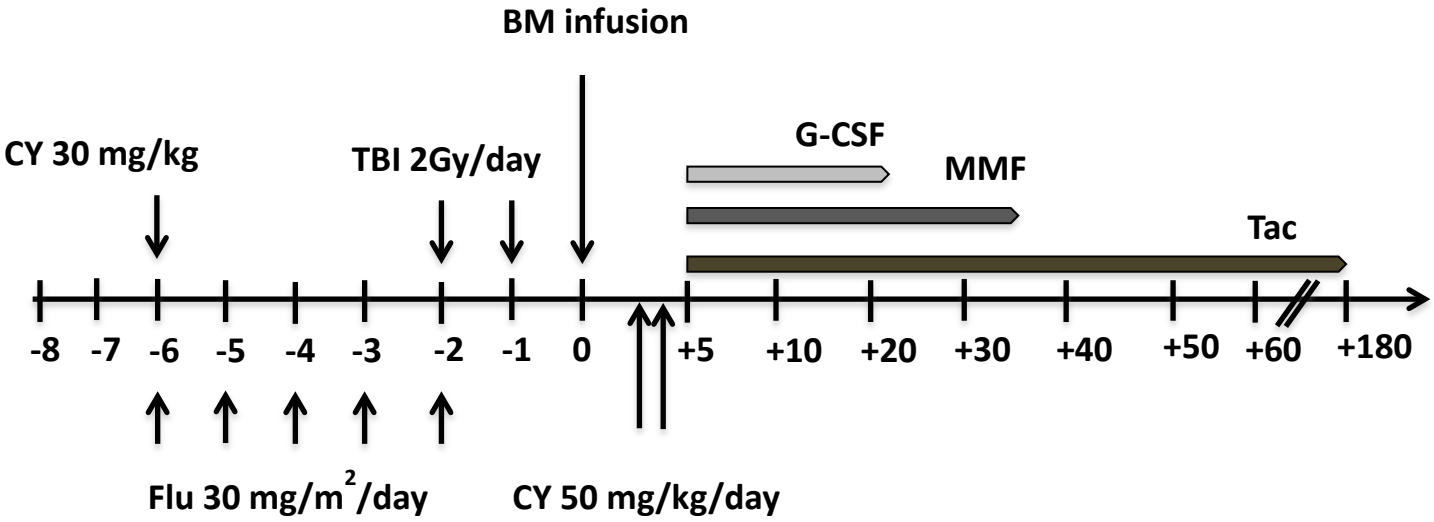
CLOSED ARM B: reduced-intensity conditioning and transplantation of HLA-haploidentical related donor stem cells for patients ≥55 years old or younger with HCT Comorbidity Index* (HCT-CI) ≥3.



ARM C: Haplo-HCT in patients with HCT-CI ≤2* aged ≥55 and < 65 years old:



ARM D: haplo-HCT in patients ≥65 and ≤75 years old OR any age group with HCT-CI ≥3* or patients who had previous allogeneic transplant, autologous transplant or cellular therapy:



* HCT-CI calculator: http://www.qxmd.com/calculate-online/hematology/hct-ci

1 Study Objectives

1.1 Primary Objective

The primary objective is to estimate probability of the 1 year disease free survival (DFS) after a HLA-haploidentical related hematopoietic cells transplant (Haplo-HCT) using a reduced intensity cyclophosphamide/fludarabine/melphalan/total body irradiation (TBI) conditioning with modifications based on factors including age and comorbidities in patients with a hematologic malignancy.

1.2 Secondary Objectives

Secondary objectives are:

- Incidence of day 100 grade II-IV and grade III-IV acute graft versus-host-disease (GVHD)
- Probability of 6 month, 1 and 2 year treatment-related mortality (TRM)
- Probability of 1 and 2 year relapse incidence
- Incidence of serious fungal and viral infections at day 100 and 1 year post-HCT

1.3 Transplant Related Objectives

- Incidence of neutrophil recovery by day +30
- Incidence of platelet recovery by day +60
- Donor cell engraftment (chimerism) at day +21, +100, +180 and + 365
- Incidence of 1 and 2 year chronic GVHD
- Probability of 1 and 2 year GVHD and relapse-free survival (GRFS)
- Probability of 2 year DFS
- Probability of 1 and 2 year overall survival (OS)

2 Background and Rationale

Allogeneic (allo) hematopoietic cell transplantation (HCT) is widely used as a curative therapy for number of hematological malignancies. Reduced intensity conditioning (RIC) opened opportunities for older patients and those with comorbid conditions to be eligible for potentially curable transplantation.[2-6]

However, donor availability still remains significant challenge for large number of patients as HLA-identical matched sibling (MSD) or adult unrelated donor (MUD) is available only for about 60% of the patients.[7] In addition, the data from the National Marrow Donor Program (NMDP) indicate that median time from donor search to adult MUD transplant is about 3-4 months. This time delay increases the risk of malignancy relapse in some patients with aggressive diseases.[2, 3]

Since adult MUD is generally not readily available for many patients with hematological malignancies who are in need for urgent HCT, recent years number of transplant centers widely expended the use of alternative graft sources such as umbilical cord blood (UCB) or haploidentical grafts. [2-6, 8-12] Although UCB is timely available for most of the Caucasian patients, its availability is significantly less for ethnic minorities such as African Americans or Asians. Furthermore, significantly high cost of UCB as compared to other donor sources remains an additional limitation.

In contrast, lower cost and easy accessibility of haploidentical transplantation (haplo-HCT) makes it an attractive alternative graft source. First-degree relative haploidentical donor is available for more than 95% of individuals with average such donor number of 2.7.[7, 13] Initial experience with haplo-HCT using T-cell replete allograft was disappointing with unacceptably high incidence of severe graft versus host disease (GVHD) and transplant-related mortality (TRM) in about half of the patients.[14-16] However, when T-cells were depleted and reduced-intensity conditioning (RIC) regimen was used there was an excessive risk of graft failure. Engraftment was improved with mega-doses of CD34 + cells (over $10x10^6$cells/kg) infusion and/or when full intensity conditioning regimen was used.[10, 13, 17] On the other hand T-cell depleted myeloablative regimen was associated with significantly increased mortality from serious infections/unacceptable immune reconstitution as reported by the European Group for Blood and Marrow Transplantation (EBMT) among 266 acute leukemia patients with 2-year TRM ranging between 36-61±10% depending on remission status at transplant.[17] Subsequently, in order to minimize GVHD risk without significantly affecting immune reconstitution following haplo-HCT several strategies were undertaken most of which are still in developmental stage. One such approach is to augment the immune reconstitution after T-cell depleted haplo-HCT by infusion of pathogen-specific T-cells,[18-22] T-cells engineered to express suicide genes,[23-25] regulatory T-cells (Tregs),[26, 27] or to perform alloreactive donor T-cell ex-vivo photodepletion.[28, 29] Another approach is to perform selective allodepletion in T-cell replete haplo-HCT by ex vivo anergy induction by costimulation blockade,[30, 31] ex vivo selective depletion of T-cells,[32-34] or use of high-dose post-transplant cyclophosphamide (PT-Cy).[11, 35-38] PT-Cy approach was pioneered by Johns Hopkins University (JHU) group using RIC regimen consisting of Flu 30 mg/m^2/day IV daily from Days -6 to -2, Cy 14.5 mg/kg IV on Day -6 and -5, and 200 cGy TBI in a single fraction on Day -1 (Flu150Cy29TBI200). [1, 39-41] PT-Cy has been shown to promote *in vivo* depletion of alloreactive T-cells that helps reducing both graft rejection and GVHD rates after transplantation.[42] In recent years PT-Cy approach either in a setting of RIC (Flu150Cy29TBI200 or other regimens) or myeloablative conditioning has become widely used in many transplant centers given its easy accessibility and lower

cost.[11, 36, 43-50] Munchel and colleagues reported 87% sustained engraftment, 27% grades II-IV acute GVHD and 13% chronic GVHD rates in 210 haplo-HCT(Flu150Cy29TBI200)/PT-Cy recipients with 5-year TRM of 18%, relapse incidence of 55% and overall survival (OS) of 35%.[35] The same group most recently reported better engraftment rate and OS after Haplo-HCT when younger donors (<40 years old) are selected for bone marrow donation.[40] They identified in that study that the yield of CD34+ dose (>2.5 $x10^6$/kg, in some cases 4-8 $x10^6$/kg) is higher in younger donors.[40] Ciurea and colleagues compared the clinical outcomes of 65 recipients of melphalan, fludarabine and thiotepa conditioning regimen and haplo-HCT with T-cell replete BMT/PT-Cy versus T-cell depleted peripheral blood HCT and demonstrated superiority of T-cell replete BMT/PT-Cy with statistically significant improvement of 1-year NRM (16% vs. 42%, p=0.03), chronic GVHD rate (8% vs. 18%, p=0.03), progression free (PFS) (45% vs. 21%, p=0.03) and OS (66% vs. 30%, p=0.02).[36]

Several recent studies also suggest improvement of immune reconstitution with preserved memory T-cells when PT-Cy is used in T-cell replete haplo-HCT.[35, 37] Brunstein et al. compared the outcomes of patients with haplo-BM/PT-Cy (BMT CTN 0603, n=50) and UCB transplantation (BMT CTN 0604, n=50) after RIC in Blood and Marrow Transplant Clinical trials Network (BMT-CTN) 2 parallel multicenter phase 2 trials.[9] Eligibility criteria for the two trials were the same and included patients up to 70 years with hematological malignancies. The target accrual of 50 patients per trial was achieved in just 20 months (16 months faster than expected). The primary endpoint of the study was to determine overall survival 180 days after BMT, with examination of neutrophil and platelet recovery, graft failure, acute GVHD, chronic GVHD, incidence of infections, transplant related mortality, time to relapse, and progression free survival as secondary endpoints. Recipients of haplo-HCT were conditioned with Flu150Cy29TBI200 and UCB recipients received Flu 40mg/m^2 Days -6 to -2, Cy 50 mg/kg Day -6 and TBI 200 cGy Day -1 (Flu200/Cy50/TBI200). GVHD prophylaxis for haplo-HCT consisted of Cy 50 mg/kg IV on Days +3 and +4 followed by MMF and tacrolimus beginning on Day +5. UCB recipients received MMF and CSA beginning on Day -3 for GVHD prophylaxis. The 1-year probabilities of OS and DFS were 54% and 46% after double UCB transplantation (n =50) and 62% and 48%, respectively, after haplo-HCT (n = 50). The cumulative incidence of neutrophil recovery at day 56 was 94% after dUCB and 96% after Haplo-HCT. The cumulative incidence of grade II-IV acute GVHD at Day 100 was 40% after UCB and 32% after haplo-HCT. The 1-year cumulative incidences of TRM and relapse after UCB transplantation were 24% and 31%, respectively, and those for haplo-HCT were 7% and 45%, respectively.

This set the stage for current ongoing BMT-CTN 1101 a multicenter, randomized phase III trial that aims to compare 2-year PFS between haplo and UCB graft sources. Despite haplo-HCT/PT-Cy after Flu150Cy29TBI200 conditioning resulting into low TRM and survival comparable to MSD or MUD transplant in some recent reports,[11, 41, 48] high risk of relapse ranging between 45-60% still remains the major challenge of haplo-HCT/PT-Cy particularly for AML diagnosis.[1, 36, 40, 43]

Efforts to reduce relapse by using full intensity conditioning regimens with haplo-HCT/PT-Cy in younger patients lowered the risk of post-transplant AML relapse to 20-45% without substantial increase in TRM in some reports.[45, 50] However, since myeloablative conditioning is not an option for older patients and for those with higher comorbidities (HCT-CI ≥3) due to an acceptably high risk of TRM, strategies identifying novel RIC regimen platforms that can reduce the risk of relapse and improve survival after haplo-HCT/PT-Cy are in great demand for those >55 years old or with comorbidities. Most recently Flu/Mel and Flu/Busulfan RIC regimens were compared in matched adult donor alloHCT setting for AML/MDS, and significantly lower relapse rate and better survival was observed in those receiving Flu/Mel conditioning regimen.[51] Intensification of Flu150/Cy50/TBI 200 RIC regimen in another study with addition of 5-10 mg/kg Thiotepa and increasing the those of TBI to total 400 cGy (200 cGy day -2 and -1) resulted into low 2-year relapse rate of 11% with TRM of 17% and encouraging 2-year DFS rate of 66% in patients receiving UCB allograft for hematological malignancies.[52] The group from MD Anderson Cancer Center (MDACC) recently reported their experience with haplo-HCT/PT-Cy with use of Flu 40 mg/m^2 Day -6 to -3, Melphalan (Mel) 140 mg/m^2 Day -8 and either Thiotepa 5 mg/kg Day -7 or TBI 200 cGy (FM140) conditioning regimen where Mel dose was reduced to 100 mg/m^2 (FM100) in patients 55 years and older. [49, 50] Despite reported low 1-year relapse rates of 11-19% with FM regimen in these studies, prolonged course of intensive immune suppression (MMF through Day +90 and Tac through Day +180) was required in order to minimize the risk of excessive acute GVHD.[49, 50] Since high dose of Mel exposure per kilogram of body weight (>3.5mg/kg) has been previously shown to increase the risk of oral mucositis and subsequent acute GVHD rate in alloHCT recipients,[53] 51% grade II-IV acute GVHD rate, despite intensive GVHD prophylaxis, at least in part can be explained by higher dose of Mel (FM140) use in MDACC study.[49]

We hypothesize that intensification of Flu150/Cy29/TBI 200 haplo-HCT/PT-Cy RIC regimen with addition of low dose Mel of 100 mg/m^2 Day -5 (70 mg/m^2 for patients ≥55 years and HCT-CI ≥3) and total TBI dose increase to 400 cGy (200 cGy Day -2 and -1) can successfully reduce the risk of relapse and improve DFS after haplo-HCT without substantially increasing the risk of TRM. Therefore, we propose to

conduct a phase II study using RIC regimen platform Flu 30 mg/m^2 IV Days -6 to -2, Cy 30 mg/kg IV Day -6; Mel 100 mg/m^2 IV Days -5 and TBI 200cGy Days -2 and -1 (Flu150/Cy30/Mel100/TBI400) followed by haplo-HCT/PT-Cy and tacrolimus (or sirolimus), mycophenolate mofetil GVHD prophylaxis for patients with hematological malignancies where Mel dose reduction to 70 mg/m^2 IV Day -5 will be used in patients ≥55 years old and those with HCT-CI ≥3 (Flu150/Cy30/Mel70/TBI400).

3 Study Design

This is a single institution phase II study of a reduced intensity conditioning (RIC) followed by a haploidentical hematopoietic cell transplant (haplo-HCT) in persons with diagnosis of hematologic malignancy.

Conditioning will consists of fludarabine, cyclophosphamide, melphalan and total body irradiation (TBI) preparative regimen with a melphalan dose reduction for patients ≥55 years old and those with HCT Comorbidity Index (CI) ≤ 2. No melphalan will be given to subjects age ≥ 65 - ≤ 75 or subjects of any age with a CI of ≥3.

This study uses a two-stage phase II design with accrual goal of 94 patients, using 28 patients separately for arms A and C; and 38 patients in Arm D (arm B has been closed).

4 Patient Selection

Study entry is open to persons less than 75 years of age, regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of a similar studies at the University of Minnesota.

4.1 Inclusion Criteria

4.1.1 Age, Performance Status, and Graft Criteria

- Must be <75 years old with no 7/8 or 8/8 HLA-matched sibling donor. We recommend counseling patients ≥ 65 about the higher risk of non-relapse mortality (NRM), especially in the context of co-morbidities
- Adequate performance status is defined as Karnofsky score ≥ 70% (> 16 years of age) or Lansky score ≥ 70 (pediatrics) (Appendix II)
- Patients and selected donor must be HLA typed at high resolution using DNA based typing at the following HLA-loci: HLA-A, -B, -C and

DRB1. Donors must be HLA-haploidentical relatives including, but not limited to, children, siblings, or parents, defined as having a shared HLA haplotype between donor and patient at HLA-A, -B, -C, and -DRB1.
Refer to donor selection in section 5.

4.1.2 Eligible Diseases

Acute Leukemias: Must be in remission by morphology (<5% blasts). Note cytogenetic relapse or persistent disease without morphologic relapse is acceptable. Also a small percentage of blasts that is equivocal between marrow regeneration vs. early relapse are acceptable provided there are no associated cytogenetic markers consistent with relapse. (Refer to exclusion criteria section 3.5 for more detailed definition).

Acute myeloid leukemia (AML): second or greater complete remission (CR); first CR (CR1) in patients ≥60 years old; CR1 in <60 years old that is NOT considered as favorable risk.

- Favorable risk AML is defined as having one of the following:
- t(8,21) without *cKIT* mutation
- inv(16) or t(16;16) without *cKIT* mutation
- Normal karyotype with mutated *NPM1* but *FLT3-ITD* wild type
- Normal karyotype with double mutated *CEBPA*
- Acute prolymphocytic leukemia (APL) in first molecular remission at the end of consolidation

Acute lymphoblastic leukemia (ALL)/lymphoma: second or greater CR; CR1 unable to tolerate consolidation chemotherapy due to chemotherapy-related toxicities; CR1 high-risk ALL.

High risk ALL is defined as having one of the following:

- Evidence of high risk cytogenetics, e.g. t(9;22), t(1;19), t(4;11), other *MLL* rearrangements, *IKZF1*
- Recipient age 30 years and older at diagnosis
- White blood cell counts of greater than 30,000/mcL (B-ALL) or greater than 100,000/mcL (T-ALL) at diagnosis
- CNS leukemia involvement during the course of disease
- Slow cytologic response (>10% lymphoblasts in bone marrow on Day 14 of induction therapy)

- Evidence of persistent immonophenotypic or molecular minimal residual disease (MRD) at the end of induction and consolidation therapy

Biphenotypic/Undifferentiated/Prolymphocytic Leukemias in first or subsequent CR.

Myelodysplastic syndrome: any subtype including refractory anemia (RA) if severe pancytopenia or complex cytogenetics. Blasts must be less than 5%. If 5% or more requires chemotherapy for cytoreduction to ≤5% prior to transplantation.

Chronic myelogenous leukemia in chronic or accelerated phase. Chronic phase patients must failed at least two different TKIs, been intolerant to all available TKIs or have *T315I* mutation.

MRD positive leukemia (AML, ALL or accelerated/blast phase CML). Selected patients in morphologic CR, but with positive immunophenotypic (flow cytometry) or molecular evidence of MRD may be eligible if recent chemotherapy has not resulted in MRD negative status.

Leukemia or MDS in aplasia. These patients may be taken to transplant if after induction therapy they remain with aplastic bone marrow and no morphological or flow-cytometry evidence of disease ≥ 28 days post-therapy. These high risk patients will be analyzed separately.

Myeloproliferative neoplasms/myelofibrosis.

Relapsed large-cell lymphoma, mantle-cell lymphoma and Hodgkin lymphoma that is chemotherapy sensitive and has failed or ineligible for an autologous transplant.

Burkitt's lymphoma in CR2 or subsequent CR.

Relapsed T-cell lymphoma that is chemotherapy sensitive in CR/PR that has failed or ineligible for an autologous transplant.

Natural Killer cell malignancies.

Relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma, which have progressed within 12 months of achieving a

partial or complete remission. Patients who had remissions lasting > 12 months, are eligible after at least two prior therapies. Patients with bulky disease should be considered for debulking chemotherapy before transplant. Patients with refractory disease are eligible, unless bulky disease and an estimated tumor doubling time of less than one month.

Lymphoplasmacytic lymphoma is eligible after initial therapy if chemotherapy sensitive.

Relapsed multiple myeloma that is chemotherapy sensitive and has failed or ineligible for an autologous transplant.

Bone marrow failure syndromes, except for Fanconi Anemia.

4.1.3 Organ Function Criteria

Adequate organ function is defined as:

Cardiac: Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction $\geq$ 40%. For children that are not able to cooperate with MUGA and echocardiography, such should be clearly stated in the physician's note

Pulmonary: DLCO, FEV_1, FVC > 40% predicted, and absence of O_2 requirements. For children that are not able to cooperate with PFTs, a pulse oximetry with exercise should be attempted. If nether test can be obtained it should be clearly stated in the provider's note.

Liver: Transaminases < 5 x upper limit of normal (ULN) and total bilirubin ≤ 2.5 mg/dL except for patients with Gilbert's syndrome or hemolysis.

Renal: Creatinine $\leq$ 2.0 mg/dL (adults) and creatinine clearance > 40 mL/min (pediatrics). Adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 40 ml/min/1.73m^2.

4.1.4 Patients who are HIV+ must have undetectable viral load. All HIV+ patients must be evaluated by Infectious Disease (ID) and a HIV management plan establish prior to transplantation.

4.1.5 Patients who had previous allogeneic transplant, autologous transplant or cellular therapy are only eligible for Arm D

4.1.6 Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control during study treatment.

4.1.7 Voluntary written consent (adult; Legally Authorized Representative on behalf of cognitively impaired adult; or parent/guardian with presentation of the minor information sheet, if appropriate)

4.2 Exclusion Criteria

4.2.1 ≤ 75 years with an available 5-6/6 HLA-A, B, DRB1 matched sibling donor

4.2.2 Pregnant or breast feeding. The agents used in this study include Pregnancy Category D: known to cause harm to a fetus. Females of childbearing potential must have a negative pregnancy test prior to starting therapy.

4.2.3 Current active and uncontrolled serious infection

4.2.4 Less than 3 months since prior myeloablative transplant (if applicable); less than 6 months since prior autologous transplant (if applicable)

4.2.5 Evidence of progressive disease by imaging modalities or biopsy - persistent PET activity, though possibly related to lymphoma, is not an exclusion criterion in the absence of CT changes indicating progression.

4.2.6 CML in blast crisis

4.2.7 Large cell lymphoma, mantle cell lymphoma and Hodgkin disease that is progressing on salvage therapy. Stable non-bulky disease is acceptable.

4.2.8 Active central nervous system malignancy

5 Donor Selection

Donor selection will be in compliance with 21 CFR 1271. Donors will be evaluated, consented and enrolled via the University of Minnesota related donor protocol (MT2012-14C); however information in this protocol (including match criteria, donor selection priority if more than 1 available donor, cell collection target) overrules that protocol. While bone marrow is preferred, peripheral blood is an acceptable graft source for those haploidentical donors who are not suitable candidates for general anesthesia for bone marrow harvest, such as, but not limited to the elderly or morbidly obese, or per discussion with the treating physician. Total volume required will be the same as above requirements for marrow.

In addition to meeting the criteria in MT2012-14C the following must be met:

5.1 Must be HLA-haploidentical relatives of the patient (biological parents, siblings, half-siblings or offspring), defined as having a shared HLA haplotype between donor and patient at HLA-A, -B, -C, and -DRB1

5.2 14 to 70 years of age

5.3 For donors less than 18 years of age, the maximum recipient weight (actual body weight) should not exceed 1.25 times the donor weight (actual body weight) and bone marrow product volume should be limited to 20 ml/kg donor weight.

5.4 Negative for HIV and active hepatitis B

5.5 Not pregnant - females of childbearing potential must have a negative pregnancy test within 7 days of marrow collection

Donor Prioritization Schema

In the event that two or more eligible donors are identified, the following order of priority is suggested:

- Medically fit to donate
- Absence of recipient donor-specific anti-HLA antibodies (DSA). Positive DSA is defined as a positive crossmatch test of any titer (by complement-dependent cytotoxicity or flow cytometric testing) or the presence of DSA to the high expression loci HLA-A, - B, -C, or -DRB1 with mean fluorescence intensity >1000 by solid phase immunoassay.
- Donor age 18-40 is prioritized over donor age < 18, then >40, with donors <70 preferred. If multiple 18-40 year old donors are available, the youngest donor is prioritized.
- Lack of major ABO incompatibility
- For cytomegalovirus (CMV) seronegative recipients, a CMV seronegative donor
- Lack of minor ABO incompatibility
- Male donor or non-parous female are preferable.

6 Patient 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.

Donors will be registered onto the University of Minnesota Related Donor protocol "Procedure Guidelines For Related Hematopoietic Stem Cell Donors" (MT2012-14C)

Patients will be registered in OnCore by the Masonic Cancer Center's Clinical Data Associates (CDA's).

At the time of registration in OnCore, the patient will be assigned to Arm A, Arm C, or Arm D:

ARM A: <55 years old with HCT-CI ≤2 (Flu150/Cy30/Mel100/TBI400)

Closed - ARM B: ≥55 years old or younger with HCT-CI ≥3 (Flu150/Cy30/Mel70/TBI400)

Arm C: patients with HCT-CI ≤2 aged ≥55 and < 65 years old

Arm D: patients ≥65 and ≤75 years old OR any age group with HCT-CI ≥3 or patients who had previous allogeneic transplant, autologous transplant or cellular therapy

7 Treatment Plan

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 drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

All patients will receive allopurinol 300 mg/day (for peds -150 mg/m^2/day) PO, unless known allergy ending one day after the last dose of chemotherapy or TBI (may continue longer if clinically indicted).

The administration of the preparative regimen will follow institutional drug and supportive care guidelines. Dose and/or schedule adjustments consistent with the standard of care may be made on an individual patient basis as needed for safety.

All drugs used in this study are commercially available by prescription.

7.1 Preparative Arm A
< 55 years of age and CI ≤2

Treatment Day	Treatment	Protocol Section
Day –6	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 30 mg/kg IV over 2 hours Mesna IV (see below for dose and schedule)	7.1
Day -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Melphalan 100 mg/ m^2 IV over 15-20 minutes (give at least 24 hours after cyclophosphamide)	7.1
Day -4	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.1
Day -3	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.1
Day -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes TBI 200 cGy	7.1 Appendix III
Day -1	TBI 200 cGy	Appendix III
Day 0*	Non-T-cell depleted bone marrow*	Appendix IV
Day 3	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 4	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 5	Begin tacrolimus (or sirolimus), mycophenolate mofetil, and G-CSF	Appendix IV

*(Peripheral blood is an acceptable graft source only for those haploidentical donors who are not suitable candidates for general anesthesia for bone marrow harvest, such as, but not limited to the elderly or morbidly obese). Refer to Appendix IV for note on timing of infusion if donor requires additional apheresis

Fludarabine is administered as a 30-60 minute infusion per institutional guidelines on Day -6 through Day -2. Dose adjustments will be made for adult patients with renal impairment defined as CrCL < 70mL/minute. Fludarabine dose MAY also be reduced to this dose if there is prior malignancy involvement of the central nervous system with intrathecal chemotherapy and/or cranio-spinal irradiation

Pre-Transplant Cyclophosphamide Hydration prior to cyclophosphamide will be given according to recommended institutional standards, starting 12 hours prior to cyclophosphamide.

Mesna dose will be 100% of the cyclophosphamide dose being given and divided into 5 doses. 20% of the total dose will be give prior to the start of cyclophosphamide, and then 3, 6, 9, and 12 hours after the start of cyclophosphamide.

Cyclophosphamide 30 mg/kg will be administered as a 2 hour intravenous infusion on Day –6. Cyclophosphamide dosing is calculated based on ABW (actual weight) unless ABW is >150% of the IBW (Ideal Body Weight). Then the dose should be computed using adjusted body weight.

Ideal body weight is calculated using 50kg + [2.3kg x(height in inches – 60)] for men; 45.5kg + [2.3kg x(height in inches – 60)] for women.

Adjusted body weight = IBW + 0.5(ABW-IBW).

Melphlan is administered on Day –5 and at least 24 hours after the Day -6 cyclophosphamide dose. The melphalan dose will be calculated based on Actual Body Weight. High-dose Melphalan is administered via a central venous catheter following reconstitution with the provided sterile diluent. High-dose melphalan should be administered diluted with sodium chloride and infused over 15-20 minutes. Vigorous maintenance hydration (> 1500ml/m2/day) will be administered with high dose melphalan starting 4 hours prior and continuing for at least 10 hours following the dose (day –5).

TBI 200 cGy will be administered on Day -2 and Day -1. Refer to appendix III.

Haploidentical Marrow Infusion will be administered on Day 0 per institutional standard of care. Refer to appendix IV.

7.2 Preparative Arm C
Patients with HCT-CI ≤2 aged ≥55 and < 65 years old

Treatment Day	Treatment	Protocol Section
Day –6	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 30 mg/kg IV over 2 hours Mesna IV (see below for dose and schedule)	7.2
Days -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Melphalan 70 mg/ m^2 IV over 15-20 minutes (give at least 24 hours after cyclophosphamide)	7.2
Day -4	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.2
Day -3	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.2
Day -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes and TBI 200 cGy	7.2 Appendix III
Day -1	TBI 200 cGy	Appendix III
Day 0*	Non-T-cell depleted bone marrow*	Appendix IV
Day 3	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 4	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 5	Begin tacrolimus (or sirolimus), mycophenolate mofetil, and G-CSF	Appendix IV

*(Peripheral blood is an acceptable graft source only for those haploidentical donors who are not suitable candidates for general anesthesia for bone marrow harvest, such as, but not limited to the elderly or morbidly obese). Refer to Appendix IV for note on timing of infusion if donor requires additional apheresis

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2 for a total dose of 150 mg/m^2. Fludarabine will be dosed according to the recipient's actual body weight. For patients who have an estimated or measured creatinine clearance < 70 ml/min/1.73 m^2, or either prior CNS disease, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Fludarabine must be administered before cyclophosphamide on Day -6 and before melphalan on Day -5.

Pre-Transplant Cyclophosphamide Hydration prior to cyclophosphamide will be given according to recommended institutional standards, starting 12 hours prior to cyclophosphamide.

Mesna dose will be 100% of the cyclophosphamide dose being given and divided into 5 doses. 20% of the total dose will be given prior to the start of cyclophosphamide, and then 3, 6, 9, and 12 hours after the start of cyclophosphamide.

Cyclophosphamide 30 mg/kg will be administered as a 2 hour intravenous infusion on Day –6. Cyclophosphamide dosing is calculated based on ABW (actual weight) unless ABW is >150% of the IBW (Ideal Body Weight). Then the dose should be computed using adjusted body weight. Ideal body weight is calculated using 50kg + [2.3kg x(height in inches – 60)] for men; 45.5kg + [2.3kg x(height in inches – 60)] for women. Adjusted body weight = IBW + 0.5(ABW-IBW).

Melphalan 70 mg/m^2 over 15-20 minutes will be administered on Day –5. Melphalan dose will be calculated based on Actual Body Weight. High-dose Melphalan is administered via a central venous catheter following reconstitution with the provided sterile diluent. High-dose melphalan should be administered diluted with sodium chloride and infused over 15-20 minutes. Vigorous maintenance hydration (> 1500ml/m^2/day) will be administered with high dose melphalan starting 4 hours prior and continuing for at least 10 hours following the dose (day –5).

TBI 200 cGy will be administered on Day -2 and Day -1. Refer to appendix III.

Haploidentical Marrow Infusion will be administered on Day 0 per institutional standard of care. Refer to appendix IV.

7.3 Preparative Arm D

Patients ≥65 and ≤75 years old OR any age group with HCT-CI ≥3 or patients who had previous allogeneic transplant, autologous transplant or cellular therapy

Treatment Day	Treatment	Protocol Section
Day –6	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 30 mg/kg IV over 2 hours Mesna IV (see below for dose and schedule)	7.3
Days -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then	7.3
Day -4	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.3
Day -3	Fludarabine 30 mg/m^2 IV over 30-60 minutes	7.3
Day -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes and TBI 200 cGy	7.3 Appendix III
Day -1	TBI 200 cGy	Appendix III
Day 0*	Non-T-cell depleted bone marrow*	Appendix IV
Day 3	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 4	Cyclophosphamide 50 mg/kg IV Mesna IV (see section 7.4 for dose and schedule)	7.4
Day 5	Begin tacrolimus (or sirolimus), mycophenolate mofetil, and G-CSF	Appendix IV

*(Peripheral blood is an acceptable graft source only for those haploidentical donors who are not suitable candidates for general anesthesia for bone marrow harvest, such as, but not limited to the elderly or morbidly obese). Refer to Appendix IV for note on timing of infusion if donor requires additional apheresis

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2 for a total dose of 150 mg/m^2. Fludarabine will be dosed according to the recipient's actual body weight. For patients who have an estimated or measured creatinine clearance < 70 ml/min/1.73 m^2, or either prior CNS disease, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Fludarabine must be administered before cyclophosphamide on Day -6.

Pre-Transplant Cyclophosphamide Hydration prior to cyclophosphamide will be given according to recommended institutional standards, starting 12 hours prior to cyclophosphamide.

Mesna dose will be 100% of the cyclophosphamide dose being given and divided into 5 doses. 20% of the total dose will be given prior to the start of cyclophosphamide, and then 3, 6, 9, and 12 hours after the start of cyclophosphamide.

Cyclophosphamide 30 mg/kg will be administered as a 2 hour intravenous infusion on Day –6. Cyclophosphamide dosing is calculated based on ABW (actual weight) unless ABW is >150% of the IBW (Ideal Body Weight). Then the dose should be computed using adjusted body weight. Ideal body weight is calculated using 50kg + [2.3kg x(height in inches – 60)] for men; 45.5kg + [2.3kg x(height in inches – 60)] for women. Adjusted body weight = IBW + 0.5(ABW-IBW).

TBI 200 cGy will be administered on Day -2 and Day -1. Refer to appendix III.

Haploidentical Marrow Infusion will be administered on Day 0 per institutional standard of care. Refer to appendix IV.

7.4 Post-Transplant Cyclophosphamide (Day 3 and Day 4)

Hydration and uroprotection will be given according to our institutional standards.

Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide).

Cyclophosphamide dosing is calculated based on ABW (actual weight) unless ABW is >150% of the IBW (Ideal Body Weight). Then the dose should be computed using adjusted body weight.

Ideal body weight is calculated using 50kg + [2.3kg x(height in inches – 60)] for men; 45.5kg + [2.3kg x(height in inches – 60)] for women.

Adjusted body weight = IBW + 0.5(ABW-IBW).

Mesna should accompany post-transplantation cyclophosphamide. Mesna will be dosed the same way as when it was given with the pre-transplantation cyclophosphamide (section 7.1 or 7.2).

7.5 Post-Transplant Support

Standard Post transplant supportive care, including GVHD prophylaxis, growth factor support, and management of slow engraftment/graft failure are outlined in Appendix IV.

7.6 Follow-up

Patients will be followed for 2 years post-transplant per the standard of care schedule in section 9 and appendix V.

Follow-up after 2 years will transition to the University of Minnesota standard hematopoietic stem cell transplantation protocol for long-term follow-up and data collection.

8 Expected Toxicities of the Treatment Plan

8.1 Preparative Regimen

Fludarabine		
Common	**Less Common**	**Rare**

• severe suppression of blood counts
• diarrhea
• anorexia
• mucositis
• nausea/vomiting
• stomatitis
• osteoporosis
• dysuria
	• chills
	• fever
	• GI bleeding
	• peripheral edema
		• neurotoxicity
		  – agitation and confusion
		  – blurred vision
		  – peripheral neuropathy
		  – hearing loss
		  – headache
		  – cerebellar syndrome
		  – blindness
		  – coma
		  – weakness
		• depression
		• insomnia
		• hemorrhagic cystitis (except in FA)
		• abnormal renal function test
		• autoimmune hemolytic anemia
		• deep venous thrombosis
		• aneurysms
		• pruritic skin rash
		• abnormal liver function/liver failure
		• constipation
		• transient ischemic attack
		• dysphagia
		• myalgia
		• arthralgia
		• renal failure

Cyclophosphamide		
Common	**Less Common**	**Rare**
• nausea/vomiting • mucositis • sterility • severe suppression of • blood counts • diarrhea • fluid weight gain/edema • alopecia	• hemorrhagic cystitis	• cardiomyopathy • skin rash • SIADH (Syndrome of Inappropriate Anti-diuretic Hormone)

Melphalan		
Common	**Less Common**	**Rare**
• nausea (at higher doses) • vomiting (at higher doses) • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • anemia (low red blood cell count) with symptoms like tiredness, paleness, or trouble catching breath	• short-term or long-term infertility (inability to have children) • weakness	• severe allergic reaction • loss of appetite • scarring (fibrosis) or inflammation of lungs • hair loss, including face and body hair • rash • itching • second type of cancer (may happen years after treatment) • death from lung damage or other causes

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)

8.2 Haploidentical Donor Stem Cell Infusion

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)

General transplant related risks

- 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

8.3 GVHD Prophylaxis

Tacrolimus		
Common	**Less Common**	**Rare, but may be serious**
▪ kidney problems ▪ loss of magnesium, calcium, potassium ▪ high blood pressure ▪ tremors ▪ increases in cholesterol and triglyceride	▪ nausea ▪ vomiting ▪ liver problems ▪ changes in how clearly one can think ▪ insomnia ▪ unwanted hair growth ▪ confusion	▪ seizures ▪ changes in vision ▪ dizziness ▪ red blood cell destruction

It is very important that grapefruit or drinks with grapefruit juice are not consumed while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study**.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be serious**
• miscarriage • birth defects • diarrhea • damage to unborn baby • limited effectiveness of birth control • stomach pain • upset stomach • vomiting • headache	• anemia • rash • difficulty falling asleep or staying asleep • dizziness • uncontrollable hand shakes	• difficulty breathing • unusual bruising • fast heartbeat • excessive tiredness • weakness • blood in stool • bloody vomit • change in vision

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be serious**
• tremors • low white blood cell count with increased risk of infection • increased blood cholesterols • swelling of the hands, feet, ankles or lower legs		• secondary cancers, such as lymphoproliferative disease or lymphoma • Progressive Multifocal Leukoencephalopathy

8.4 G-CSF

Common	Less Common	Rare, but may be serious
none	• local irritation at injection site • ache or pain inside the bones • increased levels of liver enzymes • uric acid in the blood • low number of platelets in the blood	• allergic reaction, low fever • enlargement of the spleen and even splenic rupture • worsening of pre-existing skin rashes, • hair loss • inflammation of a blood vessel in the skin

9 Clinical Care Evaluations

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

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-100	Follow-Up (>Day 100 through Day 720)
Consent	X			
Medical History	X	weekly		
Physical Exam	X	weekly		
RT consultation	X			
Karnofsky/Lansky	X			
GVHD Assessment		weekly start day 7	weekly, day 100	
CBC/diff/plt[3]	X	daily		
PT/INR	X			
Viral Screen	X			
PRA (panel reactive antibody)	X			
Comprehensive metabolic panel	X			
Urinalysis	X			
eGFR for adults with creat > 1.2 or hx or renal dysfunction	X			
Pregnancy test (females of childbearing potential)	X			
BM Biopsy	X	BM (day 21)		
BM chimerism		BM (day 21)		
Blood chimerism	Patient and donor	PB (day 21)		
PFT/DLCO	X			
MUGA or Echo	X			
Chest CT	X[2]			
Disease Evaluation[4]	X	X(day 21 to 28)	X (day 100)	X (day 360, 720)

1 engraftment defined as absolute neutrophil count (ANC) ≥ 5 X 10^8/L for 3 consecutive measurements

2 Patients with a history of MDS or a history of 2 or more consecutive inductions/re-inductions to treat acute leukemia or CML blast crisis or prolonged neutropenia of at least 2 months immediately preceding transplant should have a chest CT without contrast to exclude occult fungal infection prior to transplant.

3 If ANC<500 diff will not be calculated

4 With approval from the medical team, disease assessments may be performed at an outside institution

NOTE: In certain clinical circumstances (e.g. relapsed or terminally ill patients) study tests may be omitted at the physician's discretion).This will not be considered a deviation.

10 Adverse Event Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page http://evs.nci.nih.gov/ftp1/CTCAE/About.html

10.1 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.

10.2 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 harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu	SAE Coordinator mcc-saes@umn.edu
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	n/a

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).

11 Study Data Collection and Monitoring

11.1 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.

11.2 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 https://z.umn.edu/dsmp .

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

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress twice yearly
- 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 9.2 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).

11.3 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.

11.4 Record Retention

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

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.

12 Statistical Considerations

12.1 Statistical Endpoints

12.1.1 Primary Endpoint

The primary endpoint is the probability of disease-free survival (DFS) by 1 year post-transplant. An event will be defined as death or a relapse.

12.1.2 Secondary Endpoints

- Probability of Grade II-IV and Grade III-IV aGVHD at 180 days
- Probability of treatment-related mortality (TRM) at 6 months, 1 and 2 years
- Probability of relapse at 1 and 2 years
- Probability of serious fungal and viral infections at day +100 and 1 year post-HCT

12.1.3 Transplant Related Endpoints

The following endpoints are not stressed but will be abstracted from the BMT database:

- Probability of neutrophil recovery by day +30
- Probability of platelet recovery by day +60
- Proportion of donor cell engraftment (chimerism) at days +21, +100, +180 and +365
- Probability of 1 and 2 year chronic GVHD
- Probability of 1 and 2 year GVHD and relapse-free survival (GFRS)
- Probability of 2-year DFS
- Probability of 1 and 2 year overall survival (OS)

12.2 Statistical Analysis

Arm B has been closed due to higher toxicity but we will analyze as intended to estimate endpoints under previous eligibility and conditioning. In order to reduce treatment-related mortality, future enrollment of patients previously eligible for arm B will be placed into two separate arms (C and D) based on age and HCT-CI with reduced conditioning in arm D. Eligibility for **Arm C** will primarily be changed to allow only patients aged 55-64 with HCT-CI≤2. The conditioning will remain the same. In **Arm D**, eligible patients will be age 65-75 or have and HCT-CI ≥3 but Melphalan will be completely removed from the conditioning. Analysis will be performed separately for arms A, C and D as we are not certain if the disease-free survival will differ between the two groups. It is possible that PBSC will be used as a donor source but this is unexpected. These patients will be evaluated separately in a descriptive format. Otherwise

for the primary target study population, Kaplan-Meier curves will be used to estimate the probability of DFS, OS and GFRS along with respective 95% confidence intervals. Cumulative incidence will be used to estimate the probabilities of GVHD, relapse, infection, and neutrophil and platelet recovery treating non-event deaths as competing risks. The probability of TRM will be estimated in a similar manner but treating relapse as the competing risk. Ninety-five percent confidence intervals will be estimated from respective standard errors. The proportion of donor chimerism (classified as ≥70% donor cells at various time-points will be estimated among patients who have survived to the evaluated time-point). Descriptive plots and measures will also be used to evaluate chimerism as a continuous measure. Medians, ranges and inter-quartile ranges will be given for actual chimerism values. Analyses will be performed and plots generated using SAS 9.3 (SAS Institute, Cary, NC) and/or R 3.5.1.

12.3 Design and Sample-Size Justification

This study is designed as a two-stage phase II trial to estimate disease-free survival (DFS) by one year post-transplant. We will potentially enroll 28 patients with one interim analysis (without pause in enrollment) at 15 subjects in each arm (A and C) and 38 in Arm D. Since the goal is to estimate the DFS at a long-term time-point (1 year), we ran a simulated exponential model 10,000 times based on complete follow-up and a one-sided log-rank test through 1 year with interim analysis based on accrual of 15 subjects with incomplete follow-up to generate sample size and power estimates.

When 15 subjects have been enrolled, we will discontinue the trial if the projected kaplain-meier curve has an estimated 1 year DFS of <32%. Assuming the null hypothesis of 30% DFS is true, we have a 42% chance of stopping the trial early due to futility which may vary depending on the rate of accrual. Assuming the alternative hypothesis of 60% DFS by 1 year, we have overall power of approximately 79%. Due to the number of comparisons, the Bonferonni correction for multiple comparisons has been employed (type-I error = 0.0167 (0.05/3)) to maintain an experiment-wise type-I error of 0.05.

We expect to complete the study after 2-3 years of enrollment plus 1 year of follow-up after the last enrolled patients.

08/19/21: Arm D has been accruing faster than expected (currently at 25 patients with final enrollment of 28 patients). Given that Arm D has been shown to be efficacious with 1 year DFS of 52% (95% CL, 30-70%) and safe (2 TRM stopping rule events and 2 Grade III-IV aGVHD stopping rule events), we

propose to increase enrollment to 38 patients in Arm D. This will provide a more precise estimate of DFS for Arm D. Thirty-eight patients would decrease the 95% confidence limit width by approximately 7%.

12.4 Toxicity Monitoring and Stopping Rules

Monitoring guidelines are developed to monitor excess toxicity using a continuous monitoring strategy based on an adaptation of Pocock stopping boundaries[56]. In the event that a stopping rule is triggered, enrollment will be halted and the event reviewed by the study committee prior to re-initiation of enrollment.

08/19/21: Given limited stopping rule events to date, continuous monitoring will cease after enrollment of 28 patients on Arm D. Safety measures including stopping rule events will subsequently be monitored by the DSMC on a quarterly basis for Arm D. Other arms will be monitored on a continuous basis.

12.4.1 Treatment Related Mortality by 100 days

Stopping rules were developed for excessive non-event mortality (TRM) by day 100 post-transplant. The goal is to construct a boundary based on TRM such that the probability of early stopping is at most 10% if the true rate is equal to 12% and our sample size is 28. Given these parameters, the upper stopping boundary for TRM is 2 deaths out of 2 patients, 3 out of 6, 4 out of 11, 5 out of 16 or 6 out of 21 or 7 out of 27. The probability of early stopping of TRM if the true probability is 30% is 80%.

12.4.2 Grade III-IV by 100 days

Stopping rules were developed for excessive grade III-IV aGVHD by day 100 post-transplant. The goal is to construct a boundary based on GVHD such that the probability of early stopping is at most 10% if the true rate is equal to 13% and our sample size is 28. Given these parameters, the upper stopping boundary for GVHD is 2 events out of 2 patients, 3 out of 6, 4 out of 10, 5 out of 15 or 6 out of 20, 7 out of 26 or 8 at any time. The probability of early stopping of GVHD if the true probability is 30% is 77%.

Due to additional stopping rules, it is understood that the overall power may be slightly reduced for this study.

13 Conduct of the Study

13.1 Record Retention

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.

13.2 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.

13.3 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.

Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

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Appendix I – Eligibility Checklist

Removed – Eligibility checklists are kept in Oncore

Appendix II – Karnofsky Performance Status and Lansky Play Score

For patients 16 years of age and older:

Karnofsky Performance Scale	
Percent	**Description**
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.
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/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

For patients < 16 years of age:

Lansky Score	Play Score
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 III – TBI Guidelines

All patients who have had previous radiation therapy or TBI will be seen by Radiation Oncology prior to entrance on the protocol for approval for additional 200 cGy of TBI. TBI may be delivered by local guidelines provided the effective dose is equivalent to what is recommended in the TBI Guidelines.

Patients ineligible for this protocol include those who have had previous irradiation to areas of the body such that the Radiation Oncologist feels that even a relatively small dose of total body irradiation (TBI) cannot safely be given.

The total dose of TBI will be 400 cGy. Each fraction will be 200 cGy given on Day -2 and Day -1.

The dose rate will be between 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The TBI will be delivered with right and left lateral fields with the patient semi-recumbent in a semi-fetal position with their arms at their sides.

Based on measurement of transverse thickness, aluminum compensators will be used to ensure that the dose homogeneity across the fields 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 if the thickness of the arms, which partially shield the lung, are taken into the thickness consideration).

TBI will be delivered with a linear accelerator using 6, 10, or 18 MV photons. The energy used will be based on the calculated dose to midline at points along the patient's torso. The lowest energy that gives 90-100% of the prescriptions 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 for patients who have not previously received total body irradiation.

Updated 9/23/16 by Kathryn Dusenbery, MD

Appendix IV Standard Transplant Procedures and Supportive Care

Haploidentical Donor Marrow Collection and Infusion (Day 0)

On Day 0, patients will receive unprocessed marrow unless there is an ABO incompatibility. In case of major ABO incompatibility red blood cells will be depleted from the donor marrow using institutional practice. In case of minor ABO incompatibilities donor marrow plasma depletion and IV hydration will be used per institutional standard practice.

Donor bone marrow will be harvested with a target yield of 4 x 108 nucleated cells/kg recipient IBW, and a recommended minimum yield of 2.5 x 108 nucleated cells/kg of recipient IBW. If ABO incompatible, then a target of 6 x 108/kg will be collected to allow for cell losses during RBC removal as needed. We recommend taking no more than 10 mL per aspirate. Marrow nucleated cell count will be calculated after collection of 500 ml marrow, which will be used to calculate requited total bone marrow volume harvest as below.

If bone marrow collection volume exceeding 20 ml/kg of donor actual body weight is required, donor hemoglobin/hematocrit (Hb/Hct) should be checked STAT during bone marrow harvest procedure to document that Hct remains ≥25. Fluids and colloid such as albumin will be infused to the donor as necessary. Unrelated donor RBC transfusions can be considered in some cases if clinically indicated.

In addition to calculating the total nucleated cell dose/kg, a sample of the product to be infused will be sent for flow cytometry to determine the content of CD34+cells. The use of cryopreserved marrow is not permitted.

Calculation:

Total bone marrow volume required = (4 x 108 nucleated cells/kg x Recipient IBW (kg)) / (Marrow nucleated cell count – Peripheral blood WBC count)

E.g. Required total bone marrow volume for 50 kg IBW recipient: (4 x 108 cells/kg x 50 kg)/(25 x 106/mL marrow count - 5 x 106/mL PB WBC count) = 2 x 1010/2 x 107=1000 mL

Peripheral blood is an acceptable graft source for those haploidentical donors who are not suitable candidates for general anesthesia for bone marrow harvest, such as, but not limited to the elderly or morbidly obese. Peripheral blood is also acceptable at the discretion of treating physician and the BMT team for underlying diseases with higher risk of engraftment failure including but not limited to those with myeloproliferative neoplasms/myelofibrosis and hypercellular marrow. Total volume required will be the same as above requirements for marrow. Peripheral blood may supplement bone marrow graft if cell dose requirement is not met.

Note that if a related donor undergoes a second apheresis session to collect the target number of peripheral blood stem cells, the product should be held at MCT until both collections have been completed. The entire collection yield should be infused on the same day, the patient in effect has two “Day 0s” (a rest day, then an infusion day) and the days of post-transplant cyclophosphamide should be adjusted accordingly to be days +3 and +4 post-stem cell infusion. The start of tacrolimus and MMF should also be adjusted accordingly in this circumstance.

GVHD Prophylaxis and Growth Factor Support (begin Day 5)

All patients will receive prophylaxis for GVHD with two drugs both beginning at Day 5 as follows:

Tacrolimus

Tacrolimus will be given at a dose of 0.03 mg/kg/day IV as a continuous infusion. When tolerated, tacrolimus may be changed to PO dosing at 0.12 mg/kg/day PO divided into two doses. Initial IV and/or PO dose may be adjusted as clinically necessary to achieve desired goal levels.

Tacrolimus prophylaxis will begin on Day +5 post-transplant. Serum levels of tacrolimus will be measured around Day +7 and then should be checked twice weekly thereafter and the dose adjusted accordingly to maintain a trough level of 5-15 ng/mL for a minimum of 90 days, followed by taper through Day +180 in the absence of GVHD. Tacrolimus may be continued if active GVHD is present.

Sirolimus (trough level of 3-12 ng/ml) may be substituted for tacrolimus if the patient is intolerant of tacrolimus.

Mycophenolate Mofetil (MMF)

MMF will be given at a dose of 15 mg/kg PO TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID). MMF prophylaxis will begin on Day +5 post-transplant and will be discontinued after the last dose on Day +35, or may be continued if active GVHD is present.

Growth Factor Support

G-CSF will be given beginning on Day +5 at a dose of 5 mcg/kg/day (rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is ≥ 1,500/mm^3 for three consecutive measurements on 3 different days. G-CSF may be restarted to maintain ANC > 1,000/mm^3. G-CSF may be given by IV or subcutaneously.

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.

Management of Slow Engraftment or Graft Failure

Patients with ANC < 1000 any time after cord infusion will be started on G-CSF support at 5 mcg/kg (IV/SQ)(round to vial size) daily until ANC > 2500/µL for 2 consecutive days. Once a patient has met these criteria, the ANC will be monitored and G-CSF restarted if ANC falls to < 1000.

If no evidence of donor engraftment on the Day +21/28 bone marrow biopsy, notify the unrelated donor (URD) search coordinator to pursue back-up graft and arrange a follow-up bone marrow biopsy per current institutional slow engraftment guidelines.

Appendix V Standard of Care Clinical Follow-up

Suggested clinical care activities for post transplant follow-up. Missed assessments will not be considered study deviations.

Activity	Day 1 To Engraftment[1]	Follow-Up Days 42-100	Follow-Up (≥Day 100 through Day 720)
Medical History			X (day 180, 360, 720)
Physical Exam			X (day 180, 360, 720)
Karnofsky/Lansky			X (day100, 180, 360, 720)
GVHD Assessment			X (day 100, 180, 360)
CBC/diff/plt[2]		weekly	X (day 180, 360, 720)
Basic metabolic panel	daily		
Comprehensive metabolic panel	weekly	weekly	X (day 180, 360, 720)
BM Biopsy			BM (day100, 360, 720)
BM chimerism			BM (day 100, 360, 720)

1 engraftment defined as absolute neutrophil count (ANC) ≥ 5 X 10^8/L for 3 consecutive measurements

2 If ANC<500 diff will not be calculated

After two years post transplant, patients will transition to the BMT Database protocol for long term follow up.