Randomized (RA) phase (P) II Study to Expedite Allogeneic Transplant with Immediate (I) Haploidentical plus Unrelated Cord Donor (D) Search Versus Matched Unrelated Donor Search for AML and High-Risk MDS Patients. The RAPID Study

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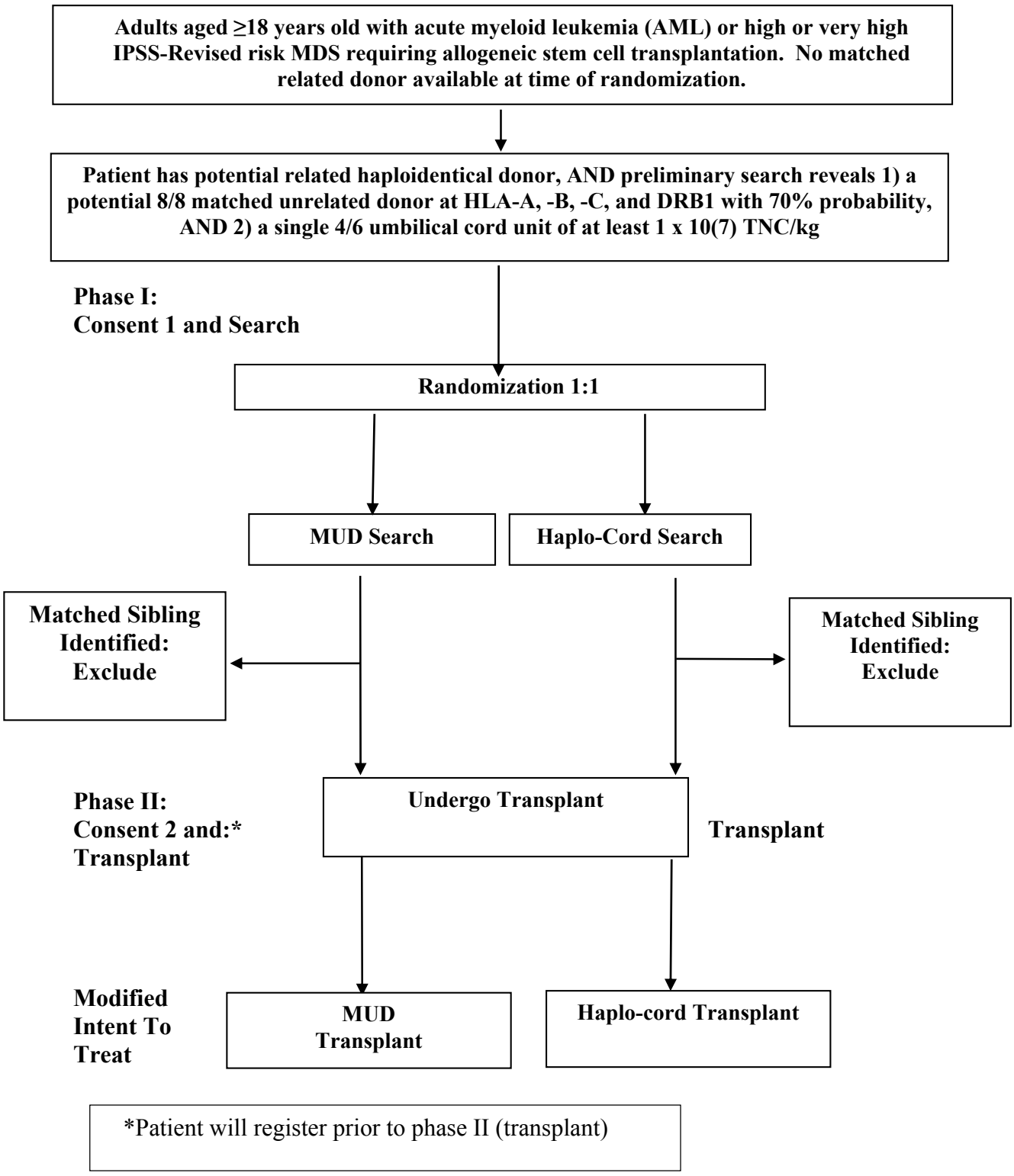
SCHEMA


Adults aged ≥18 years old with acute myeloid leukemia (AML) or high or very high IPSS-Revised risk MDS requiring allogeneic stem cell transplantation. No matched related donor available at time of randomization.
Patient has potential related haploidentical donor, AND preliminary search reveals 1) a potential 8/8 matched unrelated donor at HLA-A, -B, -C, and DRB1 with 70% probability, AND 2) a single 4/6 umbilical cord unit of at least 1 x 10(7) TNC/kg
Phase I:
Consent 1 and Search
Randomization 1:1
MUD Search
Haplo-Cord Search
Matched Sibling Identified: Exclude
Matched Sibling Identified: Exclude
Phase II:
Consent 2 and:*
Transplant
Undergo Transplant
Transplant
Modified Intent To Treat
MUD Transplant
Haplo-cord Transplant
*Patient will register prior to phase II (transplant)

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1. OBJECTIVES

1.1. PRIMARY:

- To compare time from formal search to hematopoietic cell transplantation (HCT) for patients 18 years and older, randomized between haplo-cord search and matched unrelated donor (MUD) search for patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS)

1.2. SECONDARY:

- To compare the percentage of patients who undergo HCT in each study cohort
- To evaluate overall survival from time to randomization by study cohort
- For those undergoing transplant compare outcomes by donor type received MUD vs haplo-cord for neutrophil engraftment, grade 3-5 day 100 toxicities and chimerism
- To evaluate non-relapse mortality, rates of acute and chronic GVHD, leukemia-free survival and overall survival by donor type
- To collect correlative samples for future research

2. BACKGROUND

2.1. Allogeneic Hematopoietic Stem Cell Transplantation (HCT)

Allogeneic stem cell transplantation (SCT) remains the only potentially curative treatment in high-risk and relapsed hematologic malignancies, by inducing a cell-mediated graft-versus tumor effect. Major barriers to more widespread application have been lack of an HLA identical donor and transplant related morbidity and mortality. As outlined below, these are now surmountable obstacles.

2.2. Transplant for AML

A meta-analysis of studies indicated a benefit for allogeneic transplant with a matched sibling donor compared to non-transplant treatment for AML in first remission in those with intermediate or high-risk disease by cytogenetic criteria. (1) Studies were restricted to younger adults. Observational data have shown similar outcomes for matched related and matched unrelated donor at HLA-A, B, C and DRB1 (i.e, 8 of 8 HLA match).

The number and proportion of transplants is rising markedly in older patients, particularly for AML. Historically, SCT was restricted to patients younger than 50 years of age due to high transplant-related mortality (TRM). Multiple advances, such as availability of reduced intensity (RIC) and non-myeloablative conditioning, better supportive care, and high resolution typing consequently with less graft-versus-host disease, have enabled extending transplant into the eighth decade of life in select groups. A large number of observational studies now show that patients 50 years and older have good outcomes after SCT, with limited or small differences compared to younger adults and with improved survival compared to chemotherapy-only approaches.(2, 3) In addition, new methods to appropriately assess health status and therefore predict tolerance to transplant have been developed for patients 50 and older to help medically

optimize patients in the peri-transplant period and to circumvent foreseeable complications. (4-7)

2.3. High-risk Myelodysplastic Syndromes

High-risk myelodysplastic syndromes (MDS) have similar outcomes to AML. Recent prognostic models using the International Prognostic Scoring System provide prognosis such that high-risk and very high-risk MDS have median overall survival of 1.6 and 0.8 years and median time to AML of 1.4 and 0.7 years respectively. (8) Therefore, moving quickly to transplant, similar to AML, is essential.

2.4. Donors and Donor Searches

An HLA matched sibling or related donor at HLA-A, -B, -C and -DRB1 remains the standard and optimal transplant donor. However, the majority of patients for whom transplant may be indicated lack an HLA matched related donor (MRD). Thus, matched unrelated donors (MUD) have become the most common donor source for allogeneic transplant, particularly with cooperative registries of adult donors across the world, allowing quick computer searches for potential HLA matched donors. Furthermore, complication rates of unrelated donor transplant has markedly improved with matching at allele level for at least HLA-A, -B, -C and -DRB-1 (sibling donors harbor similar haplotypes and thus are inherently allele level matches). Recent data support the present practice to consider matched unrelated donor as an equivalent stem cell source to matched sibling donor for AML. (9). Increasing data also suggest importance of partial matching for HLA DPB1 (permissive haplo types), which may further improve outcomes for unrelated donor transplants. (10, 11)

However, the use of HCT remains limited by availability of an appropriately matched donor, especially in minority groups. (12-14) In one study of transplant searches in the United Kingdom in 2005, Querol et al. found that only 38% of patients in whom unrelated donor search was initiated received a transplant. (15) Major reasons for lack of transplant included inability to secure a donor in 28%, and disease progression in 33% despite having a donor identified. Gragert et al. recently reported on the likelihood of finding a suitable donor in the US registry. (16) Whites and those of European descent had the highest chance (75%) of finding a matched unrelated donor (MUD). While those of South and Central American descent had the lowest probability of finding a MUD at 16%.

2.5. Transplant Delays for MUD

Even in those fortunate enough to have an identified MUD when a matched sibling is not available, delays to transplant are frequent and problematic, as procuring a MUD may take additional weeks or months due to donor availability, donor attrition from personal, psychosocial, or medical issues. (17-19) Such delays can result in disease relapse or administration of additional consolidation chemotherapy that may produce additional toxicities, potentially abolishing transplant eligibility or increasing risk of subsequent transplant-related mortality (TRM). (17, 20)

Moreover, registry data show that additional cytarabine consolidation for AML in first remission prior to transplant does not confer a benefit, further justifying moving to transplant quickly. (21) Alternatively, it is possible that patients who undergo one cycle of consolidation and are able to proceed to HCT are a select group, as patients with early relapse or toxicity from consolidation do not move to transplant. Therefore, equivalent results intimate a benefit among those transplanted without consolidation, as the "rapid transplant" group likely includes patients at higher risk of relapse or toxicity.

Furthermore, outcomes may suffer with delays. Craddock et al. performed multivariate and univariate analyses on factors impacting overall survival in 168 patients with primary refractory acute myeloid leukemia between 1994 and 2006. (22) They found time to transplant to be the only manipulable factor to impact outcome after unrelated donor transplantation in primary refractory AML.

The untoward consequences of delayed transplant are amplified for older adults with hematologic malignancies, particularly AML. Disease free survival hovers around 8-9 months in older AML patients despite intensive induction, and standard consolidation chemotherapy has no clear benefit in AML patients 60 years and older who have achieved remission, making allogeneic stem cell transplantation the only known curative treatment. (23) Due to shorter relapse-free intervals, ability to move more quickly to transplant in eligible older individuals could be quite beneficial.

2.6. Alternative Donors

Increasing availability of and experience with alternative donor sources such as haploidentical related donors and umbilical cord blood units has expanded access substantially. Umbilical cord blood (UCB) boasts less stringent HLA matching requirements, good graft-versus-leukemia effects, and low rates of GVHD. (24-26) In their recent report, Gragert et al. reported that while few in US registry searches had an HLA 6/6 matched umbilical cord blood (UCB) unit, UCB units mismatched at one or two HLA loci were available for almost all patients < 20 years of age and for more than 80% of those > 20 years of age, regardless of race or ethnicity. (16) All together, this suggests that most patients who would benefit from SCT are likely to find a suitable donor with recent advances.

Advantages of UCB units include no risk to the donor (mother and fetus) and ready availability due to storage at cord banks. Barker et al. retrospectively reviewed their adult and pediatric transplants at their institution over one year and found that the median time required to obtain an unrelated donor (URD; from formal search to clearance of a donor) was 49 days (range, 32-293 days) compared to only 13.5 days (range, 2-387 days) for an UCB unit (from formal search to donor unit chosen). (27) In patients who underwent both UCB and URD searches, it took 29 more days (95% confidence interval 21-37 days) to identify and clear an URD compared with a UCB unit ($p<0.01$).

A preliminary review of all allogeneic stem cell transplants at the University of Chicago Medical Center (UCMC) during 2013 and 2014 supports these findings, with median time from search to transplant 66 days for UCB and 86 days for unrelated peripheral blood stem cells or bone marrow in 2013, and 53 and 82 days, respectively, in 2014. [unpublished data].

However, UCB's relatively low cell doses are associated with delayed engraftment and slow immune reconstitution, which contribute to heightened early transplant related mortality (TRM). Various studies have compared MUD to cord blood transplant. For example, comparing AML at high risk by cytogenetics in first remission, cord blood transplantation and MUD donors had equivalent outcomes. (28)

2.7. Alternative Donors in Older Adults

Cord blood and haploidentical transplantations have increasingly been paired with reduced intensity conditioning and applied to older adults. Observational data from the registry comparing patients 50 years and older with AML in first remission showed outcomes with MUD were better than unrelated cord blood units. (29) However, in the absence of a MUD, UCB transplant can provide extended survival, and with less frequent chronic GVHD, which is of particular value in older patients. Alternative donor outcomes are improving rapidly and ready availability has prompted some centers to proceed directly to UCB or haploidentical transplant instead of MUD, rather than reserving alternative donors only for when no MUD is available, particularly for acute leukemias where time is of the essence.

To our knowledge, this strategy has never been prospectively tested.

2.8. Haplo-Cord Approach

The University of Chicago Medical Center (UCMC) and Weil Cornell Medical Center (WCMC) groups have advanced an approach to overcome UCB limitations by combining a single cord blood unit with relatively low total nucleated cell (TNC) dose of 1.0 x 10(7)/kg compared to the traditional requirement of 2.5 – 5.0 x 10(7) TNC/kg, by co-infusing G-CSF mobilized ex vivo CD34 selected haplo-identical cells. Early engraftment of the haplo-identical cells essentially protects the patient against prolonged cytopenias until the UCB cells eventually engraft and predominate in hematopoiesis and immune function. This platform incorporates reduced-intensity conditioning and thymoglobulin pre-transplantation, achieving fast engraftment, low rates of acute and chronic GVHD, acceptable risks of opportunistic infection, and promising long-term outcomes in adults, including older adults. (30) UCMC and WCMC are now testing approaches with cord doses as low as 0.5 x 10^7 TNC/kg, opening a larger menu of available cords. This allows for more refined cord blood selection, such as with allele level matching at 8/8 loci, non-inherited maternal antigen matching (clinical trial in progress), and optimizing non-HLA parameters such as cell viability.

2.9. Patient Selection and Geriatric Selection

As the majority of allogeneic transplants occur in patients 50 years and older, adjusting for health conditions in select patients who undergo transplant has always presented challenges for observational and even prospective studies. While disease features and donor type can be well-characterized, validated health measures have now been established in the transplant setting.

Comorbidity, as measured by the hematopoietic-cell transplantation-comorbidity index has become an established tool to gauge comorbid conditions and predict transplant related mortality

and overall survival. (31) Additional prognostic information can be obtained using a Geriatric Assessment. Our group has shown in patients 50 years and older, the importance of other factors, including pre-transplant c-reactive protein, functional status as measured by instrumental activities of daily living (7 questions reported by patients on their ability to function day to day without help), and possibly self-reported physical and mental function. (4, 5) Such information also provides invaluable data when comparing groups where drop-out may occur after randomization, as will occur in this study.

2.10. Rationale for this Study

Pursuing UCB transplant in patients who have potential unrelated donors identified has benefits. First, these patients will have more common haplotypes, as having potential unrelated donor matches (done by an initial computer search), and render them more likely to have better matched cord blood units relative to those without a potential MUD. Data support finding the optimal HLA matched cord blood unit based on data from Eapen and colleagues showing better allele level matching in cord blood units, similar to MUD, reduced transplant related mortality. (32)

We hypothesize that planning for a haplo-cord approach immediately relative to pursuing an 8/8 MUD will: 1) reduce time to transplant, 2) increase the proportion actually proceeding to transplant, and 3) subsequently improve outcomes through both more rapid transplantation and finding well-matched cord blood units. This could be of particular value for older patients where consolidation chemotherapy affords no clear benefit and relapse and clinical deterioration readily occur during transplant delays.

2.11. Conditioning Regimens

Allogeneic transplant requires pre-infusion conditioning chemotherapy and/or radiation to suppress host immune cells to facilitate engraftment and control residual hematologic malignancy. Historically, standard conditioning regimens not only caused myelosuppression, but extra-medullary toxicities to the gut, liver and lungs which may be prohibitive in less fit and/or older adults. Reduced intensity regimens employ less myeloablative regimens with parallel reduction in extra-medullary toxicities, and have promoted allogeneic HCT in older and less fit adults. The optimal regimen has not been established although fludarabine is commonly combined with an aklyating agent (e.g., melphalan or busulfan at various doses). The dose range of busulfan varies considerably, but higher myeloablative doses may be safely used with therapeutic drug monitoring to avoid excessive busulfan exposure and toxicity. (33) We have successfully incorporated two regimens at the University of Chicago: 1) fludarabine and melphalan at 140 mg/m2 and 2) fludarabine and IV busulfan once daily for four days to achieve a target AUC of 4800 umol/min/day (34, 35) for matched related and unrelated donor transplants, and primarily fludarabine and melphalan for haplo-cord transplants. (30)

2.12. T-cell Depletion

Graft-versus-host disease persists as one of the most dreaded complications of allogeneic transplant. T-cell depletion reduces risks of graft-versus-host disease, but at the possible expense of higher rates of infection and disease recurrence. (36-38)

In vivo T-cell depletion is most commonly accomplished by use of polyclonal anti-T cell antibodies, such as anti-thymocyte globulin (ATG), although the exact mechanism and optimal dosing remain areas of active research. Myeloablative transplant with unrelated donors may benefit in GVHD-free survival after ATG. (39) In reduced-intensity unrelated donor transplantation, observational data shows contradictory conclusions. In some studies, a possible detriment was found, while others showed reduction in GVHD with minimal or no effect on relapse. (38, 40, 41) A recent prospective randomized study from the Canadian Bone Marrow Transplant Group shows reduction in GVHD without impact on relapse rates in both myeloablative and RIC regimens (Walker I, ASH 2014, Abstract 38)

In cord blood series, data are particularly limited and observational in nature. In general, ATG appears to confer reduced risk of acute GVHD, but with possible greater risk of infection and EBV driven PTLD. (42-45)

We believe that reducing the risk of acute if not chronic GVHD is essential to successful transplantation in the growing population of transplant candidates and improves long-term quality of life. This can be accomplished by way of ATG for *in vivo* T-cell depletion. However, careful attention must be paid to prevent infection with aggressive prophylaxis and monitoring of CMV, EBV, and other infections, which are cornerstones to the allogeneic stem cell transplant program at our institutions. Absent clear data on whether T-cell depletion is beneficial or not, we believe a standardized approach in this study employing similar conditioning regimen and supportive care not only will facilitate comparisons, but will also allow standardization of patient care to optimize outcomes in both arms.

2.13. Limitations.

There may be reluctance to randomize subjects to a haplo-cord transplant when they have potential matched unrelated donors. However, our retrospective data preliminarily show no difference in outcomes after MUD and haplo-cord HCT for all hematologic malignancies in a joint analysis by the WCMC and UCMC recently (Rhodes J et al, ASH 2014). Other alternative donor sources exist, such as haploidentical. The WCMC and UCMC have developed considerable expertise in the haplo-cord approach. How haplo-cord transplantation fares relative to MUD is an important question. This can most easily be studied by randomization at time of transplant. However, we do not favor this approach for several reasons. First, one of the main benefits of haplo-cord is ready availability, and thus, study designs must account for this as survival from time of donor search is most important from a patient perspective. Secondly, a transplant requires considerable planning and cost in the donor search phase. The earlier the intended donor is identified, the more likely an optimal donor will be secured. Finally, this study is not powered to be definitive and will require a validation should the results show sufficient promise.

3. PATIENT SELECTION

3.1. Inclusion Criteria for Search Phase

1. Diagnosis of acute myeloid leukemia (AML) or high or very high-risk MDS by international prognostic scoring system revised for whom transplant is recommended

2. 18 years of age or older

3. Subject is likely to be considered for allogeneic transplant in the opinion of the transplant physician (based on age of patient, health, cytogenetics, and/or molecular characteristics).

4. Karnofsky Performance Status (KPS) >/= 70% at time of enrollment. An exception will be made for those with lower KPS at enrollment with an acute worsening that is likely to resolve in the treating physicians judgment (e.g., reversible infection, trauma, medication reaction, etc)

5. Ability to understand and the willingness to sign a written informed consent document for the Search Phase.

6. Patient willing to consider HCT

7. A preliminary search has identified:
   a) An appropriate minimum 4/6 matched umbilical cord unit at intermediate resolution at HLA-A and B, and high resolution at HLA-DRB with a cell dose above 1 x 10(7) TNC/kg for a single umbilical cord blood (UCB) transplant AND
   b) At least one potential 8/8 HLA-matched (HLA-A, -B, -C, and –DRB1) unrelated donor with a probability of 70% AND
   c) Availability of a potential related haploidentical donor.

3.2. Exclusion Criteria for Search Phase

1. Prior formal search was instituted

2. Diagnosis of acute promyelocytic leukemia (APL)

3. Known HLA matched related donor without contraindications to donate

4. Life expectancy severely limited by concomitant illness or uncontrolled infection

3.3. Inclusion Criteria for Transplant Phase

It is recognized that only some subjects will undergo transplant.

1. High-risk AML for which transplant is recommend based on cytogenetic, molecular and morphologic features. Patients must meet institutional standards for disease control prior to transplant.

2. For MDS. IPSS-revised criteria of high or very high at diagnosis.

3. Subject meets institutional criteria for transplant and has acceptable organ and marrow function as defined below:

a) Serum bilirubin < 2.0mg/dL unless Gilberts disease
b) Creatinine Clearance > 45 mL/min.1.73m2 as estimated by modified MDRD equation
c) Left ventricular function 40% or greater
d) DLCO corrected for hemoglobin >50%
e) KPS 70% or greater

4. An adequate graft for the defined donor type
   a) Haplo-cord requires a haploidentical adult donor of 14 years of age and at least 50 kg, and a cord blood unit with at least 1.0 x 10(7) TNC/kg and a match of at least 4/6 by intermediate resolution for HLA-A and B and high resolution at DRB1. Donor provides standard of care consent for harvest following institutional policy. Any donor samples or donor research data would be obtained on separate donor research protocol.
   b) For MUD requires a 7/8 or 8/8 HLA matched unrelated donor with high resolution matching at HLA-A, -B, -C, and DRB1. DP matching or DP permissive should be achieved when possible using T-cell epitope strategy.

5. Written informed consent for the transplant phase

3.4. Exclusion Criteria for Transplant Phase

1. Life expectancy severely limited by concomitant illness or uncontrolled infection

2. HIV-positive

4. ENROLLMENT, RANDOMIZATION, AND REGISTRATION

4.1. Enrollment and Randomization

Subjects at the University of Chicago (UCMC) and at the Weill Cornell Medical College (WCMC) will be enrolled simultaneously to reach the end goal of about 180 total subjects across both sites for the Search Phase of the trial. Other sites may be asked to participate in the future.

The study's biostatistician at the University of Chicago will provide the study randomization table, eligibility checklist will be completed for each subject, a study ID will be given, and the study arm assigned.

4.2. Central Patient Registration

Subjects will be centrally registered with the University of Chicago (UCMC), Division of Hematology and Medical Oncology Clinical Research Office. To register a subject, fax the following documents to the Clinical Research Office at 773-834-0188:

- UCMC Subject registration form

- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Eligibility checklist signed and dated by investigator and research nurse

Central registration information is reviewed and entered into the Hem-Onc centralized research database. Emailing of eligibility to the study PI and staff are acceptable.
PI email: aartz@medicine.bsd.uchicago.edu

5. STUDY DESIGN

5.1. General Organization

A. Search Phase

Subjects with AML or high risk MDS, who may benefit from HCT based on the treating physician's recommendation, ages 18 years and older, with adequate performance status, will be eligible. Those for whom a preliminary computer search identifies a potential matched unrelated donor (MUD; 8/8 match with at least 70% probability of matching) and a potential umbilical cord blood unit (at least 4/6 match with at least 1.2 x 10(7) TNC/kg), who also have a potential haploidentical donor, will be eligible for enrollment. It is encouraged prior to registration, to HLA type available siblings to exclude such patients from the time and effort of formal search if a sibling match is available. Having children, parents, or full-siblings who have no known health contraindications, even prior to HLA typing, will be considered evidence of a potential haplo-identical donor. Subjects will be randomized 1:1 to proceed with planning for a MUD or a haplo-cord HCT. For those where an HLA sibling or other HLA matched related donor are later found, they will be removed from additional study procedures and only be followed to determine if they undergo transplant.

B. Transplant phase

A second registration will occur for those who proceed to transplant in the Transplant Phase of this study. Due to attrition from health impairments, identification of a related donor, lack of a reasonable donor, and lack of disease control, we expect considerable drop-out of 50% or more from the Search Phase prior to the Transplant Phase. Patients will be removed from study if greater than 1 year has elapsed from enrollment after search phase without a transplant unless permission from the PI is granted. We expect accrual of 180 subjects over a course of two years at two institutions in the Search Phase to achieve 96 patients who pursue HCT in the Transplant Phase. Enrollment will continue until 96 patients have pursued a MUD or haplo-cord HCT on study. If this requires more than 180 subjects to be recruited, an amendment will be submitted for additional recruitment.

Eligible subjects who enrolled on this study and are pursuing transplant will be encouraged to consent to the transplant phase on this study. Consent with details specific for each donor source is warranted and will not be confirmed until the time of transplantation. Additionally, correlatively samples will be requested warranting a second consent. Patients will be eligible for transplant regimens and post-transplant maintenance as long as ATG is included in the regimen. For subjects randomized to the haplo-cord arm who subsequently do not have an adequate haploidentical donor or umbilical cord blood unit, a MUD approach will be pursued if available.

Likewise, subjects randomized to the MUD search arm may proceed with a 7/8 MUD or another donor source for transplant such as haplo-cord if no MUD can be procured. Should subjects not consent on this protocol but pursue transplant, the data on stem cell source and outcomes will be captured.

5.2. Search Evaluation

Subjects will present for a Screening Visit. After it has been established that the subject has consented, is confirmed to be eligible for search phase, he/she will be assigned a study number and be "randomized" by REDCap into one of the study groups: Arm A - the haplo-cord group or Arm B - the matched unrelated donor (MUD) group. The donor search will then proceed quickly to identify the best donor following the above criteria and initiate institutional standards for potential transplant recipients without delay. The intent of this protocol is to identify donors and prepare patients for transplant as quickly as possible.

Pre-transplant testing:
The following items are considered standard evaluations for transplant eligibility and should be determined within 12 weeks before initiation of conditioning therapy, unless otherwise noted to determine transplant eligibility. They are not required to enroll in search phase.

The following tests are required unless otherwise specified below:

1. Medical history, physical examination, vital signs, height and weight.
2. KPS (Karnofsky Performance Score)
3. Complete blood count (CBC) with differential and platelet count, serum creatinine, bilirubin, alkaline phosphate, Cytomegalovirus (CMV) antibody test *
4. Infectious disease and hepatitis panel (HepAAb, HepB Sab, HepB Sag, HepB Core Ab, HepCAb), herpes simplex, syphilis, HIV and HTLV 1 antibody, & varicella zoster virus.*
5. Immunoglobulin levels
6. High resolution HLA typing (at any time per institutional policy)
7. Electrocardiogram (ECG), and left ventricular ejection fraction or shortening fraction,
8. Diffusing capacity of the lung for carbon monoxide (DLCO), Forced Expiratory Volume in One Second (FEVI)
9. Bone marrow aspirates for pathology and cytogenetics and/or biopsy
10. Beta-HCG serum pregnancy test for females of childbearing potential
11. Chest CT preferred or chest radiograph
12. Peripheral blood for pre-transplant restriction fragment length polymorphism (RFLP) analysis to establish a reference profile of host hematopoiesis*
13. HLA antibody testing (panel reactive antibody)*

*within 24 weeks of planned transplant.

5.3. Conditioning Regimens

Two conditioning regimens will be utilized. The fludarabine-melphalan-ATG regimen is preferred for adults 55 years and older, KPS 80%, and/or HCT-CI score or 4 or more. For those

under 55 years of age, or particularly fit patients up to 65 years of age (e.g. comorbidity score < 3 and KPS 90% or more), the fludarabine-busulfan-ATG regimen may be used.

Fludarabine-Melphalan and ATG:

Day	-7	-6	-5	-4	-3	-2	-1	0	1
Fludarabine (mg/m2)	30	30	30	30	30			Haplo[2] or MUD	Cord
Melphalan [1] (mg/m2)						140			
rATG (mg/kg)			1.5		1.5		1.5		
TBI* (cGY)						200	200		

Fludarabine-Busulfan and ATG:

Day	-7	-6	-5	-4	-3	-2	-1	0	1
Fludarabine (mg/m2)	30	30	30	30	30			Haplo[2] or MUD	Cord
Busulfan[3] (mg/kg)		3.2	3.2	3.2	3.2				
rATG (mg/kg)			1.5		1.5		1.5		

[1]In patients at high risk for graft rejection (i.e., donor-specific HLA antibodies, or those who have not received cytotoxic chemotherapy in the 3 months prior to conditioning), the treating investigator may use total body irradiation (TBI) for 2 doses at 200 cGy to reduce the risk of graft failure in the reduced intensity arm. TBI days may be modified from day 0 prior to stem cells to start day -4 to account for scheduling but should be two consecutive days.
[2]Haplo-identical grafts will be CD34+ selected by Miltenyi Device. When possible, grafts should be administered without cryopreservation.

[3]Recommended to achieve an AUC of goal of 4800 mcmol/minute/day +/- 20%. The last day of busulfan may be moved to day -2 and a test dose may be used to achieve desired ablative AUC. The dosing of 3.2 mg/kg is recommended dose prior to obtaining therapeutic drug levels or if no drug levels are obtained for adjustment. Anti-seizure prophylaxis is required Levetiracetam 1000 mg po BID is recommended starting 12 hours before the first dose of busulfan and continuing for 48 hours after the last dose. Clonazepam 1 mg po TID starting 12 hours before busulfan and continuing for 24 hours after the last dose of busulfan is the recommended alternative

DRUG INFORMATION:

Fludarabine: 30 mg/m2 /day intravenously x 5 days total dose 150 mg/m2. Fludarabine will be dosed according to actual body weight.

Melphalan: 70mg/m2/day intravenously x 2 days or 140 mg/m2 x 1 day. Melphalan will be dosed according to actual body weight. Cryotherapy with ice chips will be administered to prevent mucositis.

Busulfan:. 3.2 mg/kg/day intravenously x 4 days. This will be dosed on actual body weight. Therapeutic drug monitoring is recommended to achieve a target an AUC of 4800/day +/- 20% for each day on average, which will be considered equivalent to 3.2 mg/kg/day. Anti-seizure prophylaxis is mandatory.

Rabbit ATG (rATG): 1.5 mg/kg/day intravenously x 3 days, total 4.5 mg/kg. ATG will be dosed according to actual body weight. The first dose will be infused over at least six hours, and subsequent doses over at least 4 hours. Pre-medications include acetaminophen 650 mg by mouth, diphenhydramine 25-50 mg by mouth or intravenously, and methylprednisolone 2 mg/kg (1 mg/ kg at the initiation and 1 mg/kg half-way through anti-thymocyte globulin administration).

Circumstances may require minor changes in scheduling of chemotherapy. Variations of up to 24 hours in scheduling will be acceptable.

5.4. GVHD Prophylaxis

Tacrolimus: 0.03 mg/kg/day using continuous intravenous infusion over 24 hour time period or equivalent given as a 3 hour infusion every 12 hours from Day -2 until engraftment or when subject is able to take by mouth, then tacrolimus approximately 0.09 mg/kg by mouth in 2 divided doses. Tacrolimus should be given at full dose to maintain levels of 5-15 ng/mL through Day 180, tapered by 20% every week thereafter. We recommend a level of 10-15 until engraftment. Infection, toxicity or other clinical circumstances may prompt earlier discontinuation. In the presence of GVHD, a clinical decision by the attending physician will determine if tacrolimus can be tapered or should be continued. PO tacrolimus can be used in the pre-engraftment period when IV access for tacrolimus is not available.

Mycophenolate Mofetil (MMF): Will be started on Day -2 and given at a dose of 1000 mg every 8 hours until Day 28. Infection, toxicity, very low patient weight (< 50kg) may prompt earlier discontinuation or adjustment of doses.

Alternative GVHD prophylaxis: Should tacrolimus require discontinuation in the first 100 days without ability to restart it, it is strongly encouraged to use another agent such as sirolimus or cyclosporine A.

5.5. Supportive Care

Format: Supportive Care Schedule for CMV seropositive patients and/or seropositive MUD or haploidentical donors.

Admission to Day -2	Day -1 until engraftment	Engraftment until Day 210	Day 210
Ganciclovir 5mg/kg IV every 12 hrs	Acyclovir 500mg/m^2 IV every 8hrs (or equivalent IV)	Valaciclovir 2gm by mouth four times per day	Acyclovir 400 mg by mouth two to three times per day (or equivalent IV)

Changes and incorporation of alternative medications, unless dictated by clinical circumstances (side-effect, intolerance, failure, contra-indication), require discussion with the Principal Investigator.

- For patients who are not at risk of CMV (i.e, seronegative recipient and seronegative MUD) an alternative CMV strategy of acyclovir alone is acceptable. Cord blood is considered at low risk for CMV unless specific testing of CMV virus is available.
- Cytomegalovirus (CMV) monitoring at least weekly until Day 100 and at least monthly until Day 180 regardless of donor/recipient CMV status. We recommend at least monthly monitoring if on immune suppression past day 180 or more often if prior CMV reactivation.
- A prophylactic broad-spectrum antifungal with anti-mold activity is strongly recommended.
- Other infection prophylaxis and supportive care will be as per institutional unit policy.
- All subjects, regardless of disease histology will receive filgrastim (G-CSF) 5 mcg/kg (rounded to 300 mcg or 480 mcg, depending on subject weight) SQ daily starting day + 1 to day + 5 until ANC >1000/uL.
- Blood transfusions should follow institutional policies.
- Epstein-Barr virus (EBV) monitoring:
    - EBV monitoring at least weekly until Day 100 and at least monthly until off immune suppression is required.
    - Rising EBV titers should warrant investigation for an EBV post-transplant lymphoproliferative disorder (PTLD).
        - Evidence of PTLD or consecutive increases in EBV polymerase chain reaction should lead to treatment with rituximab.
- Donor specific antibodies: Patients with donor DSA in high titers may undergo therapeutic procedures prior to transplant in order to reduce DSA levels. Such treatments may include but are not limited to: bortezomib, intravenous immunoglobulins, rituximab and plasma exchange.
- Cytoreduction for those not in remission. Patients may receive pre transplant treatments meant for disease reduction or disease sensitization. This may include, but is not limited to clofarabine and hypomethylating agents.

All aspects of care will be identical between the two groups, except for the choice of donor.

Patients may participate in investigational drug studies to prevent infection or preventing relapse unless they interfere with time to transplant or engraftment after transplant. Interventional studies designed primarily to mitigate GVHD are prohibited.

6. TRANSPLANT STEM CELL SOURCE AND CELL DOSE

All recipients should be tested for Panel Reactive Antibody (PRA) for Class I and Class II HLA antibodies. If antibodies are present, the donor should be chosen whose antigens are not targeted by antibodies present in the recipient (donor specific antibodies; DSA) if possible. This may require DQ and DP testing of the donor.

6.1. Haplo-cord

Umbilical Cord Blood (UCB) Unit
The UCB unit must supply a minimum of 1.0 $x10^7$/kg pre-cryopreserved total nucleated cell dose. The unit must match at a minimum of 4 of 6 at HLA-A, -B, -DRB1 loci with the recipient. This may include 0-2 antigen mismatches at each A or B (at the antigen level) or DRB1 (at the allele level) loci. The optimal cord unit will be identified by high-resolution matching at 8/8 HLA loci, similar to unrelated donors taking preference for the cord blood unit that contains an adequate cell dose and the fewest mismatches. (32) Cord viability should be 85% or more by tryphan blue or flow cytometry post-processing from the cord bank.

Third Party Donor
The preferred 3rd party donor will be a young HLA haplo-identical relative. After appropriate evaluation per transplant program criteria, the donor will receive G-CSF (filgrastim or equivalent) 5 mcg/kg subcutaneous two times per day or 10 mcg/kg subcutaneous daily for four to five consecutive days (doses rounded to the nearest vial size). Apheresis will start on the morning of the fifth day and proceed until sufficient cells have been collected following institutional policies and procedures. Scheduling may require collection on day 4 or 6.

The use of pediatric donors is restricted to donors who are 14 years and older and weigh more than 50 kg. After collection and prior to cryopreservation, cells will be T-cell depleted using the Milteny Clinimax® depletion device. The target will be to obtain a product containing less than $1x10^4$CD3+ cells per kg of recipient body weight and no more than $5x10^6$/kg CD34 positive cells. The haplo-identical unit may be cryopreserved if required for logistical reasons.

6.2. Matched Unrelated Donor

Matched unrelated donors will be sought through the National Marrow Donor Program. Suitable donors will match at a minimum at HLA-A, -B, -C, and –DRB1 at high-resolution, which has been shown to maximize post-transplantation survival. HLA-DQ matching is encouraged and DP permissive matching using a T-cell epitope (TCE) strategy is strongly encouraged.

Peripheral blood or bone marrow harvests will be acceptable.

6.3. Infusion of Cells

The infusion of UCB and the haplo-identical units will be separated by at least 1 hour and preferably will occur on successive days (Day 0 and Day 1). The haplo-identical unit is preferred, but not required, to be infused first.

An emergency second cord may be given in the haplo-cord arm under extenuating circumstances: post-thaw cord viability exceptionally low, HLA matching show that incorrect unit or less matched unit was found, or <1.0 x 10(7) TNC/kg was able to be infused due to illness or infusion reaction.

MUD infusion: The MUD infusion may occur on day +1 (1 day after planned infusion) when products arrive late or require processing. This will not be considered a deviation.

6.4. Prior to Transplant

Patients must consent a second time to undergoing transplant in the Transplant Phase of the study. Because transplant has considerable toxicities, a dedicated second consent at the time of transplant is optimal to ensure patients are aware of and comprehend the risks and the pre-transplant evaluation has been completed to properly advise patients of their specific risks. This evaluation may include the following.

1. Additional testing prior to transplant for patients 50 years and older: modified Geriatric Assessment (Demographics, Patient reported Karnofsky PS, falls, weight loss, hematopoietic-cell transplantation-comorbidity index, OARS comorbidity, OARS IADL, OARS physical activity, MHI-17, caregiver support, social activity, blessed orientation memory concentration, grip strength and 4 meter walk speed)
2. Short-form MOS-36 Quality of Life survey (SF-36)

Should patients or clinicians not pursue transplant on study, their choice will be documented along with the reason. These patients will still be followed for overall survival and if they do eventually undergo transplant off-protocol.

Reasons to not to pursue transplant may include:

1. Death
2. Impaired disease control
3. Impaired patient health, making transplant risks too great
4. Inability to find a donor
5. Patient preference
6. Clinician decision not listed above
7. One year elapsed since time of search

6.5. Post-Transplant Evaluations

The follow-up schedule for scheduled study visits is outlined in Table 1 below.

Table 1

Study Visit	Target Day Post-Transplant (Day 0)
4 week	28 ± 5 days
7 week	56 ± 7 days
100 days	100 ± 7days
6 month	180 ± 28 days
12 month	365 ± 28 days
24 months	730 +/- 56 days
36 months	3 yrs +/- 90 days

6.6. Study Calendars

Table 2. Study calendar for Search Phase

Exam	Baseline
Physical exam, height, weight, and KPS performance status	X
Geriatric Assessment (GA) for pts 50 and older*	X

* See Appendix B for GA tools

Table 3: Transplant Phase including pre and post-transplant testing
The follow-up schedule for scheduled study visits is outlined in Table 1 and tests also noted in section 5.2 Institutional transplant work up guidelines may demand additional testing.

Exam	Baseline**	Day 28	Day 56	Day 100	Day 180	Day 365 and 730
Physical exam, height, weight, and KPS performance status	X	X		X	X	X
GVHD and other morbidity assessments[5]		X		X	X	X
Geriatric Assessment (GA) for pts 50 and older[7]	X					
Short-form 36 Quality of Life (SF-36)	X	X		X	X	X
Toxicity assessments	X	X		X	X	X
Electrocardiogram	X					
Infectious disease titers[3]	X					
Chest CT or chest x-ray	X					
LVEF, or shortening fraction	X					

Exam	Baseline**	Day 28	Day 56	Day 100	Day 180	Day 365 and 730
DLCO corrected, FEV 1 and FVC	X					
High Resolution HLA typing	X					
B-HCG serum pregnancy test (pre-menopausal females only) within 4 week of conditioning	X					
CBC[1] , differential, platelet count, and blood chemistries[2]	X	X		X	X	X
CMV and EBV PCR Titres[6]	X	X	X	X	X	X
Bone marrow biopsy and aspirate for pathology	X	X		X	X	X
Chimerism	X	X	X	X	X	X
Lymphocyte Subsets and Ig Levels	X	X		X	X	X
HLA Antibodies	X					
Correlative assays [4, 5] BM/PB	BM/PB	BM/PB	PB	BM/PB	BM/PB	BM/PB

Note:
*The exact day of the tests is approximate. Tests can be scheduled several days before or after. See table 1 for windows of testing.
**Baseline tests: see also section 5.2

1. CBC performed at least three times a week from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28. CBC performed approximately weekly after Day 28 until 12 weeks post-transplant.
2. Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly if possible until Day 28. Blood chemistries performed weekly if possible after Day 28 until day 100 post-transplant.
3. Infectious disease titers include: CMV, Hepatitis B and C (HepBSAb, HepBSAg, HepB Core Ab, HepCAb), syphilis, HIV, toxoplasmosis, and HTLV antibody
4. Correlative Assays may include studies of immune reconstitution, novel prognostic factors, or minimal residual disease assays.
   a) BM: bone marrow: 10 cc green top from marrow. If unavailable, sample may be drawn from PB
   b) PB: Peripheral blood. 10 cc serum/plasma red top.
5. Recommended, not required.

6. Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) monitoring at least weekly until Day 100 and at least monthly until off immune suppression.
7. Geriatric assessment. Involves patient report questions and bedside testing by health care professional (appendix B for complete list). This may be performed by electronic survey through REDCap or paper for patient reported instruments). The GA administered during search phase will be used. However, GA may be repeated if additional chemotherapy consolidation has been given since the initial GA was administered, clinical change in status and/or 3 months have elapsed since initial GA prior to transplant conditioning.

7. ADVERSE EVENTS MONITORING AND REPORTING:

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, and may require investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

7.1. Investigational Risks

See consent form. There are no known side-effects related to the use of the Miltenyi CliniMacs device to select cells.

There are potential risks to undergoing hematopoietic stem cell transplantation using an alternative donor source, such as with a haplo-cord approach in this protocol, in comparison to stem cell transplantation using matched unrelated donors. Risks of using umbilical cord blood, which is the intended source of permanent engraftment, include late engraftment with resulting prolonged pancytopenia, increased risk of graft failure, and delayed immune reconstitution, infection, post-transplant lymphoproliferative disorder and increased treatment related mortality. {Eapen, 2010 #109;Laughlin, 2004 #111}(26)

For the unrelated donor arm, relative to haplo-cord, acute and chronic graft-versus-host disease may be greater and disease relapse may be greater. Time to transplant may be longer.

7.2. Definitions

7.2.1. Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes

in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 100 days after transplant.

7.2.2. Serious Adverse Event

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours (see below)
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.3. Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol (Section **Error! Reference source not found.**), informed consent, FDA-approved drug package insert(s). An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent.

Events related to transplant as described in Section 7.4 will not be considered unexpected.

7.2.4. Adverse Reactions

An adverse event is considered to be an adverse reaction if there evidence to suggest a causal relationship to the study agents. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

7.3. Adverse Event Characteristics

The National Cancer Institute Common Toxicity Criteria Scale (version 4.0) will be used to grade toxicities.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4. Protocol-Specific Expedited Adverse Event Reporting Exclusions

Many toxicities that are grade 3 by CTCAE are expected and routine for transplant. Toxicities are common following transplant. Therefore, only unexpected, grades 3-5 adverse events (AEs) will be reported via the expedited reporting mechanisms as defined in Section 7.6.

For this protocol only, the AEs/grades listed below do not require expedited reporting to the responsible parties listed Section 7.6. However, they still must be reported through the routine reporting mechanism.

Expected Grade 3 -4 Toxicities for Transplant (NOT SAE)	**Not Routinely Expected Grade 3-4 for Transplant (SAE)**
Fever after engraftment without a source requiring several additional hospital days	Intensive care unit admission
Fever/infection requiring IV antibiotics during neutropenia or related to catheter	Infection requiring a major surgical procedure
Confusion requiring additional monitoring in the room	Seizure
Atrial fibrillation or flutter or arrhythmias monitoring on the transplant floor	Arrhythmia requiring monitoring outside of the transplant unit, a pacemaker, or cardioversion
Electrolyte disturbances requiring IV repletion	
Poor nutrition requiring parenteral or enteral nutrition	
Acute or chronic GVHD	
VOD (for busulfan treated)	

7.5. Adverse Event Reporting Requirements

All Adverse Events must be reported in routine study data submissions. AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must also be reported in routine study data submissions.

7.5.1. Serious Adverse Event Reporting to the Coordinating Center

All serious adverse events except for those routinely expected due to transplant (as defined in sections 7.2.2 and 7.4) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Principal Investigator and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day.

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

7.6. Supportive Therapy and Other Investigational Drugs

Symptomatic care may be given as required with medications such as anti-emetics and analgesics, according to institution's standard operating protocols. Investigational drugs that may influence time to transplant, engraftment, or rates of GVHD are not permitted. It is anticipated patients may participate in supportive care studies such as treatment of GVHD, prevention or treatment of CMV etc.

8. CORRELATIVE/SPECIAL STUDIES

In addition to routine clinical tests, we will collect additional samples for possible correlative studies.

In addition to the standard immune reconstitution studies including lymphocyte subset panel 3 and quantitative immunoglobulin levels, an additional 10 cc heparinized (Green Top) from bone marrow (or blood if marrow not available) will be cryopreserved at each center. The samples will be batch shipped to the University of Chicago periodically. Samples will be shared with Weill Cornell to perform correlative studies. We anticipate several correlative studies.

A. Minimal Residual Disease Monitoring. The presence of minimal residual disease in myeloid leukemia or MDS may be assessed by monitoring of WT1 transcript levels in blood or bone marrow using a quantitative RT-PCR assay. Briefly, total RNA will be extracted from blood and bone marrow and cDNA synthesized using standard techniques. Amplifications of patient samples, K562 cell line cDNA, and no template controls will be performed in triplicate. WT-1 expression levels will be detected using a transcript specific primer and probe set. In order to compensate for differences in RNA integrity and cDNA synthesis efficiency, the absolute WT1 transcript copy number will be normalized to the endogenous control gene Abl.
B. Additional studies. There may be additional studies geared toward gaining a better understanding and predictors of disease relapse, GVHD, and immunologic activity of this strategy.

9. CRITERIA FOR STUDY EVALUATION

9.1. Time to Transplant

Time to transplant will be measured from time of date of formal request to stem cell infusion date. We will also capture time from preliminary search to both formal search and transplant date.

9.2. Proportion undergoing transplant

The proportion undergoing transplant in 3 months and 1 year from randomization will be captured. This will first be captured by transplant to assigned arm and to any transplant. The percent adherence to the assigned arm of those transplanted will be measured.

9.3. Leukemia Free Survival

Relapse will be recorded by the day of initial detection of malignant cells if these cells were on subsequent testing confirmed to be increasing in number or by unequivocal radiological progression. The diagnosis of disease recurrence will be based on clinical and pathological criteria.

9.4. Overall Survival

Overall survival will be recorded from day of enrollment until death by any cause. Overall survival from time of transplant in the transplant phase will also be captured.

9.5. Graft Failure

Primary graft failure day 28 will be defined as lack of neutrophil engraftment at day 28. Primary graft failure day 48 will be defined as lack of neutrophil engraftment at day 48
Secondary graft failure will be defined as lack of donor chimerism defined as <5% donor chimerism and an absolute neutrophil count below 500/uL .

9.6. Treatment Related Mortality

Treatment related mortality is considered any death that cannot be explained by persistence, relapse or progression of the underlying malignancy once the preparative regimen starts.

9.7. Time to Neutrophil Recovery

Neutrophil engraftment will be defined as the first day in which the ANC is > 500/mm^3 for three consecutive days. Time to neutrophil recovery will be recorded from the first day of donor cell infusion until neutrophil engraftment.

9.8. Time to Platelet Recovery

Platelet engraftment will be defined as the first day the platelet count is > 20,000/mm^3 without transfusion support for seven consecutive days. Time to platelet recovery will be recorded from the first day of donor cell infusion until platelet engraftment.

9.9. Acute GVHD

Acute GVHD will be scored according to the criteria proposed by Przepiorka et al. (Appendix A)

9.10. Chronic GVHD

Chronic GVHD will be scored according to the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease:
I. Diagnosis and Staging Working Report

9.11. Length of Stay

The length of stay will be defined as the number of days spent in the hospital between Day 0 and Day 100 after transplant. This will include time spent for readmissions.

9.12. Transfusion Support

The total number of transfusion episodes and the total transfused PLT and RBC units

10. CRITERIA FOR REMOVAL OF PATIENTS FROM STUDY

Disease Progression or Disease Persistence
Patients with progressive disease or relapse will be removed from protocol therapy and followed for survival.

Extraordinary Medical Circumstances
If, at any time, the constraints of this protocol are detrimental to the subjects' health and/or the subject no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Principal Investigator.
- Document the reason(s) for discontinuation of therapy in patient records.
- Follow the patient for survival, progression, relapse, and secondary malignancy

11. DATA REPORTING / REGULATORY CONSIDERATIONS

A. The University of Chicago or Weil Cornell Medical Center medical records will be utilized for all patients. Data will be entered into a data management file within 3 weeks after each evaluation of the patient. After the patient goes off treatment, follow-up information will be collected per the study calendar. .

B. Pathologic diagnosis and HLA typing will be recorded in a conventional way with a record being placed in the patient's permanent record and data management file. However, investigational correlative assay results will not be made part of the medical record.

C. Data and safety monitoring for this trial will be carried out in accordance with the University of Chicago Comprehensive Cancer Center Data and Safety Monitoring (DSM) Plan. Briefly, accrual, toxicity, and response data will be reviewed weekly at the transplant patient care conference for all patients enrolled at all centers. Adverse events will be reported to the principal investigator, IRB, and FDA as described in section 7. Decisions will be made regarding study continuation, amendment, or closure at the weekly meeting and a note will be signed by the principal investigator or his designee documenting this decision. External monitoring of accrual is performed by the Accrual Monitoring Committee.

D. In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority,

the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

12. STATISTICAL CONSIDERATIONS

Blocked randomization will be performed at each participating site with a 1:1 allocation ratio. Such randomization will allow for equal numbers of haplo-cord SCT and MUD SCT subjects to be enrolled at each participating site.

The primary endpoint is time to transplant, specifically from donor formal request until stem cell infusion. Time to transplant in the standard Arm A (MUD) is expected to be 87 days. The expected difference between the two arms is about 25 days (ie: time to transplant in the haplo-cord group will be about 25 days faster than in the MUD group).

Group sample sizes of 48 and 48 in the MUD and haplo-cord groups achieve 80% power to detect a difference of 25 days between the null hypothesis that both group means are 87 days, and the alternative hypothesis that the mean of the haplo-cord group is 62 days, with estimated group standard deviations of 43 and 43, and with a significance level (alpha) of 0.050000 using a two-sided two-sample t-test. Standard deviations of both groups is expected to be the same given relatively uniform regimens.

Assuming approximately 50% drop-out rate in those enrolled at the Search Phase due to inability to undergo transplant, prior to re-consenting for the Transplant Phase, this design will still have 80% power to detect the hypothesized difference in time to transplant between the two arms. We will budget for 180 subjects to achieve 96 total subjects (48 per arm)

Analysis Plan for Endpoints:
The primary endpoint in both treatment arms is time to transplant as measured from the date of formal donor request to the date of stem cell infusion. Standard deviations, means, and medians will be estimated for the time to event measures in both arms in a modified-intent to treat fashion. In other words, those who register for the Search Phase of the study, but who are eventually unable to proceed to transplant, will be excluded from analysis of the primary endpoint. However, they will retained for secondary analyses as discussed below.

Secondary endpoints include the proportion of patients who undergo transplantation by modified intention to treat in each arm. Group sample sizes of 90 in the MUD group and 90 in the haplo-cord group (before the 50% drop out expected prior to transplant) achieve 80% power to detect a difference between the group proportions of 0.2000. The proportion in the experimental haplo-cord group who successfully proceed to transplant is assumed to be 0.2000 under the null hypothesis, and 0.4000 under the alternative hypothesis. The proportion in the MUD group proceeding to transplant is estimated to be about 0.2000. The test statistic used is the two-sided Fisher's Exact test. The significance level of the test is targeted at 0.0500. We will summarize subjects who drop-out and primary reason (i.e, disease progression, ineligible due to health, patient defers, insurance denial, physician choice)

For those registered to transplant in the Transplant Phase, comparing the two graft sources is of considerable interest and will be analyzed by biologic choice (rather than by intent to treat by

randomization arm) MUD vs haplo-cord. We anticipate some patients, especially those randomized to MUD, will ultimately undergo haplo-cord. Occasionally, patients randomized to an immediate haplo-cord may pursue MUD. Specifically, we will compare acute toxicities including grade 3-5 non-hematologic toxicities, rates of full donor chimerism at day 100, overall survival, leukemia-free survival, non-relapse rates of aGVHD and cGVHD, days in the hospital and transfusion requirements within the first 100 days post-transplant.

Progression-free survival (time to relapse or death as a result of any cause) and overall survival will be computed using the Kaplan-Meier product-limit estimate and expressed as probabilities with a 95% CI. Acute and chronic GVHD, treatment-related mortality will be estimated by cumulative incidence method. Cumulative incidence of treatment-related mortality with relapse of the original disease as the competing risk factor will be calculated. In order to compare the cumulative incidence curves, we will use Gray's test. Log rank test will be used to compare the Kaplan Meier curves. Hazard ratios and appropriate confidence intervals will be estimated from Cox regression models. Multivariate models when needed will use Cox proportional hazards regression analysis.

13. DATA, SAMPLE AND PROTOCOL MANAGEMENT

- PROTOCOL COMPLIANCE: Subjects will be reviewed weekly during admission by the study investigators who will score the patient for standard endpoints. After discharge they will be reviewed at least once a month.

- DATA ENTRY: REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

- ACCURACY OF DATA COLLECTION The Study Chairman will be the final arbiter of toxicity should a difference of opinion exist

- Management of Research samples: Research samples will be cryopreserved after ficolling and isolation of viable cells. The serum will be stored separately. Part of the product may be stored after DNA extraction. The samples will be stored securely. They will coded with the key to identification of the samples kept in a secure location and available only to the PI or his delegate. Samples and appropriate clinical information may be shared with other investigators at WCMC and elsewhere, but will be de-identified. Samples will be kept indefinitely.

14. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) is not required. This protocol will undergo weekly review at the transplant program data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

15. REGULATORY CONSIDERATIONS

15.1. Institutional Review Board/Ethics Committee Approvals

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

15.2. Informed Consent Procedures

The Treating Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedure as per GCP's as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, patients will be fully informed as to the purposes and potential risks and benefits involved in this study. Patients will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

15.3. Protecting Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Subject names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell University, the Food and Drug Administration, or other study support such as the National Cancer Institute will be able to review subject medical records.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

15.4. Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Andrew Artz, MD at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

15.5. Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures

- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

15.6. Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter. The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

15.7. Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

15.8. Protection of Human Rights

Participation in this trial is voluntary. All subjects will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines.

Subjects will be eligible for this trial regardless of gender or racial/ethnic background.

16. APPENDICES

APPENDIX A

PRZEPIORKA CRITERIAFOR ACUTE GVHD

Consensus Criteria for Grading of Acute GVHD

Acute GVHD Assessment Worksheet

(Acute GVHD assessment should be completed at onset, on change of treatment or when GVHD resolves. Assessment should follow the CIBMTR guidelin

Patient Name_____ **MRN** _____

Immunosuppression therapy ☐Prograf_____ ☐ Steroids_____ ☐ Other _____

ORGAN /SYSTEM	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV
PERFORMANCE STATUS: ☐	☐ ECOG 0, KPS or LPS 100%	☐ ECOG 1, KPS or LPS 80-90%	☐ ECOG 2, KPS or LPS 70-80%)	☐ ECOG 3, KPS or LPS 60-70%)	☐ ECOG 4, KPS or <60%)
SKIN : (RASH) %BSA	☐ No rash	☐ Maculopapular rash on <25% BSA	☐ Maculopapular rash on <25% to 50%BSA	☐ Rash >50% with generalized erythroderma	☐ Stage 3 rash plus bullae and desquama
LOWER GI (DIARRHEA) : Stool volume _____mL	☐ ≤500mL/day or <280mL/m² per day	☐ 501- 1000mL/day or 280- 555mL/m² per day	☐ 1001- 1500mL/day or <556- 833mL/m² per day	☐ >1500mL/day or >833mL/m² per day	☐Severe abdominal with or without ileus
UPPER GI:	☐ No protracted nausea or vomiting	☐ Persistent nausea, vomiting or anorexia			
LIVER (BILIRUBIN) : _____mg/dL	☐ <2mg/dl or <34 µmol/L	☐ 2-3mg/dl or 34-52 µmol/L	☐ 3.1-6mg/dl or 53-103 µmol/L	☐ 6.1-15mg/dl or 104-256 µmol/L	☐ >15mg/dl or >256 µmol/L

Overall grading of acute GVHD

☐ GRADE I	☐ GRADE II	☐ GRADE III	☐ GRADE IV
Stage I or II skin involvement. No gut or liver involvement. Stage 0 or I performance status	Stage I gut with or without Stage I-II skin. Stage I liver GVHD with or without Stage I-II skin. Stage III skin without other organ involvement. Stage II performance status	Stage II-III liver or Stage II -IV gut or Stage III performance status	Stage IV skin rash Stage IV liver or Stage IV performance status w lesser organ involvement.

Appendix B

Geriatric Assessment Tools

	Patient Report (P), Health Care team (H)	Items
Demographic and baseline	P	6
Hematopoietic cell comorbidity index	H	17
OARS Comorbidity	P	15-30
MOS Physical function	P	10
4 meter walk speed	H	3
Grip strength	H	3
Timed up and go	H	1
Nutrition	P	3
KPS patient	P	1
KPS provider	H	1
Polypharmacy	P	1-10
MHI-17	P	17
MOS social Activity Limitation Scale	P	4
MOS social support	P	12
Blessed Orientation Memory Concentration	H	6
Survey feedback	P	7

Medical Outcomes Study (MOS)
OARS:Older American Resources and Services
IADL: Instrumental Activities of daily living

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