Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT SOURCES & MANIPULATION
Salt Lake City, UT
Monday, April 25, 2022, 12:15 pm – 1:45 pm

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1. **Introduction**
   a. Minutes from February 2021 meeting (Attachment 1)
   b. Biorepository Accrual Tables (Attachment 2)
   c. Introduction of incoming Co-Chair:
   Cara Benjamin, MD, PhD; University of Miami;
   E-mail: c.benjamin3@miami.edu; Telephone: (305) 243-5534

2. **Presentations, published or submitted papers**

   a. **GS18-04** Grunwald MR, Zhang M-J, Elmariah H, Johnson MH, St Martin A, Bashey A, Battiwalla M, Bredeson CN, Copelan E, Cutler CS, George BR, Gupta V, Kanakry C, Mehta RS, Milano F, Mussetti A, Nakamura R, Nishihori T, Saber W, Solh M, Weisdorf DJ, Eapen M. Alternative donor transplantation for myelodysplastic syndromes: Haploidentical relative and matched unrelated donors. ***Blood Advances. 2021 Feb 23; 5(4):975-983. doi:10.1182/bloodadvances.2020003654. Epub 2021 Feb 12. PMCID:PMC7903230.***
   b. **GS19-01** Wagner JE, Ballen KK, Zhang M-J, Allbee-Johnson M, Karanes C, Milano F, Verneris MR, Eapen M, Brunstein CG. Comparison of haploidentical and umbilical cord blood transplantation after myeloablative conditioning. ***Blood Advances. 2021 Oct 26; 5(20):4064-4072. doi:10.1182/ bloodadvances.2021004462. Epub 2021 Aug 30.***

c. **GS19-03** Orfali N, Zhang MJ, Allbee-Johnson M, Boelens JJ, Artz AS, Brunstein CG, McNiece IK, Milano F, Abid MB, Chee L, Diaz MA, Grunwald MR, Hematti P, Hsu J, Lazarus HM, Munshi PN, Prestidge T, Ringden O, Rizzieri D, Riches ML, Seo S, Solh M, Solomon S, Szwajcer D, Yared J, Besien KV, Eapen M. Planned granulocyte-colony stimulating factor adversely impacts survival after allogeneic hematopoietic cell transplantation performed with Thymoglobulin for myeloid malignancy. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.08.031. Epub 2021 Sep 8. Poster presentation, EBMT 2021.***

d. **GS20-01** O' Donnell PV, Brunstein CG, Fuchs EJ, Zhang M-J, Allbee-Johnson M, Antin JH, Leifer ES, Elmariah H, Grunwald MR, Hashmi H, Horowitz MM, Magenau JM, Majhail NS, Milano F, Morris LE, Rezvani AR, McGuirk JP, Jones RJ, Eapen M. Umbilical cord blood or HLA-haploidentical transplantation: Real world outcomes vs randomized trial outcomes. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.11.002. Epub 2021 Nov 11.***

e. **CV20-01** Hamadani M, Zhang M-J, Tang X-Y, Fei M, Brunstein C, Chhabra S, D'Souza A, Milano F, Phelan R, Saber W, Shaw BE, Weisdorf D, Devine SM, Horowitz MM. Graft cryopreservation does not impact overall survival after allogeneic hematopoietic cell transplantation using post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2020 Jul 1; 26(7):1312-1317. doi:10.1016/j.bbmt.2020.04.001. Epub 2020 Apr 10. PMCID:PMC7194895.***

3. Studies in Progress (Attachment 3)

a. **GS19-02** Graft Failure in MDS and Acute Leukemia Patients After Allogeneic Stem Cell Transplantation Receiving Post Transplant Cyclophosphamide (C Hickey et al) **Analysis**

4. Proposals

Future/proposed studies

a. **PROP 2110-79/ PROP 2110-125/ PROP 211-284/ PROP 2110-300** Outcomes for Haploidentical Transplantation using post-transplant cyclophosphamide for non-first degree relatives (K Poonsombudlert/ C Strouse/ P Munshi/ M Hamadani/ L Caroline Mariano Compte/ V Rocha/ S Mirza/ L Gowda) (Attachment 4)

b. **PROP 2110-113/ PROP 2110-248/ PROP 2110-340** Impact of donor source in second allogeneic hematopoietic cell transplant (HCT) in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020) (E Bezerra/ M Litzow/ I Amanam/ R Nakamura/ A Scaradavou/ C Lindemans) (Attachment 5)

c. **PROP 2110-250** Impact of CD34+ Cell Dose on Outcomes After Matched Sibling and Unrelated Donor Peripheral Blood Stem Cell Transplantation (M Umair Mushtaq/ M Shahzad) (Attachment 6)

d. **PROP 2110-301** Identifying the Optimal Stem Cell Dosing for Peripheral Blood Stem Cell Transplantation with Post-Transplant Cyclophosphamide (H Elmariah/N Benjanyan) (Attachment 7)

Future/proposed studies to be presented at the CIBMTR Collaborative Working Committee Study Proposals Session

e. **PROP 2110-50/ PROP 2110-317** Optimizing HLA Matched Sibling versus Alternative (Well-Matched Unrelated and Haploidentical) Donor Selection: Update Including Donor Age and HLA-DPB1 Match Status in Recipients of Allogeneic Hematopoietic Cell Transplantation (K Nath/ B Shaffer/ H Choe) (Attachment 8)

Dropped proposed studies

a. **PROP 2110-13** Microbial contamination of hematopoietic stem cell products and its impact on early transplant outcomes. A CIBMTR analysis. *Limited sample size and lower scientific impact relative to other proposals*
b. **PROP 2110-49** Clinical impact of Rh D antigen on allogeneic transplant outcomes: A retrospective CIBMTR analysis. *Concerns about availability of sensitivity data*
c. **PROP 2110-59** Trends in Graft Failure in Hematopoietic stem Cell Transplant Recipients. *Dropped due to lower scientific impact relative to other proposals*
d. **PROP 2110-91** Impact of cryopreservation of allogeneic peripheral blood stem cell grafts on outcomes in AML. *Overlap with recent publication*
e. **PROP 2110-110** HLA-haploidentical versus Mismatched Unrelated Donor Transplants with Post-transplant Cyclophosphamide based prophylaxis for Acute Leukemia and MDS. *Overlap with recent publication*
f. **PROP 2110-142** Comparison of Bone Marrow versus Peripheral Blood in Haploidentical Transplantation using Post-Transplant Cyclophosphamide. *Overlap with recent publication*
g. **PROP 2110-158** Outcomes of Patients Undergoing Haploidentical, Matched and Mismatched Unrelated Peripheral Blood Stem Cells (PBSC) Transplant for Acute Myeloid Leukemia and Myelodysplastic Syndrome with PTCy for GvHD prophylaxis. *Overlap with recent publication*
h. **PROP 2110-188** Graft Infusion Time as Risk Factor for Primary Graft Failure. *Concerns about data availability and lower scientific impact relative to other proposals*
i. **PROP 2110-251** Outcomes with CD34+ selected stem cell boost for poor graft function after allogeneic hematopoietic stem cell transplantation. *Limited sample size*
j. **PROP 2110-320** 7/8 HLA-Matched Unrelated Donor vs. Haploidentical Related and 8/8 HLA-Matched Unrelated Donor Hematopoietic Cell Transplantation using Posttransplant Cyclophosphamide-Based Prophylaxis for Acute Leukemia and Myelodysplastic Syndrome. *Overlap with recent publication*

5. Other Business

a. Discussion on Future Research Priorities

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

Accrual Summary

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	44543	15903	8657
Source of data			
CRF	24072 (54)	6924 (44)	4451 (51)
TED	20471 (46)	8979 (56)	4206 (49)
Number of centers	258	232	351
Disease at transplant			
AML	15294 (34)	5896 (37)	2918 (34)
ALL	6535 (15)	2123 (13)	1370 (16)
Other leukemia	1408 (3)	385 (2)	249 (3)
CML	3509 (8)	1045 (7)	695 (8)
MDS	6346 (14)	2568 (16)	1072 (12)
Other acute leukemia	462 (1)	185 (1)	106 (1)
NHL	4032 (9)	1194 (8)	710 (8)
Hodgkin Lymphoma	917 (2)	220 (1)	160 (2)
Plasma Cell Disorders, MM	892 (2)	270 (2)	159 (2)
Other malignancies	59 (<1)	13 (<1)	18 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1428 (3)	485 (3)	344 (4)
Inherited abnormalities erythrocyte diff fxn	727 (2)	251 (2)	157 (2)
Inherited bone marrow failure syndromes	9 (<1)	9 (<1)	11 (<1)
Hemoglobinopathies	8 (<1)	6 (<1)	4 (<1)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	4 (<1)	0
SCIDs	780 (2)	280 (2)	253 (3)
Inherited abnormalities of platelets	40 (<1)	14 (<1)	11 (<1)
Inherited disorders of metabolism	292 (1)	79 (<1)	95 (1)
Histiocytic disorders	376 (1)	107 (1)	94 (1)
Autoimmune disorders	22 (<1)	12 (<1)	5 (<1)
Other	51 (<1)	21 (<1)	19 (<1)
MPN	1347 (3)	733 (5)	204 (2)
Disease missing	1 (N/A)	0 (N/A)	2 (N/A)
AML Disease status at transplant			
CR1	8061 (53)	3434 (58)	1439 (49)
CR2	2975 (19)	1072 (18)	590 (20)
CR3+	330 (2)	95 (2)	67 (2)
Advanced or active disease	3783 (25)	1262 (21)	767 (26)
Missing	145 (1)	33 (1)	55 (2)
ALL Disease status at transplant			
CR1	3206 (49)	1180 (56)	585 (43)
CR2	1873 (29)	548 (26)	393 (29)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR3+	558 (9)	157 (7)	139 (10)
Advanced or active disease	852 (13)	222 (10)	217 (16)
Missing	46 (1)	16 (1)	36 (3)
MDS Disease status at transplant			
Early	1380 (22)	488 (19)	256 (24)
Advanced	4003 (63)	1854 (72)	592 (55)
Missing	963 (15)	226 (9)	224 (21)
NHL Disease status at transplant			
CR1	556 (14)	205 (17)	90 (13)
CR2	741 (18)	223 (19)	117 (17)
CR3+	345 (9)	102 (9)	66 (9)
PR	439 (11)	110 (9)	76 (11)
Advanced	1866 (47)	531 (45)	346 (49)
Missing	65 (2)	15 (1)	12 (2)
Recipient age at transplant			
0-9 years	3829 (9)	1110 (7)	1068 (12)
10-19 years	3937 (9)	1138 (7)	978 (11)
20-29 years	4617 (10)	1454 (9)	981 (11)
30-39 years	5099 (11)	1604 (10)	1015 (12)
40-49 years	6813 (15)	2184 (14)	1294 (15)
50-59 years	9175 (21)	3138 (20)	1573 (18)
60-69 years	9168 (21)	4145 (26)	1465 (17)
70+ years	1905 (4)	1130 (7)	283 (3)
Median (Range)	47 (0-84)	52 (0-82)	43 (0-81)
Recipient race/ethnicity			
Caucasian, non-Hispanic	36965 (83)	13172 (83)	6184 (71)
African-American, non-Hispanic	2018 (5)	651 (4)	388 (4)
Asian, non-Hispanic	1027 (2)	498 (3)	331 (4)
Pacific islander, non-Hispanic	55 (<1)	25 (<1)	23 (<1)
Native American, non-Hispanic	168 (<1)	66 (<1)	33 (<1)
Hispanic	2662 (6)	861 (5)	468 (5)
Missing	1648 (4)	630 (4)	1230 (14)
Recipient sex			
Male	25968 (58)	9313 (59)	5132 (59)
Female	18575 (42)	6590 (41)	3525 (41)
Karnofsky score			
10-80	15260 (34)	5968 (38)	2755 (32)
90-100	27634 (62)	9412 (59)	5408 (62)
Missing	1649 (4)	523 (3)	494 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	28 (<1)	37 (<1)	3 (<1)
4/6	235 (1)	102 (1)	45 (1)
5/6	6059 (14)	1819 (13)	1217 (15)
6/6	37443 (86)	12508 (86)	6817 (84)
Unknown	778 (N/A)	1437 (N/A)	575 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	884 (2)	102 (1)	45 (1)
6/8	1724 (4)	139 (1)	152 (3)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
7/8	8420 (20)	1863 (16)	1254 (22)
8/8	31783 (74)	9524 (82)	4335 (75)
Unknown	1732 (N/A)	4275 (N/A)	2871 (N/A)
HLA-DPB1 Match			
Double allele mismatch	10933 (29)	1275 (23)	590 (26)
Single allele mismatch	20128 (54)	2834 (51)	1199 (52)
Full allele matched	6179 (17)	1427 (26)	512 (22)
Unknown	7303 (N/A)	10367 (N/A)	6356 (N/A)
High resolution release score			
No	9149 (21)	15838 (>99)	8450 (98)
Yes	35394 (79)	65 (<1)	207 (2)
KIR typing available			
No	30764 (69)	15880 (>99)	8609 (99)
Yes	13779 (31)	23 (<1)	48 (1)
Graft type			
Marrow	16082 (36)	4740 (30)	3436 (40)
PBSC	28404 (64)	11007 (69)	5187 (60)
BM+PBSC	11 (<1)	7 (<1)	3 (<1)
PBSC+UCB	27 (<1)	137 (1)	5 (<1)
Others	19 (<1)	12 (<1)	26 (<1)
Conditioning regimen			
Myeloablative	27651 (62)	8835 (56)	5389 (62)
RIC/Nonmyeloablative	16685 (37)	7019 (44)	3146 (36)
TBD	207 (<1)	49 (<1)	122 (1)
Donor age at donation			
To Be Determined/NA	410 (1)	1434 (9)	126 (1)
0-9 years	8 (<1)	36 (<1)	3 (<1)
10-19 years	1223 (3)	550 (3)	184 (2)
20-29 years	20165 (45)	7124 (45)	3529 (41)
30-39 years	12640 (28)	3985 (25)	2591 (30)
40-49 years	7729 (17)	2111 (13)	1682 (19)
50+ years	2368 (5)	663 (4)	542 (6)
Median (Range)	30 (0-69)	29 (0-109)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	11076 (25)	4431 (28)	2157 (25)
+/-	5279 (12)	2016 (13)	1101 (13)
-/+	14617 (33)	4780 (30)	2679 (31)
-/-	12957 (29)	4204 (26)	2327 (27)
CB - recipient +	3 (<1)	17 (<1)	0
CB - recipient -	1 (<1)	8 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	610 (1)	446 (3)	393 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	146 (<1)	65 (<1)	45 (1)
TDEPLETION alone	100 (<1)	31 (<1)	31 (<1)
TDEPLETION +- other	1068 (2)	278 (2)	261 (3)
CD34 select alone	272 (1)	129 (1)	62 (1)
CD34 select +- other	881 (2)	628 (4)	194 (2)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Cyclophosphamide alone	785 (2)	676 (4)	226 (3)
Cyclophosphamide +- others	2016 (5)	1404 (9)	426 (5)
FK506 + MMF +- others	4990 (11)	1515 (10)	694 (8)
FK506 + MTX +- others(not MMF)	18673 (42)	6475 (41)	2380 (27)
FK506 +- others(not MMF,MTX)	2264 (5)	958 (6)	320 (4)
FK506 alone	1019 (2)	361 (2)	147 (2)
CSA + MMF +- others(not FK506)	2904 (7)	746 (5)	700 (8)
CSA + MTX +- others(not MMF,FK506)	6888 (15)	1819 (11)	2318 (27)
CSA +- others(not FK506,MMF,MTX)	1112 (2)	333 (2)	299 (3)
CSA alone	448 (1)	121 (1)	292 (3)
Other GVHD Prophylaxis	735 (2)	250 (2)	145 (2)
Missing	242 (1)	114 (1)	117 (1)
Donor/Recipient sex match			
Male-Male	18261 (41)	6197 (39)	3395 (39)
Male-Female	11147 (25)	3783 (24)	1963 (23)
Female-Male	7474 (17)	2729 (17)	1655 (19)
Female-Female	7249 (16)	2505 (16)	1506 (17)
CB - recipient M	13 (<1)	78 (<1)	0
CB - recipient F	14 (<1)	67 (<1)	6 (<1)
Missing	385 (1)	544 (3)	132 (2)
Year of transplant			
1986-1990	383 (1)	49 (<1)	53 (1)
1991-1995	1959 (4)	460 (3)	503 (6)
1996-2000	3363 (8)	1200 (8)	823 (10)
2001-2005	5238 (12)	1036 (7)	1553 (18)
2006-2010	9426 (21)	1872 (12)	1486 (17)
2011-2015	13159 (30)	3524 (22)	1900 (22)
2016-2020	10087 (23)	6869 (43)	2066 (24)
2021	928 (2)	893 (6)	273 (3)
Follow-up among survivors, Months			
N Eval	18378	7541	3603
Median (Range)	63 (0-385)	36 (0-362)	47 (0-365)

Unrelated Cord Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	5894	1566	1557
Source of data			
CRF	4361 (74)	1124 (72)	947 (61)
TED	1533 (26)	442 (28)	610 (39)
Number of centers	152	138	201
Disease at transplant			
AML	2221 (38)	529 (34)	505 (32)
ALL	1222 (21)	344 (22)	347 (22)
Other leukemia	93 (2)	30 (2)	27 (2)
CML	128 (2)	35 (2)	38 (2)
MDS	523 (9)	151 (10)	119 (8)
Other acute leukemia	93 (2)	26 (2)	28 (2)
NHL	394 (7)	89 (6)	100 (6)
Hodgkin Lymphoma	97 (2)	27 (2)	27 (2)
Plasma Cell Disorders, MM	37 (1)	12 (1)	11 (1)
Other malignancies	11 (<1)	1 (<1)	1 (<1)
SAA	93 (2)	31 (2)	27 (2)
Inherited abnormalities erythrocyte diff fxn	165 (3)	50 (3)	33 (2)
Inherited bone marrow failure syndromes	2 (<1)	2 (<1)	1 (<1)
Hemoglobinopathies	1 (<1)	0	0
SCIDs	262 (4)	87 (6)	122 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	7 (<1)
Inherited disorders of metabolism	361 (6)	105 (7)	105 (7)
Histiocytic disorders	105 (2)	27 (2)	38 (2)
Autoimmune disorders	9 (<1)	0	2 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
MPN	46 (1)	13 (1)	14 (1)
AML Disease status at transplant			
CR1	1147 (52)	287 (54)	241 (48)
CR2	608 (27)	139 (26)	139 (28)
CR3+	62 (3)	8 (2)	22 (4)
Advanced or active disease	398 (18)	93 (18)	101 (20)
Missing	6 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	550 (45)	146 (42)	146 (42)
CR2	451 (37)	124 (36)	125 (36)
CR3+	143 (12)	51 (15)	48 (14)
Advanced or active disease	77 (6)	21 (6)	28 (8)
Missing	1 (<1)	2 (1)	0
MDS Disease status at transplant			
Early	163 (31)	41 (27)	52 (44)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced	315 (60)	95 (63)	48 (40)
Missing	45 (9)	15 (10)	19 (16)
NHL Disease status at transplant			
CR1	60 (15)	6 (7)	18 (18)
CR2	74 (19)	20 (22)	31 (31)
CR3+	44 (11)	10 (11)	9 (9)
PR	67 (17)	12 (13)	11 (11)
Advanced	146 (37)	40 (45)	28 (28)
Missing	0	1 (1)	2 (2)
Recipient age at transplant			
0-9 years	1776 (30)	580 (37)	578 (37)
10-19 years	776 (13)	175 (11)	211 (14)
20-29 years	556 (9)	110 (7)	131 (8)
30-39 years	569 (10)	141 (9)	153 (10)
40-49 years	623 (11)	154 (10)	144 (9)
50-59 years	803 (14)	190 (12)	184 (12)
60-69 years	683 (12)	188 (12)	145 (9)
70+ years	108 (2)	28 (2)	11 (1)
Median (Range)	27 (0-83)	22 (0-76)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3254 (55)	917 (59)	834 (54)
African-American, non-Hispanic	841 (14)	204 (13)	176 (11)
Asian, non-Hispanic	340 (6)	107 (7)	105 (7)
Pacific islander, non-Hispanic	30 (1)	3 (<1)	16 (1)
Native American, non-Hispanic	42 (1)	9 (1)	18 (1)
Hispanic	1054 (18)	229 (15)	209 (13)
Missing	333 (6)	97 (6)	199 (13)
Recipient sex			
Male	3249 (55)	892 (57)	879 (56)
Female	2645 (45)	674 (43)	678 (44)
Karnofsky score			
10-80	1563 (27)	400 (26)	391 (25)
90-100	4149 (70)	1075 (69)	1056 (68)
Missing	182 (3)	91 (6)	110 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	97 (2)	38 (3)	12 (1)
4/6	2341 (41)	537 (40)	555 (39)
5/6	2550 (45)	566 (42)	647 (46)
6/6	718 (13)	191 (14)	202 (14)
Unknown	188 (N/A)	234 (N/A)	141 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2777 (55)	537 (56)	609 (54)
6/8	1193 (24)	228 (24)	279 (25)
7/8	701 (14)	129 (13)	166 (15)
8/8	333 (7)	70 (7)	79 (7)
Unknown	890 (N/A)	602 (N/A)	424 (N/A)
HLA-DPB1 Match			
Double allele mismatch	815 (39)	97 (43)	109 (39)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Single allele mismatch	1065 (51)	108 (48)	145 (51)
Full allele matched	199 (10)	21 (9)	28 (10)
Unknown	3815 (N/A)	1340 (N/A)	1275 (N/A)
High resolution release score			
No	4378 (74)	1500 (96)	1539 (99)
Yes	1516 (26)	66 (4)	18 (1)
KIR typing available			
No	4634 (79)	1560 (>99)	1545 (99)
Yes	1260 (21)	6 (<1)	12 (1)
Graft type			
UCB	5557 (94)	1429 (91)	1472 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	307 (5)	137 (9)	78 (5)
Others	29 (<1)	0	7 (<1)
Number of cord units			
1	4944 (84)	0	1310 (84)
2	946 (16)	0	247 (16)
3	2 (<1)	0	0
Unknown	2 (N/A)	1566 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3852 (65)	1008 (64)	978 (63)
RIC/Nonmyeloablative	2029 (34)	554 (35)	570 (37)
TBD	13 (<1)	4 (<1)	9 (1)
Donor age at donation			
To Be Determined/NA	209 (4)	113 (7)	120 (8)
0-9 years	5183 (88)	1205 (77)	1316 (85)
10-19 years	296 (5)	141 (9)	70 (4)
20-29 years	65 (1)	35 (2)	11 (1)
30-39 years	56 (1)	34 (2)	18 (1)
40-49 years	39 (1)	17 (1)	8 (1)
50+ years	46 (1)	21 (1)	14 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-69)
Donor/Recipient CMV serostatus			
+/+	1338 (23)	309 (20)	307 (20)
+/-	573 (10)	148 (9)	145 (9)
-/+	1084 (18)	283 (18)	267 (17)
-/-	724 (12)	195 (12)	201 (13)
CB - recipient +	1253 (21)	336 (21)	339 (22)
CB - recipient -	828 (14)	238 (15)	238 (15)
CB - recipient CMV unknown	94 (2)	57 (4)	60 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	21 (<1)	8 (1)	9 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	5 (<1)
CD34 select alone	0	2 (<1)	2 (<1)
CD34 select +- other	287 (5)	136 (9)	84 (5)
Cyclophosphamide alone	0	0	2 (<1)
Cyclophosphamide +- others	47 (1)	27 (2)	53 (3)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
FK506 + MMF +- others	1622 (28)	415 (27)	260 (17)
FK506 + MTX +- others(not MMF)	214 (4)	56 (4)	71 (5)
FK506 +- others(not MMF,MTX)	221 (4)	63 (4)	65 (4)
FK506 alone	139 (2)	43 (3)	23 (1)
CSA + MMF +- others(not FK506)	2689 (46)	610 (39)	707 (45)
CSA + MTX +- others(not MMF,FK506)	99 (2)	33 (2)	41 (3)
CSA +- others(not FK506,MMF,MTX)	333 (6)	124 (8)	151 (10)
CSA alone	50 (1)	18 (1)	50 (3)
Other GVHD Prophylaxis	132 (2)	19 (1)	25 (2)
Missing	12 (<1)	3 (<1)	9 (1)
Donor/Recipient sex match			
CB - recipient M	3249 (55)	892 (57)	878 (56)
CB - recipient F	2645 (45)	674 (43)	678 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	115 (2)	108 (7)	27 (2)
2006-2010	1811 (31)	413 (26)	492 (32)
2011-2015	2613 (44)	501 (32)	608 (39)
2016-2020	1300 (22)	506 (32)	389 (25)
2021	54 (1)	36 (2)	36 (2)
Follow-up among survivors, Months			
N Eval	2805	808	788
Median (Range)	66 (1-196)	56 (3-213)	52 (1-240)

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	9695	1555	646
Source of data			
CRF	3455 (36)	446 (29)	245 (38)
TED	6240 (64)	1109 (71)	401 (62)
Number of centers	90	72	59
Disease at transplant			
AML	3214 (33)	506 (33)	206 (32)
ALL	1578 (16)	299 (19)	124 (19)
Other leukemia	189 (2)	35 (2)	14 (2)
CML	314 (3)	36 (2)	20 (3)
MDS	1277 (13)	191 (12)	92 (14)
Other acute leukemia	133 (1)	29 (2)	7 (1)
NHL	856 (9)	141 (9)	61 (9)
Hodgkin Lymphoma	188 (2)	37 (2)	17 (3)
Plasma Cell Disorders, MM	254 (3)	40 (3)	18 (3)
Other malignancies	24 (<1)	0	0
Breast cancer	1 (<1)	0	0
SAA	442 (5)	62 (4)	20 (3)
Inherited abnormalities erythrocyte diff fxn	484 (5)	69 (4)	20 (3)
Inherited bone marrow failure syndromes	7 (<1)	1 (<1)	0
Hemoglobinopathies	35 (<1)	7 (<1)	2 (<1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	201 (2)	33 (2)	11 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	14 (<1)	3 (<1)	2 (<1)
Histiocytic disorders	57 (1)	6 (<1)	3 (<1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	11 (<1)	3 (<1)	1 (<1)
MPN	393 (4)	57 (4)	27 (4)
AML Disease status at transplant			
CR1	2063 (64)	340 (67)	134 (65)
CR2	486 (15)	66 (13)	26 (13)
CR3+	38 (1)	13 (3)	1 (<1)
Advanced or active disease	619 (19)	83 (16)	45 (22)
Missing	8 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	974 (62)	195 (65)	76 (61)
CR2	437 (28)	69 (23)	31 (25)
CR3+	88 (6)	13 (4)	10 (8)
Advanced or active disease	78 (5)	22 (7)	7 (6)
Missing	1 (<1)	0	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
MDS Disease status at transplant			
Early	209 (16)	26 (14)	18 (20)
Advanced	1026 (80)	154 (81)	69 (75)
Missing	42 (3)	11 (6)	5 (5)
NHL Disease status at transplant			
CR1	154 (18)	32 (23)	11 (18)
CR2	162 (19)	31 (22)	8 (13)
CR3+	93 (11)	15 (11)	2 (3)
PR	67 (8)	13 (9)	5 (8)
Advanced	371 (44)	49 (35)	34 (56)
Missing	5 (1)	0	1 (2)
Recipient age at transplant			
0-9 years	961 (10)	137 (9)	48 (7)
10-19 years	1139 (12)	139 (9)	56 (9)
20-29 years	829 (9)	169 (11)	51 (8)
30-39 years	763 (8)	137 (9)	66 (10)
40-49 years	1226 (13)	196 (13)	77 (12)
50-59 years	2129 (22)	350 (23)	133 (21)
60-69 years	2254 (23)	369 (24)	190 (29)
70+ years	394 (4)	58 (4)	25 (4)
Median (Range)	50 (0-82)	50 (0-76)	52 (0-83)
Recipient race/ethnicity			
Caucasian, non-Hispanic	6077 (63)	825 (53)	421 (65)
African-American, non-Hispanic	1174 (12)	188 (12)	55 (9)
Asian, non-Hispanic	438 (5)	116 (7)	31 (5)
Pacific islander, non-Hispanic	30 (<1)	3 (<1)	1 (<1)
Native American, non-Hispanic	37 (<1)	4 (<1)	2 (<1)
Hispanic	1434 (15)	298 (19)	102 (16)
Missing	505 (5)	121 (8)	34 (5)
Recipient sex			
Male	5676 (59)	917 (59)	380 (59)
Female	4019 (41)	638 (41)	266 (41)
Karnofsky score			
10-80	3458 (36)	625 (40)	284 (44)
90-100	5979 (62)	887 (57)	338 (52)
Missing	258 (3)	43 (3)	24 (4)
Graft type			
Marrow	2780 (29)	348 (22)	168 (26)
PBSC	6834 (70)	1181 (76)	464 (72)
UCB (related)	2 (<1)	10 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)
BM+UCB	38 (<1)	11 (1)	2 (<1)
PBSC+UCB	0	0	11 (2)
Others	33 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	5411 (56)	862 (55)	327 (51)
RIC/Nonmyeloablative	4233 (44)	683 (44)	307 (48)
TBD	51 (1)	10 (1)	12 (2)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Donor age at donation			
To Be Determined/NA	16 (<1)	10 (1)	1 (<1)
0-9 years	659 (7)	89 (6)	28 (4)
10-19 years	983 (10)	140 (9)	56 (9)
20-29 years	1354 (14)	231 (15)	97 (15)
30-39 years	1382 (14)	246 (16)	121 (19)
40-49 years	1574 (16)	258 (17)	88 (14)
50+ years	3727 (38)	581 (37)	255 (39)
Median (Range)	43 (0-82)	43 (0-79)	43 (1-76)
Donor/Recipient CMV serostatus			
+/+	3949 (41)	706 (45)	248 (38)
+/-	1079 (11)	127 (8)	60 (9)
-/+	2411 (25)	368 (24)	163 (25)
-/-	2115 (22)	325 (21)	151 (23)
CB - recipient +	0	3 (<1)	0
CB - recipient -	0	0	3 (<1)
Missing	141 (1)	26 (2)	21 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	103 (1)	14 (1)	6 (1)
TDEPLETION alone	40 (<1)	17 (1)	4 (1)
TDEPLETION +- other	63 (1)	19 (1)	7 (1)
CD34 select alone	77 (1)	20 (1)	6 (1)
CD34 select +- other	371 (4)	86 (6)	47 (7)
Cyclophosphamide alone	261 (3)	50 (3)	24 (4)
Cyclophosphamide +- others	2500 (26)	360 (23)	176 (27)
FK506 + MMF +- others	690 (7)	73 (5)	19 (3)
FK506 + MTX +- others(not MMF)	3524 (36)	478 (31)	233 (36)
FK506 +- others(not MMF,MTX)	713 (7)	253 (16)	49 (8)
FK506 alone	67 (1)	9 (1)	3 (<1)
CSA + MMF +- others(not FK506)	223 (2)	33 (2)	12 (2)
CSA + MTX +- others(not MMF,FK506)	666 (7)	83 (5)	33 (5)
CSA +- others(not FK506,MMF,MTX)	80 (1)	10 (1)	1 (<1)
CSA alone	76 (1)	9 (1)	3 (<1)
Other GVHD Prophylaxis	136 (1)	16 (1)	12 (2)
Missing	105 (1)	25 (2)	11 (2)
Donor/Recipient sex match			
Male-Male	3212 (33)	546 (35)	222 (34)
Male-Female	2068 (21)	313 (20)	136 (21)
Female-Male	2436 (25)	350 (23)	150 (23)
Female-Female	1934 (20)	317 (20)	125 (19)
CB - recipient M	24 (<1)	15 (1)	8 (1)
CB - recipient F	16 (<1)	6 (<1)	5 (1)
Missing	5 (<1)	8 (1)	0
Year of transplant			
2006-2010	604 (6)	72 (5)	38 (6)
2011-2015	3665 (38)	491 (32)	181 (28)
2016-2020	4930 (51)	874 (56)	361 (56)
2021	496 (5)	118 (8)	66 (10)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Follow-up among survivors, Months			
N Eval	5758	893	368
Median (Range)	37 (1-150)	29 (0-124)	27 (2-143)

HLA Mis-Matched Related Donor with Post-Transplant Cyclophosphamide HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	2163	306	152
Source of data			
CRF	1103 (51)	138 (45)	92 (61)
TED	1060 (49)	168 (55)	60 (39)
Number of centers	70	41	31
Disease at transplant			
AML	813 (38)	115 (38)	53 (35)
ALL	375 (17)	64 (21)	33 (22)
Other leukemia	29 (1)	5 (2)	4 (3)
CML	89 (4)	10 (3)	3 (2)
MDS	307 (14)	38 (12)	22 (14)
Other acute leukemia	30 (1)	5 (2)	2 (1)
NHL	165 (8)	24 (8)	13 (9)
Hodgkins Lymphoma	57 (3)	11 (4)	4 (3)
Plasma Cell Disorders, MM	37 (2)	4 (1)	3 (2)
Other malignancies	8 (<1)	0	0
SAA	77 (4)	8 (3)	2 (1)
Inherited abnormalities erythrocyte diff fxn	62 (3)	10 (3)	3 (2)
SCIDs	15 (1)	1 (<1)	1 (1)
Inherited abnormalities of platelets	1 (<1)	0	0
Inherited disorders of metabolism	2 (<1)	0	0
Histiocytic disorders	12 (1)	1 (<1)	1 (1)
Autoimmune disorders	2 (<1)	0	0
Other	1 (<1)	1 (<1)	0
MPN	81 (4)	9 (3)	8 (5)
AML Disease status at transplant			
CR1	482 (59)	71 (62)	32 (60)
CR2	136 (17)	20 (17)	8 (15)
CR3+	13 (1)	3 (3)	1 (2)
Advanced or active disease	181 (22)	20 (17)	12 (23)
Missing	1 (<1)	1 (<1)	0
ALL Disease status at transplant			
CR1	225 (60)	40 (63)	20 (61)
CR2	104 (28)	18 (28)	9 (27)
CR3+	27 (7)	4 (6)	2 (6)
Advanced or active disease	19 (5)	2 (3)	2 (6)
Missing	0	0	0
MDS Disease status at transplant			
Early	43 (14)	5 (13)	2 (9)
Advanced	253 (82)	31 (82)	18 (82)
Missing	11 (4)	2 (5)	2 (9)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
NHL Disease status at transplant			
CR1	38 (23)	6 (25)	3 (23)
CR2	38 (23)	6 (25)	2 (15)
CR3+	14 (8)	6 (25)	1 (8)
PR	4 (2)	0	0
Advanced	68 (41)	5 (21)	6 (46)
Missing	3 (2)	1 (4)	1 (8)
Recipient age at transplant			
0-9 years	127 (6)	11 (4)	6 (4)
10-19 years	200 (9)	18 (6)	10 (7)
20-29 years	260 (12)	39 (13)	16 (11)
30-39 years	202 (9)	29 (9)	19 (13)
40-49 years	286 (13)	45 (15)	16 (11)
50-59 years	422 (20)	64 (21)	27 (18)
60-69 years	523 (24)	89 (29)	50 (33)
70+ years	143 (7)	11 (4)	8 (5)
Median (Range)	50 (0-82)	52 (0-76)	54 (2-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1113 (51)	125 (41)	96 (63)
African-American, non-Hispanic	415 (19)	61 (20)	17 (11)
Asian, non-Hispanic	107 (5)	25 (8)	7 (5)
Pacific islander, non-Hispanic	4 (<1)	1 (<1)	1 (1)
Native American, non-Hispanic	7 (<1)	0	2 (1)
Hispanic	374 (17)	70 (23)	17 (11)
Missing	143 (7)	24 (8)	12 (8)
Recipient sex			
Male	1281 (59)	195 (64)	102 (67)
Female	882 (41)	111 (36)	50 (33)
Karnofsky score			
10-80	929 (43)	135 (44)	83 (55)
90-100	1191 (55)	164 (54)	62 (41)
Missing	43 (2)	7 (2)	7 (5)
Graft type			
Marrow	949 (44)	106 (35)	69 (45)
PBSC	1211 (56)	199 (65)	83 (55)
BM+PBSC	3 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	979 (45)	137 (45)	58 (38)
RIC/Nonmyeloablative	1184 (55)	169 (55)	94 (62)
Donor age at donation			
0-9 years	23 (1)	2 (1)	1 (1)
10-19 years	176 (8)	27 (9)	13 (9)
20-29 years	552 (26)	91 (30)	35 (23)
30-39 years	597 (28)	88 (29)	53 (35)
40-49 years	470 (22)	59 (19)	29 (19)
50+ years	345 (16)	39 (13)	21 (14)
Median (Range)	36 (2-77)	34 (1-70)	34 (10-74)
Donor/Recipient CMV serostatus			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
+/+	919 (42)	159 (52)	54 (36)
+/-	245 (11)	18 (6)	16 (11)
-/+	569 (26)	75 (25)	38 (25)
-/-	412 (19)	53 (17)	38 (25)
Missing	18 (1)	1 (<1)	6 (4)
GvHD Prophylaxis			
Cyclophosphamide alone	12 (1)	3 (1)	0
Cyclophosphamide +- others	2151 (99)	303 (99)	152 (100)
Donor/Recipient sex match			
Male-Male	826 (38)	140 (46)	63 (41)
Male-Female	476 (22)	67 (22)	24 (16)
Female-Male	455 (21)	55 (18)	39 (26)
Female-Female	406 (19)	44 (14)	26 (17)
Year of transplant			
2006-2010	16 (1)	1 (<1)	1 (1)
2011-2015	456 (21)	55 (18)	23 (15)
2016-2020	1675 (77)	244 (80)	126 (83)
2021	16 (1)	6 (2)	2 (1)
Follow-up among survivors, Months			
N Eval	1336	185	100
Median (Range)	25 (1-133)	24 (3-82)	23 (2-100)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Graft Sources and Manipulation Working Committee Members

FROM: Steve Spellman; Scientific Director for the Graft Sources Working Committee

RE: Studies in Progress Summary

GS19-02: Graft Failure in MDS and Acute Leukemia Patients After Allogeneic Stem Cell Transplantation Receiving Post Transplant Cyclophosphamide (C Hickey et al). The aim of this study is to examine graft failure and overall survival of haploidentical with PTCy, matched donor with PTCy in the reduced intensity conditioning setting. This study is currently in analysis, we plan to complete the study by July 2022.

Proposal Title:

Outcomes for Haploidentical Transplantation using post-transplant cyclophosphamide for non-first degree relatives

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Conflicts of Interest: All other authors have no conflict of interest or relevant/non-relevant disclosures.

Hypothesis:

Outcomes of haploidentical hematopoietic cell transplantation (haplo-HCT) from non-first-degree relative (non-FDR) donors are non-inferior compared to first-degree relative (FDR) donors.

Specific Aims:

Primary aim: Determine the overall survival of patients who receive haplo-HCT from non-FDR donors compared to FDR donors.

Secondary aims including studying the following parameters between non-FDR vs. FDRs:

- Progression free survival (PFS)
- Causes of death
- Cumulative incidence (CuI) of relapse, non-relapse mortality (NRM) and transplant related mortality (TRM) at day 100
- CuI of grade II-IV acute GVHD and moderate-severe chronic GVHD
- Graft versus host disease and relapse free survival (GRFS)
- Predictive factors (age, ABO, CMV) of relapse, NRM, GVHD

Scientific Justification:

Stem cell transplantation remains the only curative therapy for several high-risk malignancies, but its application is somewhat limited by lack of a suitable donor. Only 30% of patients have potential HLA-identical sibling donors, who are considered the gold standard over matched unrelated, haploidentical or mis-matched donors due to decreased incidence of GVHD and transplant related mortality.[1, 2] The development of post-transplant cyclophosphamide (PTCY) that specifically depletes allo-reactive T-cells [3, 4] has enabled the use of less stringently HLA matched grafts due to decreased incidence of aGVHD [5,6,7]. As a consequence, recent studies have reported non-inferior outcomes for haplo-identical donors compared to matched sibling donor [8,9], matched related donor [10] matched unrelated donor [11,12] as well as mismatch unrelated donor [13,14] transplants.

Given advances in conditioning regimen, incorporation of PTCY, GVHD prophylaxis, among other things, second or 3rd degree relative donors (i.e. nephew, niece, uncle, aunts) may be considered a viable graft source. A few single institution prospective studies by Elmariah et al. [15] and Ye et al [16] evaluated 33 and 99 non-first degree haplo-identical related donors respectively as graft source and showed effective outcome with acceptable toxicity profile compared to first-degree related donors.

In a CIBMTR study [9] patient and disease characteristics had more importance than either the age of the donor or donor-recipient relationship with regards to survival and GVHD which was contrary to the authors' initial hypothesis. Graft failure rates were highest when transplanted from a parent donor without any difference in maternal or paternal donor source. Thus, there are many nuances in selecting the best available donor. Despite advances in haplo-HCTs there is still much to learn about graft sources, HLA disparities and donor selections. While these questions are best answered in prospective clinical

trials, the CIBMTR database will provide a sound resource with expected largest numbers that can be effectively studied to answer these important practice-guiding questions when faced with limited first-degree donor selections.

Scientific Impact:

The data describing haplo-HCT outcomes using non-first-degree related donors are currently limited to single institution experiences or case series. Given limited existing data regarding on efficacy and safety of the use of non-first-degree relatives for haploidentical transplantation, we propose the use of the CIBMTR database to explore the feasibility of expanding the potential donor pool to non-first degree relative. This will be greatly beneficial to patients who otherwise lack a suitable donor. Current donor selection algorithm is mainly focused on donor age, sex, blood groups and CMV status, therefore we aim to explore other variables that might need to be prioritized if the potential donor pool is further expanded.

Patient Eligibility Population:

- Inclusion:
  - Patient's age ≥18 undergoing first haplo-SCT followed by post-transplant cyclophosphamide for hematologic malignancies between the years 2010-2020.
  - Non-FDR may include second- or third-degree relatives who shared 1 inherited haplotype with the patient.
- Exclusion:
  - Unrelated donors
  - Ex vivo graft manipulation or T-cell depletion (e.g. ATG, alemtuzumab, CD34 selection)

Data Requirements:

Patient related:

- Age at HCT - as a continuous variable in increments of 10 years
- Performance status - KPS at HCT
- HCT-CI at HCT
- Sex
- Ethnicity
- Diagnosis
- Time from diagnosis to HCT: 0-6 versus 6-12 versus >12 months and continuous
- Prior lines of therapy
- Remission status at the time of transplant
- CMV status
- ABO blood type
- Donor chimerism at days +30, +100, +180

Donor:

- HLA matching level (5/10, 6/10, 7/10, 8/10,9/10)
- Donor age
- Donor-recipient gender match: M-M vs. M-F vs. F-M vs. F-F
- Donor-recipient CMV status: +/+ or -/+ vs. +/- vs. -/-
- Donor type (1st degree – parents/full siblings/children, 2nd degree - grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings, 3rd degree - first-cousins, great-grandparents or great grandchildren)
- Donor-recipient ABO
- HLA typing: KIR typing if available

Disease related:

- Myeloid vs lymphoid
- Last 2 lines of Treatment type prior to HCT: immunosuppressive (MTX, Cy, L-asparaginase, vincristine, fludarabine-FLAG, cladribine) vs. nonimmunosuppresive1 (HMA-based, targeted therapies-e.g., IDH1/2 inhibitors, FLT3 inhibitor alone vs conventional chemo) vs. intermediate (conventional AML combinations-e.g., 7+3, HidAC)
- Time from last treatment to haplo-HCT
- CR1 vs. CR2 vs. >CR2
- Causes of death
- Graft failure, immune reconstitution, and infection data

Transplant related:

- Consolidation prior to transplant
- Conditioning regimen (MAC or RIC vs NMA)
- In vivo or in vitro T-cell depletion
- GVHD prophylaxis ; post-transplant cyclophosphamide +/- others
- Viable CD34+ cells/kg of recipient infused (if available)
- TNC/kg of recipient before thawing
- CD3+/kg of recipient before thawing
- DSA present (yes/no)
- Prior allogeneic HCT (yes/no)
- Graft source: PBSC vs BM

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Characteristics of patients who underwent haploidentical HCT for any malignant disease reported to the CIBMTR 2008-2019

Characteristic	Not First Degree	First degree
No. of patients	152	3160
No. of centers	50	131
Age at HCT - no. (%)		
18-29	65 (43)	381 (12)
30-39	28 (18)	316 (10)
40-49	12 (8)	455 (14)
50-59	7 (5)	748 (24)
60-69	28 (18)	994 (31)
>=70	12 (8)	266 (8)
Relationship of donor - no. (%)		
Sibling, not identical twin	0 (0)	970 (31)
Child	0 (0)	67 (2)
Parent	0 (0)	1800 (57)
Half-sibling	0 (0)	323 (10)
Uncle/Aunt	120 (79)	0 (0)
Cousin	7 (5)	0 (0)
Grandchild	4 (3)	0 (0)
Niece/Nephew	21 (14)	0 (0)
Donor age group - no. (%)		
<18	0 (0)	112 (4)
18-29	16 (11)	932 (29)
30-39	19 (13)	918 (29)
40-49	48 (32)	659 (21)
50-59	43 (28)	346 (11)
60-69	22 (14)	164 (5)
>=70	2 (1)	21 (1)
Not reported	2 (1)	8 (0)
Primary disease for HCT - no. (%)		
AML	73 (48)	1314 (42)
ALL	40 (26)	497 (16)
Other leukemia	1 (1)	79 (3)
CML	5 (3)	111 (4)
MDS	16 (11)	613 (19)
Other acute leukemia	2 (1)	48 (2)
NHL	9 (6)	328 (10)
HD	6 (4)	111 (4)
PCD	0 (0)	59 (2)
Graft Source - no. (%)		
Bone marrow	54 (36)	1069 (34)
Peripheral blood	98 (64)	2091 (66)
Indicator of HCT cases in CRF retrieval - no. (%)		

Characteristic	Not First Degree	First degree
No	118 (78)	857 (27)
Yes	34 (22)	2303 (73)
Year of Transplant - no. (%)		
2008 - 2013	11 (7)	268 (8)
2014 - 2019	141 (93)	2892 (92)
Follow-up - median (range)	36 (6-122)	36 (3-151)

CIBMTR Proposal

I. Study Title:

Impact of donor source in second allogeneic hematopoietic cell transplant (HCT) in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020)

II. Keywords:

HCT, relapse, donor, second transplant, haplo-identical donor, cord blood, GvHD, GvL

III. Principal Investigator Information:

This proposal combines three previously submitted proposals from the following PIs:

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Andromachi Scaradavou, MD *(presenter at TCT 2022 if the proposal is selected by the GSWC)*
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IV. Proposed Working Committee:

Graft Sources Working Committee. Project was discussed with the Scientific Director.

V. Research Question:

Is there an impact of donor source (related, unrelated, haplo-identical or unrelated CB graft) on outcomes of second allogeneic HCT for treatment of relapse in pediatric and adult patients with acute leukemia/MDS who were transplanted during the current era (2014-2020)?

VI. Research Hypothesis:

The optimal donor for second allogeneic HCT (HCT-2) for patients who relapsed after their first transplant has not been established. Older retrospective studies have identified prognostic variables, but these may not be directly applicable to current practice. With recent treatment advances and expanded donor and graft choices, we expect improved Leukemia-free Survival (LFS) after HCT-2 performed during the period 2014-2020 compared to previously reported outcomes (1,2). We hypothesize that there is an impact of donor source on LFS, and this may be different for pediatric and adult recipients.

VII. Specific Objectives/Outcomes to be Investigated:

Primary Aim:

Evaluate the impact of HCT-2 donor (related, unrelated, haplo-identical or CB) on Leukemia-free Survival (LFS) at 1 year in patients transplanted during the period 2014-2020.

Secondary Aims:

1. Evaluate transplant outcomes after HCT-2 (LFS, overall survival [OS], relapse, transplant-related mortality [TRM], graft failure and acute/chronic GVHD) in the subgroup of patients who received unrelated CB grafts stratified by TNC/CD34 cell dose; analyze separately pediatric and adult patients.

2. Evaluate transplant outcomes after HCT-2 (LFS, OS, relapse, TRM, graft failure and acute/chronic GVHD) in the subgroup of patients who had haplo-donors stratified for same or different donor – with different shared haplotype.

3. Evaluate whether development of GvHD (acute or chronic) after HCT-1 impacts the incidence of relapse after HCT-2 stratified by the donor for HCT-2: same vs. different donor.

VIII. Scientific Impact:

Relapse after allogeneic HCT remains the leading cause of mortality for patients with acute leukemia. The only potentially curative approach is a second transplant (1,2,3). As these patients have very high-risk disease the anti-leukemic potential of the donor graft of HCT-2 is of critical importance. This proposal evaluates donor-related variables that may enhance LFS after HCT-2.

There is an unmet need, in our opinion, to define optimal donor selection and identify modifiable variables that can further improve outcomes in children and adults after HCT-2. The strength of our study is to use data of a “contemporary” patient cohort, i.e., transplants performed during the period 2014-2020, so that results can be easily applicable to current practice and facilitate patient counseling and treatment decisions.

IX. Scientific Justification:

Patients who relapse after allo-HCT have limited treatment options and poor survival. A second transplant represents the only curative treatment (1,2). The optimal donor for second allogeneic HCT (HCT-2) has not been established. Donor selection is based on prompt availability and potent antileukemic effect. This proposal evaluates donor-related variables that may improve outcomes after HCT-2.

Unrelated CB grafts exert a strong Graft-versus-Leukemia (GVL) effect after first allo-HCT (HCT-1), particularly in patients with Minimal Residual Disease (MRD) (4,5,6). Based on clinical experience and preclinical data, there is growing evidence of the unique immunological properties of CB T cells (7,8), making these grafts 'intrinsically' more effective as anti-leukemia treatment, and therefore preferable for HCT-2.

Changing the donor for HCT-2 to enhance the GVL effect has shown limited or no benefit in several prior analyses (9,10,11). Recently, however, promising data on improved leukemia control after HCT-2 using a different donor, HLA-haploidentical, have been reported (12). An advantage was also seen by switching the haplo donor of HCT-1 to another haplo donor sharing a different haplotype for HCT-2, in a single institution study (13). A more extensive analysis is needed to help define the optimal haploidentical donor for HCT-2.

Importantly, both alternative donor sources (haplo-donors and CB grafts) can be readily available so that transplant logistics are simplified and treatment can be expedited.

Finally, it is understood that GvHD and GVL may have shared immunobiology, and thus GvHD can influence relapse (14). While several factors including disease status, time of relapse after HCT-1, and interval between the two transplants have an effect on outcomes (1-3, 9-13), the impact of GvHD following HCT-1 and/or HCT-2, as an indication of a possible GVL effect, has not been evaluated in association with the outcomes of HCT-2. This question becomes particularly relevant in the context of selecting the donor source for HCT-2, i.e., same vs. different donor, and donor types including CB grafts or haplo.

Historically, HCT-2 has been hampered with a high incidence of TRM. A CIBMTR analysis of second transplants in pediatric patients performed primarily before 2010 showed similar disappointing outcomes (2). However, these results do not reflect current treatment modalities and standards of care. In recent years, improved survival and lower TRM have been achieved with the use of new, less toxic cytoreduction regimens and better GvHD prophylaxis. For CB grafts, in particular, optimization of cytoreduction with omission of ATG treatment (15,16) and better graft selection (17,18) have led to improved survival after CB HCT-1 (7,19). Our institutional data show lower TRM after CB HCT-2 in the recent period (20) and it would be important to evaluate the findings in a larger patient cohort.

In summary, we propose to evaluate the impact of donor source, and donor change, on outcomes of HCT-2 by analyzing a contemporary cohort of patients and identifying donor characteristics that may enhance the GVL effect and the efficacy of the transplant. The results will be directly applicable to current practice.

- Age: all ages; age groups: 10 years;
  For specific analyses: pediatric patients: 0-19 years
- Performance score: <80, 80 and above
- Comorbidity Index: 0, 1-2, ≥3
- CMV status: positive, negative

Transplant characteristics at HCT-1

- Donor: any (related, unrelated, haplo)
- Graft: any (BM, PB or CB)
- Cytoreduction: myeloablative or reduced-intensity
- GvHD prophylaxis: T cell depletion, CNI, PTCy, other
- Acute GvHD or not (if yes, grade); chronic GvHD or not
- Time to relapse after HCT-1: < 6 months, 6-12 months, >12 months

Disease characteristics at HCT-2

- Diagnosis: AML, ALL, other acute leukemia, MDS
- Status: CR or not, if CR, MRD present or not
- Disease Risk Index (DRI)
- Reason for HCT-2: relapse

Transplant characteristics at HCT-2

- Donor: any (related, unrelated, haplo)
  Same or different donor
  For CB: TNC and CD34 cell dose; HLA match; single/double CB graft
- Graft: any (BM, PB or CB)
- Cytoreduction: myeloablative or reduced-intensity; ATG or not
- GvHD prophylaxis: T cell depletion, CNI, PTCy, other
- Time from relapse to HCT-2: < 6 months, 6-12 months, >12 months
- Interval between HCT-1 and HCT-2: < 6 months, 6-12 months, >12 months
- Follow-up after HCT-2: ≥1 year
- Acute GvHD or not (if yes, grade); chronic GvHD or not
- Cause of death (if applicable)
- TC experience with haplo or CB transplants (reported ≥5 vs. less than 5)

Note 1: Patients could have received DLI of CAR T cell therapy before HCT-2.
Note 2: CB grafts will not be considered in the analysis of “different donor” for HCT-2.

Exclusion criteria:

For HCT-2 CB analysis: patients who received ATG; patients who received ex vivo expanded CB grafts; patients who received haplo+CB graft

Does this study include pediatric patients? Yes

XI. Data Requirements (variables to be considered in the multivariate analysis):

Age, diagnosis, disease status at HCT-1 (CR or not, MRD positive or negative), DRI, HCT-1 cytoreduction (myeloablative or not), HCT-1 donor (related, unrelated, haplo, CB), HCT-1 GvHD prophylaxis (T cell depletion, CNI, PTCy, other), acute GvHD (and stage), chronic GvHD, time to relapse after HCT-1, disease status at HCT-2, (MRD status if in remission, DRI), time interval between HCT-1 and HCT-2, cytoreduction for HCT-2 (myeloablative or not), ATG or not, HCT-2 donor (related, unrelated, haplo, CB), same or different donor, HCT-2 GvHD prophylaxis (T cell depletion, CNI, PTCy, other), time to ANC>500, time to plts>50K, donor chimerism, acute GVHD (and stage), chronic GVHD, CMV status, TC experience with haplo or CB transplants (reported ≥5 vs less than 5).
For haplo: same or different haplo donor
For CB grafts: TNC/CD34 cell dose, single or double, HLA match to patient (preferably allele level).

Statistical analysis: Cox proportional hazard and Fine-Gray competing risk analyses will be used. Statistical analyses will be done under the guidance of the CIBMTR Working Committee Statistician and Medical Director.

XII. Patient Reported Outcomes:

No

XIII. Sample Requirements:

No biologic sample requirements from the NMDP repository.

XIV. Non-CIBMTR data Source

N/A

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16. Boelens JJ. The power of cord blood cells. Blood. 2016;127(26):3302-3303.
17. Barker JN, Kurtzberg J, Ballen K, et al. Optimal Practices in Unrelated Donor Cord Blood Transplantation for Hematologic Malignancies. Biol Blood Marrow Transplant. 2017;23: 882-896.
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19. Kurtzberg J, Troy JD, Page KM, et al. Review of Unrelated Donor Cord Blood Transplantation in Children over te hPast 3 Decades. [Abstract] Blood 2021;138 (Supplement 1): 2903. To be presented at ASH 2021.
20. Lucas AGT, Boelens JJ, Kernan NA, et al. Encouraging Outcomes after Unrelated Cord Blood Grafts for Post-Transplant Relapse in Pediatric Patients. [Abstract] To be presented at TCT 2022.

XVI. Conflict of Interest

No conflicts of interest for this work.

Characteristics of patients who underwent second allo HCT for relapsed malignant disease reported to the CIBMTR 2014-2019

Characteristic	Different Donor	Same Donor
No. of patients	970	262
No. of centers	142	96
Age at HCT - no. (%)		
<10	103 (11)	18 (7)
10-17	91 (9)	14 (5)
18-29	144 (15)	39 (15)
30-39	116 (12)	31 (12)
40-49	148 (15)	38 (15)
50-59	168 (17)	66 (25)
60-69	177 (18)	48 (18)
>=70	23 (2)	8 (3)
Interval between first and second allo transplant - no. (%)		
<6 months	27 (3)	27 (10)
6-12 months	183 (19)	66 (25)
12-24 months	340 (35)	79 (30)
24+ months	420 (43)	90 (34)
Primary disease for HCT - no. (%)		
AML	607 (63)	174 (66)
ALL	222 (23)	50 (19)
Other leukemia	13 (1)	2 (1)
CML	20 (2)	3 (1)
MDS	89 (9)	27 (10)
MPN	19 (2)	6 (2)
Donor type - no. (%)		
HLA-identical sibling	58 (6)	132 (50)
HLA-matched other relative	1 (0)	1 (0)
HLA 1-antigen mismatched other relative	7 (1)	4 (2)
Full haploidentical donor	279 (29)	25 (10)
Other mismatched relative, degree of mismatch unknown	9 (1)	3 (1)
Related CB	9 (1)	2 (1)
HLA-Matched Unrelated Donor	389 (40)	79 (30)
HLA-Mismatched Unrelated Donor	95 (10)	14 (5)
Unrelated Donor, HLA-match unknown	12 (1)	2 (1)
Unrelated single CB, 6/6	10 (1)	0 (0)
Unrelated single CB, 5/6	19 (2)	0 (0)
Unrelated single CB, LE4/6	16 (2)	0 (0)
Unrelated single CB, degree of match Unknown	3 (0)	0 (0)
Unrelated double CB, 6/6	1 (0)	0 (0)
Unrelated double CB, 5/6	12 (1)	0 (0)
Unrelated double CB, LE 4/6	40 (4)	0 (0)

Characteristic	Different Donor	Same Donor
Unrelated double CB, degree of match Unknown	10 (1)	0 (0)
Graft Source - no. (%)		
Bone marrow	132 (14)	28 (11)
Peripheral blood	718 (74)	232 (89)
Umbilical cord blood	120 (12)	2 (1)
Indicator of HCT cases in CRF retrieval - no. (%)		
No	567 (58)	181 (69)
Yes	403 (42)	81 (31)
Year of HCT - no. (%)		
2014	128 (13)	51 (19)
2015	145 (15)	48 (18)
2016	134 (14)	42 (16)
2017	165 (17)	36 (14)
2018	205 (21)	38 (15)
2019	193 (20)	47 (18)
Follow-up - median (range)	36 (3-75)	45 (6-84)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Impact of CD34+ Cell Dose on Outcomes After Matched Sibling and Unrelated Donor Peripheral Blood Stem Cell Transplantation

Q2. Key Words

Allogeneic hematopoietic stem cell transplantation; Peripheral blood stem cells; Graft cell dose; CD34+ cell dose; Matched unrelated donor; Matched sibling donor

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Muhammad Umair Mushtaq, MD
Email address:	mmushtaq@kumc.edu
Institution name:	University of Kansas Medical Center, Kansas City, KS
Academic rank:	Assistant Professor of Medicine

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Moazzam Shahzad, MD
Email address:	moazzamshahzad1@gmail.com
Institution name:	St. Mary's Medical Center, Huntington, WV
Academic rank:	Clinical Assistant Professor of Medicine

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q8. Do you identify as an underrepresented/minority?

- Yes

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Muhammad Umair Mushtaq, MD

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Graft Sources and Manipulation

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

Impact of CD34+ Cell Dose on Outcomes After Matched Sibling and Unrelated Donor Peripheral Blood Stem Cell Transplantation

Q16. RESEARCH HYPOTHESIS:

We hypothesize that graft cell dose (CD34+ cells) has a significant impact on outcomes after matched sibling donor (MSD) and matched unrelated donor (MUD) peripheral blood stem cell transplantation (PBSCT), and may predict engraftment, acute and chronic graft-versus-host disease (GvHD), immune reconstitution, disease relapse, non-relapse mortality (NRM) and overall survival (OS).

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

The primary objective is to determine the impact of CD34+ cell dose on OS after MSD/MUD PBSCT. The secondary objectives are to determine the rates of neutrophil and platelet engraftment, lymphocyte recovery/immune reconstitution, relapse, NRM, acute (grade III-IV) and chronic (requiring systemic steroids) GvHD, death, relapse-free survival (RFS), and GvHD-free relapse-free survival (GRFS).

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The optimal dose of CD34+ cells in allogeneic hematopoietic stem cell transplantation is not defined. Institutional practices are heterogeneous and there is a lack of uniform recommendations. There are no prospective trials or large registry datasets to answer this important question. The current literature consists of retrospective studies, mostly single-center and over a decade old. The proposed study will define the optimal dose of CD34+ cells in MSD and MUD PBSCT.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Graft cell dose has considerable therapeutic implications in hematopoietic stem cell transplantation (HSCT); however, there is no consensus on the optimal graft dose in allogeneic HSCT. Successful blood and marrow transplantation depend on the adequate dose of CD34+ cells and the marrow microenvironment that is affected by conditioning regimens, disease status, and GvHD prophylaxis [1]. Early studies in 1980s used granulocyte-macrophage colony-forming units (CFU-GM) and suggested a dose of at least 15 × 104 CFU-GM/kg (equivalent to 2.5 x 106 CD34+ cells/kg) and optimally over 50 × 104 CFU-GM/kg (equivalent to 8 x 106 CD34+ cells/kg) for successful engraftment [2]. With advances in flow cytometry and ease of CD34+ cell enumeration for clinical use, a dose of at least 105 CD34+ cells/kg was noted to be needed for an engraftment rate of 90% in preclinical studies [3]. The first prospective trial to establish the feasibility of PBSCT in the setting of MSD suggested a CD34+ cell dose of at least 4 x 106 cells/kg and a preferred dose of 6-7 x 106 cells/kg [4]. There have been several studies thereafter addressing CD34+ cell dose; however, these mostly comprise of single-center retrospective analysis. In 181 MUD-PBSCT patients (2000-04), a CD34+ cell dose of 4.2 × 106 cells/kg or above was associated with significantly lower relapse risk [5]. In a study of 1054 patients with AML/MDS (2002-2011) undergoing reduced-intensity conditioning/non-myeloablative PBSCT, a low CD34+ cell dose (<4 × 106 cells/kg in MSD and <6 × 106 cells/kg in MUD) predicted a higher non-relapse and overall mortality and an upper cell dose limit was not associated with adverse outcomes [6]. In 932 recipients of MUD PBSCT (1999-2003), a CD34+ cell dose >4.5 × 106 cells/kg resulted in rapid engraftment, lower NRM and higher OS, and higher infused doses of CD34+ cells did not result in increased acute or chronic GvHD [7]. Recent studies have shown that low CD34+ cell doses lead to an increased risk of graft failure [8, 9]. In 144 patients receiving allogeneic PBSCT with post-transplant cyclophosphamide (2012-18), CD34+ cell doses <5 x 106 cells/kg yielded inferior OS and PFS, attributable to higher NRM [10]. There have been significant advances in HSCT in recent years, including pre-transplant disease control, conditioning regimens, GvHD prophylaxis, and supportive care. There is a lack of literature regarding the optimal CD34+ cell dose and the impact of the number of infused CD34+ cells per kg of body weight on the outcomes after HSCT. We aim to address this question and provide evidence-based recommendations for the preferred graft cell dose in the setting of MSD and MUD PBSCT.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

A retrospective study will be conducted. We will include all adult patients, who underwent MSD and MUD PBSCT in the past 10 years (2010-2020), from the database maintained by the CIBMTR.

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

The study is specific to the adult patient population

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Baseline data at the time of MSD and MUD PBSCT will be ascertained, including socio-demographics, clinical and laboratory characteristics. Graft cell dose (CD34+) will be obtained per kg of body weight as well as the graft source (peripheral blood or bone marrow). Outcome measures will include minimal residual disease (MRD), immune reconstitution, viral infections, relapse, GvHD, NRM, death, RFS, GRFS, and OS. No supplemental data is required.

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

Not applicable.

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

No biological samples are required.

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

Not applicable.

Q26. REFERENCES:

1. Siena S, Schiavo R, Pedrazzoli P, Carlo-Stella C: Therapeutic relevance of CD34 cell dose in blood cell transplantation for cancer therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2000, 18(6):1360-1377.
2. To LB, Dyson PG, Juttner CA: Cell-dose effect in circulating stem-cell autografting. Lancet (London, England) 1986, 2(8503):404-405.
3. Gordon MY, Blackett NM: Some factors determining the minimum number of cells required for successful clinical engraftment. Bone marrow transplantation 1995, 15(5):659-662.
4. Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, Bourquelot P, Greinix H, Frickhofen N, Ringdén O et al: Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. Bone marrow transplantation 1998, 21(10):995-1003.
5. Nakamura R, Auayporn N, Smith DD, Palmer J, Sun JY, Schriber J, Pullarkat V, Parker P, Rodriguez R, Stein A et al: Impact of graft cell dose on transplant outcomes following unrelated donor allogeneic peripheral blood stem cell transplantation: higher CD34+ cell doses are associated with decreased relapse rates. Biol Blood Marrow Transplant 2008, 14(4):449-457.
6. Törlén J, Ringdén O, Le Rademacher J, Batiwalla M, Chen J, Erkers T, Ho V, Kebriaei P, Keever-Taylor C, Kindwall-Keller T et al: Low CD34 dose is associated with poor survival after reduced-intensity conditioning allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant 2014, 20(9):1418-1425.
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10. Elmariah H, Naqvi SMH, Kim J, Nishihori T, Mishra A, Perez L, Liu HD, Khimani F, Nieder M, Pidala J et al: CD34+ Cell Dose Influences Survival after Allogeneic Peripheral Blood Stem Cell Transplantation with Post-Transplant Cyclophosphamide. Blood 2019, 134(Supplement_1):3329-3329.

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Characteristics of patients who underwent first allo HCT for any malignant disease with peripheral blood reported to the CIBMTR 2008-2019

Characteristic	HLA-identical sibling	Matched Unrelated
No. of patients	7665	17092
No. of centers	141	167
CD34 Cell Dose x10^6/kg – Median (IQR)	5.53 (4.11, 7.69)	6.36 (4.88, 8.60)
Age at HCT - no. (%)		
18-29	544 (7)	1301 (8)
30-39	703 (9)	1481 (9)
40-49	1262 (16)	2332 (14)
50-59	2452 (32)	4294 (25)
60-69	2402 (31)	6058 (35)
>=70	301 (4)	1628 (10)
Primary disease for HCT - no. (%)		
AML	2966 (39)	7184 (42)
ALL	993 (13)	1937 (11)
Other leukemia	244 (3)	507 (3)
CML	235 (3)	512 (3)
MDS/MF	1580 (21)	3680 (22)
Other acute leukemia	80 (1)	153 (1)
NHL	763 (10)	1524 (9)
HD	120 (2)	250 (1)
PCD	219 (3)	342 (2)
MPN	464 (6)	1005 (6)
Indicator of HCT cases in CRF retrieval - no. (%)		
No	2730 (36)	9452 (55)
Yes	4935 (64)	7640 (45)
Year of Transplant - no. (%)		
2008 - 2013	2802 (37)	4359 (26)
2014 - 2019	4862 (63)	12735 (74)
Follow-up - median (range)	60 (3-157)	49 (3-154)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Identifying the Optimal Stem Cell Dosing for Peripheral Blood Stem Cell Transplantation with Post-Transplant Cyclophosphamide

Q2. Key Words

CD34, stem cell dose, haploidentical, post-transplant cyclophosphamide

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hany Elmariah
Email address:	hany.elmariah@moffitt.org
Institution name:	H. Lee Moffitt Cancer Center
Academic rank:	Assistant Member

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Nelli Bejanyan
Email address:	nelli.bejanyan@moffitt.org
Institution name:	H. Lee Moffitt Cancer Center
Academic rank:	Associate Member

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Hany Elmariah

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

#CK27-01: Haploidentical donor transplantation versus matched donor allogeneic hematopoietic cell transplantation outcomes in patients with myelofibrosis: Co-PI
#2010-258: Impact of Measurable Residual Disease Status on Outcomes of Acute Myeloid Leukemia Patients 18-65 Years Old in First Complete Remission Undergoing Allogeneic Hematopoietic Cell Transplantation (El Chaer, Hourigan): Co-Investigator
#AC17-01: Impact of hematopoietic cell transplantation following CD19 CAR T cells for the treatment of acute lymphoblastic leukemia: Co-investigator
#CT20-04: Outcomes of CART for ALL: Co-investigator

Q13. PROPOSED WORKING COMMITTEE:

- Graft Sources and Manipulation

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

In the setting of haploidentical peripheral blood stem cell transplant with post-transplant cyclophosphamide, what are the optimal CD34+, CD3+, and total nucleated cell doses?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that CD34+ cell dose is an important predictor of post-transplant outcomes in the setting of allogeneic haploidentical donor peripheral blood stem cell transplant (PBSCT) with post-transplant cyclophosphamide (PTCy).

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1. Determine the impact of infused CD34+ cell dose on transplant outcomes following allogeneic haploidentical donor PBSCT with PTCy.
2. Determine the impact of infused total nucleated cell (TNC) dose on transplant outcomes following allogeneic haploidentical donor PBSCT with PTCy.
3. Determine the impact of infused CD3+ cell dose on transplant outcomes following allogeneic haploidentical donor PBSCT with PTCy.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Allogeneic haploidentical HCT with PTCy is an increasingly utilized platform to expand the donor pool for patients requiring transplant. Though this platform was initially developed with bone marrow grafts, peripheral blood stem cell grafts are commonly substituted due to potential improvements in engraftment and relapse.1 Prior studies have suggested that infused cell dose influences outcomes of haploidentical bone marrow transplant with PTCy.2 Thus, it is likely that infused cell dose may also impact outcomes following peripheral blood stem cell transplants (PBSCT) with PTCy. As cell dose is a modifiable variable, identifying the optimal cell dose would result in a feasible strategy to improve outcomes for patients receiving allogeneic PBSCT with PTCy.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The administration of high doses of post-transplant cyclophosphamide (PTCy) has proven to be a potent intervention to control donor/recipient alloreactivity and allow for safe HCT even when using HLA disparate donors.3 Multiple studies have shown that HLA haploidentical (haplo) HCT with PTCy results in low rates of GVHD, NRM, and comparable survival compared to outcomes with matched donor transplants.3-7 However, rates of relapse may be higher with this HCT platform, particularly in the setting of diseases at high risk for relapse such as myeloid neoplasms.7

Optimization of the graft source is one strategy to potentially improve the efficacy of HCT with PTCy. McCurdy, et al. demonstrated that administration of higher total nucleated cell dose with haplo bone marrow transplant (BMT) with PTCy yields decreased relapse rates and improved progression free survival (PFS) and overall survival (OS), without increased GVHD.2 However, this study did not address the use of peripheral blood stem cell grafts with PTCy. Subsequently, Bashey, et al. demonstrated that using peripheral blood stem cell transplant (PBSCT) with PTCy instead of bone marrow may reduce relapse rates and improve PFS in high risk diseases, though does result in higher rates of GVHD.1

In light of these results, many institutions prefer PBSCT as the graft source for haplo HCT with PTCy. Published trials have set varying caps on infused doses, though no study has compared outcomes based on cell dose to identify the optimal dose cap.8,9 Single institution data published by our center suggested that patients receiving a CD34+ cell dose <5x106/kg had worse non-relapse mortality (HR = 4.51, 95% CI: 1.92-10.58, $p < 0.001$), progression- free survival (HR = 4.11, 95% CI: 2.07-8.15, $p < 0.001$), and overall survival (HR = 4.06, 95% CI: 2.00-8.25, $p \leq 0.001$) compared to higher CD34+ cell doses.10 Larger studies are warranted to confirm this finding.

Existing data suggests that cell dose is likely to impact outcomes of allogeneic haplo PBSCT with PTCy. Thus, we propose to better characterize this impact in order to identify optimal cell doses and improve outcomes in patients receiving haplo PBSCT with PTCy.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

1. Patients having received allogeneic haploidentical PBSCT with PTCy for hematologic malignancy

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Patient Related Variables:
1. Age
2. Gender
3. Ethnicity
4. Functional status (ECOG or KPS)
5. Hematopoietic cell transplant comorbidity index (HCT-CI)11

Disease Related Variables:
1. Date of diagnosis
2. BMT Disease Risk Index (DRI)12
3. Remission status at time of HCT
6. Treatments prior to HCT

BMT Related Variables:
1. Date of diagnosis
2. Conditioning regimen
3. Conditioning intensity (myeloablative, reduced intensity, nonmyeloablative)
4. Donor age
5. Donor gender
6. Graft cell dose (TNC, CD34+ cells, and CD3+ cells)
7. Date of transplant
8. Donor/Recipient Cytomegalovirus matching
9. Donor/recipient ABO compatibility
10. GVHD prophylactic regimen (including duration)
11. Post-BMT maintenance therapy

Outcomes
1. Death (yes/no)
2. Date of Death
3. Cause of death
4. Relapse (yes/no)
5. Date of relapse
6. Nonrelapse mortality (yes/no)
7. Date of absolute neutrophil recovery >0.5k/uL
8. Date of platelet recovery date >20k/uL
9. CD33+ Chimerism results (days 30, 60, 90, 6 months, 1 year)
10. CD3+ Chimerism results (days 30, 60, 90, 6 months, 1 year)
11. Date of last follow up
12. Acute GVHD grade (none, I-IV)
13. Date of acute GVHD grade II-IV
14. Date of acute GVHD grade III-IV
15. Chronic GVHD severity (limited vs. extensive vs. none)
16. Date of chronic GVHD
17. Treatment for GVHD (type)
18. Cytokine release syndrome (non-infectious fevers)

Study Design:
This is a retrospective data review of all patients with who have undergone allogeneic haploidentical PBSCT with PTCy within the CIBMTR database. The primary endpoint is progression free survival (PFS). Other endpoints of interest will include OS, relapse rates, NRM, GVHD, engraftment, and GRFS, all calculated from the time of HCT. Survival endpoints will be calculated using the Kaplan-Meier method. Cumulative Incidences (CuI) of other endpoints including GVHD, relapse rates, and NRM will be determined. Outcomes will be compared based on the total nucleated cell dose, the CD34+ cell dose, and the CD3+ cell dose given with the graft in order to determine the impact of these cell doses on outcomes. Univariate and multivariate analyses will be pursued to determine variables associated with outcomes. For comparisons, p-values < 0.05 will be considered significant.

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

n/a

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

n/a

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

n/a

Q26. REFERENCES:

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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Characteristics of patients who underwent haploidentical HCT for AML, ALL, or MDS with PTCY reported to the CIBMTR 2014-2019

Characteristic	Haplo
No. of patients	1729
No. of centers	121
CD34 Cell Dose x10^6/kg – Median (25th, 75th percentiles)	5.16 (4.48, 7.52)
TNC Cell Dose x10^8/kg – Median (25th, 75th percentiles) *	7.88 (5.48, 10.85)
CD3+ Cell Dose Available	
Yes	747 (43)
No	982 (57)
Age at HCT - no. (%)	
<10	22 (1)
10-17	31 (2)
18-29	206 (12)
30-39	162 (9)
40-49	228 (13)
50-59	388 (22)
60-69	522 (30)
>=70	170 (10)
HCT-CI Score - no. (%)	
0-2	782 (45)
3+	930 (54)
TBD	17 (1)
Primary disease for HCT - no. (%)	
AML	955 (55)
ALL	370 (21)
MDS/MF	404 (23)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	503 (29)
Yes	1226 (71)
Year of Transplant - no. (%)	
2014 - 2019	1729 (100)
Follow-up - median (range)	35 (4-78)

*Not available for n=761

I. Study Title

Optimizing HLA Matched Sibling *versus* Alternative (Well-Matched Unrelated, Haploidentical and Mismatched Unrelated) Donor Selection: Update Including Donor Age and HLA-DPB1 Match Status in Recipients of Allogeneic Hematopoietic Cell Transplantation

II. Key Words

Donor source, donor age, HLA-DPB1, donor selection, allogeneic hematopoietic stem cell transplant

III. PI Information

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IV. Current Ongoing Work with CIBMTR

Shaffer: IB21-01, sub-investigator

Choe: Limited to participation in the Acute Leukemia and GVHD Working Committees

V. Proposed Working Committee:

Graft Sources and Manipulation

VI. Research Question

Previous studies have not yielded a conclusion as to whether younger 8/8 matched unrelated donors (URDs) or younger haploidentical or mismatched unrelated donors are better than older matched sibling donors. Here we ask if revisiting this question with registry data and incorporating HLA-DPB1 donor/recipient matching will provide greater clarity as to whether younger matched URDs, mismatched URDs or haploidentical donors are preferred over older sibling donors. A second goal of this study is to use the composite endpoint of GVHD-free/relapse-free survival (GRFS), which captures important causes of transplant morbidity and mortality.

VII. Research Hypothesis

The hypothesis of this study is that allogeneic hematopoietic cell transplant (allo-HCT) recipients aged ≥ 50 years have higher overall survival (OS) with a young (18-32 years of age) HLA 8/8 matched URD compared to an older aged (≥ 50 years) fully matched sibling donor. We also hypothesize that allo-HCT recipients aged ≥ 50 years may have higher OS with a young (18-32 years of age) HLA-haploidentical related or mismatched unrelated donor when compared to recipients of an older aged (≥ 50 years) fully matched sibling donor.

Furthermore, we hypothesize that HLA 8/8 matched URDs with HLA-DPB1 matched or that is T-cell epitope functional-distance (TCE-FD) permissive further increases OS compared to HLA-DPB1 mismatched and TCE-FD non-permissive URD recipients vs older aged (≥ 50 years) fully matched sibling donor.

VIII. Specific Objectives

The primary aim of the study will be to compare the OS in recipients of allo-HCT (aged ≥ 50-years) between two main groups: the reference arm of the study will be recipients of an HLA matched sibling donor allo-HCT, with donors that are aged ≥ 50 years. Because the majority of patients undergoing older sibling donor allo-HCT are ≥ 50 years old themselves, and this population is vulnerable to transplant toxicity, we will limit the analysis to recipients ≥ 50 years old.

The three experimental arms of the study will be recipients of (1) HLA 8/8 (HLA-A, -B, -C, -DRB1) matched URD allo-HCT aged 18-32 years, (2) HLA-haploidentical donors aged 18-32 years and (3) HLA-mismatched (4/8-7/8 at HLA-A, -B. -C, -DRB1) URD aged 18-32 years. The matched URD group will be subdivided based on HLA-DPB1 matching status (matched, mismatched/TCE-FD permissive, mismatched/TCE-FD non permissive). Graft *versus* host disease prophylaxis in the haploidentical and mismatched URD groups will be limited to post-transplant cyclophosphamide. The study will be limited to allo-HCT performed in 2013-2019.

The secondary aims of the study are to determine the GRFS, relapse-free survival, cumulative incidence of relapse, non-relapse mortality (NRM), cumulative incidence of grades II-IV acute GVHD and NIH consensus criteria moderate to severe chronic GVHD in the above cohorts.

An adjusted Cox model will be performed to compare clinical outcomes between the reference and experimental arms, adjusted for informative covariates tested in a univariate analysis. A secondary sensitivity analysis will also be performed using 5-year age increments to determine if there are greater risks associated with specific donor and recipients ages, between the reference arm compared with the three experimental groups.

IX. Scientific Impact

There has been a marked rise in the median age of patients receiving allo-HCT. Because sibling age correlates with patient age, transplant physicians are often faced with the choice of using an older-aged, matched sibling donor *versus* using a young, HLA-matched URD or young, HLA-haploidentical donor for allo-HCT.

The current published data are inadequate to inform this important clinical decision. A Center for International Blood and Marrow Research (CIBMTR) analysis analyzed outcomes in transplant recipients aged ≥ 50-years from either matched sibling donor ≥ 50-years or matched URD < 50-years (1). In recipients with a performance score of 90 or 100, overall mortality was higher after URD compared to sibling donor transplants. However, this CIBMTR analysis was performed in a cohort of patients who received transplants from 1995 to 2005. Although all donor-recipient pairs were 8/8 HLA-matched, given the historical nature of the cohort, HLA-DPB1 status was not evaluated. Furthermore, the findings were not observed in recipients with a performance score < 90. The analysis also identified an age cut-off of 67 years at which point regardless of performance score, overall survival and relapse were worse with a matched sibling donor. This indicates an existing standard of increasing age in matched sibling donors outweighing the benefits of sibling versus unrelated transplantation. Additionally, there is some conflicting data suggesting that a young URD may be associated with improved outcomes (2-5). In a retrospective analysis limited to allo-HCT for acute myeloid leukemia (AML), a matched URD donor age of ≤ 39-years was associated with improved overall survival of recipients compared to a matched sibling donor > 39-years of age (2). Similarly, compared to a matched URD < 60-years, matched related donors ≥ 60-years of age were associated with higher risks for late mortality and treatment failure in transplant recipients (4). A similar finding was also observed in a single center, retrospective analysis of 179 patients with myelodysplastic syndrome (MDS) or AML transplanted between 2000-2013, where matched related donors > 50-years had lower 3-year OS than matched URD < 50-years (54% vs 72%, p<0.001) (5). In another study of reduced intensity conditioning allo-HCT in AML patients aged > 55-years, there was no significant difference in clinical outcomes from a matched URD compared to an older matched sibling donor (3). A study of 442 patients (278 MRD, 174 MUD) showed higher risks for late mortality (>18 months post-transplant) and treatment failure in matched sibling donors ≥ 60-years compared to matched URD (HR 4.41 (1.52-12.8), p=0<0.006) and matched sibling donors < 60-years (6).

Additionally, non-permissive mismatching between donor and recipient HLA-DPB1 in the GVH direction, as defined by the TCE-FD method, has been shown to be a predictive biomarker for increased risk of GVHD and transplant related mortality (TRM) and may confer similar risk to HLA class I or HLA-DRB1 mismatching (7-10). Varying expression levels of DPB1 alleles in the setting of GVH mismatches have been shown to influence the risk for GVHD (11-13). It has been demonstrated that approximately 30% of otherwise HLA well matched unrelated donor/recipient pairs are TCE-FD non-permissively mismatched at HLA-DPB1 (14).

Despite these data, the impact of HLA-DPB1 status has not been evaluated in large-scale studies comparing donor options of the older matched sibling donor to a young matched URD.

A more recent analysis of transplant recipients in the CIBMTR reproduced data supporting a strong preference for a younger unrelated donor after allo-HCT (15, 16). Here, analysis of over 10,000 8/8 MUD allo-HCT recipients demonstrated that transplantation of grafts from young donors aged 18-32 years were associated with improved survival compared to older aged donor cohorts, and that for every 10-year increment in donor age, there was a 5.5% increase in the hazard ratio for overall mortality (15). Older donor transplants were associated with greater non-relapse mortality (NRM) and acute GVHD. Indeed, current National Marrow Donor Program (NMDP)/CIBMTR guidelines for matched URD donor selection prioritizes donor age (17). In contrast, donor age is not considered as carefully for related transplants.

The effect of donor age with the use of post-transplant cyclophosphamide is also unknown. The impact of post-transplant cyclophosphamide and donor age in haploidentical and matched URD in comparison to MRD has not been definitively determined. This will be increasingly important to understand given the increasing use of post-transplant cyclophosphamide in the setting of HLA-haploidentical transplantation. In a single institution retrospective analysis of 406 patients, HLA-haploidentical transplants with donors <

35-years of age had lower incidence of GVHD, and similar OS, DFS, relapse, and TRM compared to matched sibling donors and matched URD ≥35-years (18). However, further studies regarding the use of post-transplant cyclophosphamide or analysis of donor age in haploidentical related donor transplants are lacking. Further age stratification may demonstrate improved survival with haploidentical donor compared to older-aged, matched sibling donors with a greater age differential (higher age cut-offs) or in a large registry analysis. This would have important clinical practice implications.

Transplantation of HLA-mismatched (4/8-7/8) URD using post-transplant cyclophosphamide based GvHD prophylaxis is being increasingly utilized in recent years, especially in recipients of racial/ethnic minorities. The NMDP recently published a phase II, multi-center trial of mismatched URD allo-HCT in 80 transplant recipients. Despite over half the patients having an HCT-Comorbidity Index (HCT-CI) score of ≥ 3, there was an encouraging OS of 76% at 1-year, with an average donor age of 29-years (19). Additionally, no significant differences were reported based on conditioning intensity or HLA-match grade. Younger donors were associated with significant improved OS in this study. Another study of mismatched (≥ 6/8) URD with post-transplant cyclophosphamide GvHD prophylaxis and a median donor age of 32-years has also demonstrated promising results with a 1-year OS of 87% and GRFS of 68% (20). The HLA-Mismatched Unrelated Donor with peripheral-blood stem cell graft and post-transplantation cyclophosphamide (ACCESS) study is enrolling patients (NCT04904588). Although the current donor selection priority has been selecting a matched sibling donor and avoiding HLA-mismatches, this has not been well studied in the setting of post-transplant cyclophosphamide. Indeed, there has been provocative data demonstrating improved outcomes with selective HLA-mismatching at individual HLA loci in haploidentical transplantation (21). Together, based on these data, we include young (18-32 years) mismatched URDs as our third experimental arm.

As the field has evolved to transplant older patients and consequently older related donors, donor age discrepancies and its impact are becoming increasingly important. This is perhaps why the algorithm for donor selection weights is inconsistent over time as demonstrated by Shaw et al, where donor age emerged as the sole determinant for survival (16). As we are seeing that matched URD age is more definitively impactful on survival, we should similarly analyze the effect of donor age on matched sibling donor and haploidentical transplants in comparison. The results of this analysis will directly inform donor selection for patients with multiple donor options.

Together, these data support that older donor age and HLA-DPB1 are risk factors for GVHD. Relieving both with the use of a young HLA-DPB1 matched/mismatched permissive matched URD or using a young haploidentical or mismatched donor over an older aged fully matched MSD in allo-HCT recipients aged ≥ 50 years would have a significant effect on this large, and progressively increasing group of transplant recipients. Indeed, the effects of donor age have not been recently evaluated rigorously in a large cohort and it is critical to study this question in the modern era. Understanding the outcomes of donor age across these graft sources will optimize donor selection and improve transplant outcomes.

X. Scientific Justification

Allo-HCT is a curative therapy for many patients with high-risk neoplasia; however, the propensity to cause transplant related morbidity and mortality via GVHD limits the application of the procedure. Matching of the canonical class I human leukocyte antigens (HLA) HLA-A, -B, -C, as well as the class II HLA DRB1 between donor and recipient reduces the likelihood of transplant related mortality via a reduction in severe GVHD (22). The current standard of care is to use an HLA matched donor at HLA-A, -B, -C, and DRB1. However, the weight of that benefit may also hinge on donor age, which is increasingly more notable as transplant age has increased.

The HLA-DP locus of the HLA class II system is comprised of two polymorphic heterodimers: HLA-DPA1 and HLA-DPB1. Of these two heterodimers, HLA-DPB1 is more polymorphic and known to have > 900 alleles. In a large CIBMTR series, it was found that only 10-20% of 8/8 (HLA-A, -B, -C, DRB1) HLA-matched unrelated donors were matched at both HLA-DPB1 alleles. Therefore, the majority of URD allo-HCT are performed across HLA-DPB1 mismatches (7). In contrast, although HLA-DPB1 mismatches are reported from patient-HLA matched sibling pairs, the rates are significantly lower, at approximately 2% (23).

In recent years, there has been development of the T-cell epitope (TCE) grouping method, which has allowed for the identification of so-called “permissive” and “non-permissive” HLA-DPB1 mismatches. HLA-DPB1 permissive mismatches are those that can be tolerated post-transplantation due to low immunogenic potential, whereas non-permissive mismatches are believed to be associated with higher immunogenicity and consequently, a higher risk of developing host-versus-graft or GVH effects, depending on the direction of the mismatch (8, 14, 24, 25).

The TCE methodology was further refined to use an *in silico* numerical functional distance scoring system (TCE-FD) for the prediction of TCE groups and confirmed using a large registry-based analysis (8). Collectively, these results indicated that the TCE-FD defines a group of donor/recipient pairs that are permissively mismatched and have similar outcomes to HLA-DPB1 matched donor recipients, whereas non-permissive mismatches are immunogenic, leading to greater acute GVHD, and increasing the risk for non-relapse mortality in recipients of 8/8-HLA matched URD transplants (8, 14, 26). Recent data support that disparity in peptide repertoires between non-permissively mismatched HLA-DPB1 alleles may play a significant role in immunogenicity (27). The potential impact of HLA-DQB1 status will also be studied by including it as a covariate in the URD analysis.

Younger donor age has been established to improve survival and enhance protection from GVHD after matched URD allo-HCT compared to older URDs. The benefit of a young URD age may be hypothetically related to the longevity of older hematopoietic stem cells, thereby potentially increasing the risk for developing mutagenic changes, and subsequently malignant clones (28). Additionally, some murine

models have suggested an altered functional status of older hematopoietic stem cells (29). Variations in T-lymphocyte populations in old versus younger-aged stem cell grafts may also be contributing to differences in transplant outcomes within these groups (30). Together, these data support the notion that when comparing matched sibling donor to URD allo-HCT outcomes, the impact of HLA-DBP1 status needs to be considered within the context of donor age. With respect to HLA-haploidentical donor options, retrospective data has suggested that a young, haploidentical relative donor may be preferred over an older matched unrelated donor due to significantly lower rates of chronic GVHD (18). However, this question has not been definitively answered in a registry setting.

In the context of the current study, we propose to determine the prognostic implications of HLA-DPB1 status and a young donor age on 8/8 matched URDs. If our hypothesis is confirmed, this would suggest that a young, HLA-DPB1 matched or mismatched permissive unrelated donor should be preferentially used over older-aged fully matched sibling donor in allo-HCT recipients that are aged ≥ 50 years. We also propose to determine clinical outcomes of young haploidentical, or mismatched URD donor age compared to older aged fully matched donors. These outcome data would be practice changing and immediately relevant to a large and progressively increasing population of older transplant recipients globally. Due to the sample size requirements of this study the CIBMTR is uniquely positioned to support this research.

XI. Scientific Justification Graphic (see attached)

XII. Participant Selection criteria

1. ≥50-year-old recipients of HL*A* matched sibling and unrelated donor allo-HCT (matched at HLA-A, -B, -C, -DRB1) using high-resolution HLA typing
2. Available HLA-DPB1 typing of the donor and recipient (for 8/8 matched unrelated donor recipients)
3. Peripheral blood stem cell or bone marrow allografts
4. Year of transplant: 2013-2019
5. Donor age: ≥50-year-old matched sibling donor (reference cohort) and 18 to 32-year-old matched URD, mismatched URD and haploidentical donor (experimental arm)
6. Disease histology: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS) and chronic myeloid leukemia (CML) will be included.
7. Only first allo-HCT recipients will be included
8. Conditioning Regimen: Myeloablative or non-myeloablative
9. Transplants using T-cell depletion will be excluded

XIII. If this study does not include pediatric patients, please provide justification

The reference cohort for this study are transplant recipients aged ≥ 50-years with MSD. Sibling donors in this older population would be anticipated to be of similar age to the transplant recipient.

XIV. Data Requirements (list patient-, disease- and infusion-variables to be considered in MVA)

1. Clinical data:

a. The study does not require collection of additional data beyond that contained in existing CIBMTR forms.
b. The clinical data points required for this study are summarized in the below table.

2. HLA-DBP1 typing
    a. Donor/recipient pairs with existing HLA-DPB1 typing are included without need for further biospecimen analysis.

Patient specific
Age HCT-CI Revised disease risk index Gender ABO Disease histology Disease status CMV serostatus Karnofsky performance status Race: White vs. Black vs. Asian/Pacific Islander vs. Hispanics vs Others
Transplant specific
Donor/recipient HLA-DPB1 typing / status Donor age Donor gender Donor ABO Year of transplant CMV serostatus Conditioning regimen: myeloablative vs. non-myeloablative Graft type: bone marrow or peripheral blood GVHD prophylaxis: CSA/MTX, Tac/MTX, CSA/MMF, Tac/MMF, CNI alone, post-transplant cyclophosphamide Post-transplant variables of interest: Date of engraftment Date of acute GVHD diagnosis Organ involvement of acute GVHD Treated with steroids: yes or no Date of chronic GVHD diagnosis Date of relapse Date of death

XV. Sample Requirements (if study will use biologic samples from the CIBMTR Repository)

Biologic samples will not be required for this study.

XVI. Non-CIBMTR Data Source

This study uses data from the CIBMTR Research Database and CIBMTR Sample Repository. No external data sources will be used.

XVII. References

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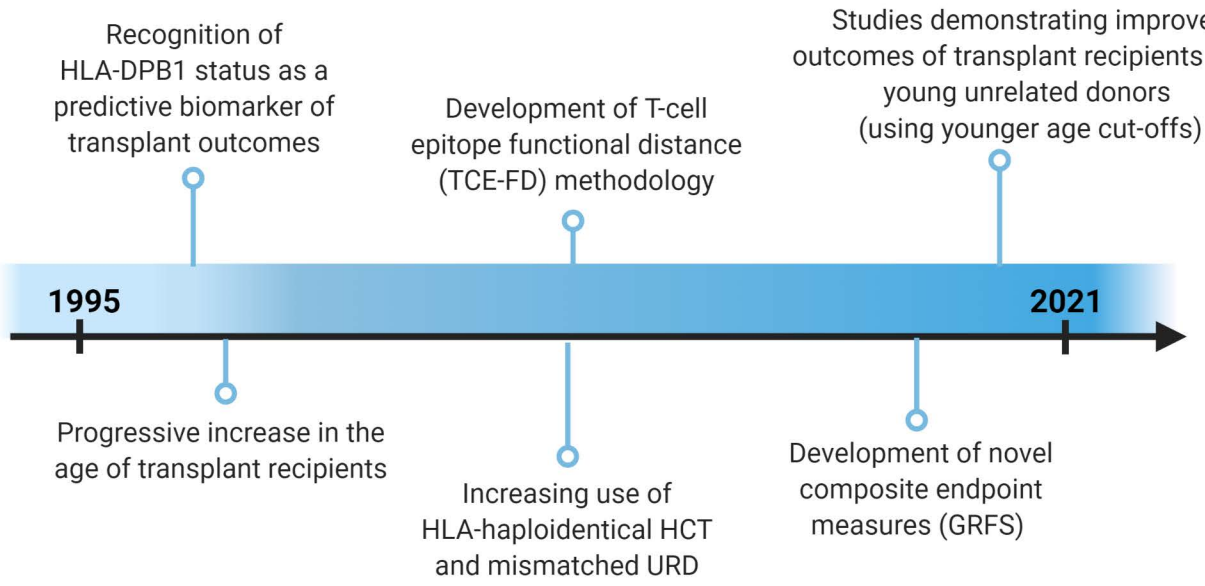
XVIII. Conflicts of Interest

Do you have any conflicts of interest pertinent to this proposal concerning?

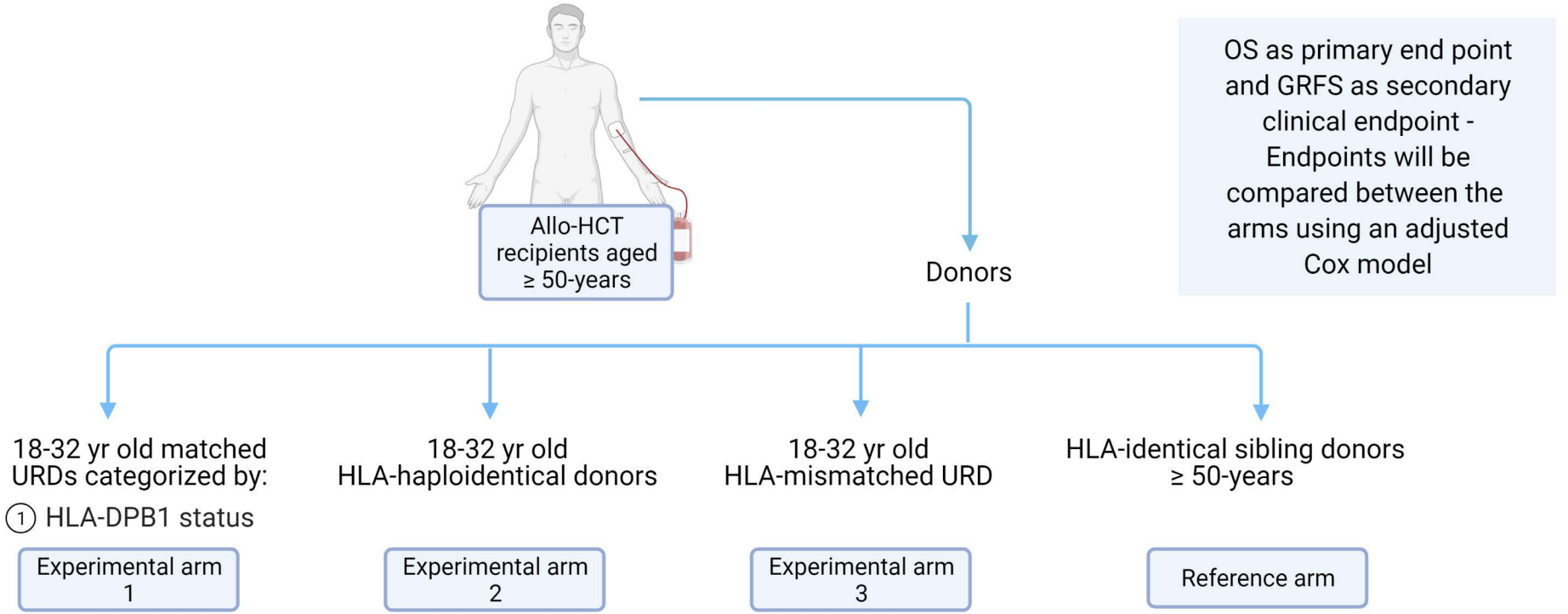
- Employment (such as an independent contractor, consultant or providing expert testimony)?
- Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
- Ownership (such as equity, ownership, or financial interests)?
- Transactions (such as honoraria, patents, royalties, and licenses)?
- Legal (such as pending or current arbitration or legal proceedings)?

□ Yes.
⊟ No.

Changes over time



Study Schematic



Characteristics of patients who underwent first allo HCT for AML, ALL, MDS, CML disease reported to the CIBMTR 2013-2019

Characteristic	HLA-identical sibling	Haploidentical	HLA-Matched Unrelated	HLA-Mismatched Unrelated
No. of patients	4794	873	6970	845
No. of centers	134	105	129	102
Age at HCT - no. (%)				
50-59	1918 (40)	504 (58)	2211 (32)	316 (37)
60-69	2506 (52)	339 (39)	3602 (52)	426 (50)
≥70	370 (8)	30 (3)	1157 (17)	103 (12)
Donor age group - no. (%)				
18-32	0 (0)	873 (100)	6970 (100)	845 (100)
50-59	2377 (50)	0 (0)	0 (0)	0 (0)
60-69	2137 (45)	0 (0)	0 (0)	0 (0)
≥70	280 (6)	0 (0)	0 (0)	0 (0)
Primary disease for HCT - no. (%)				
AML	2649 (55)	469 (54)	3773 (54)	469 (56)
ALL	531 (11)	138 (16)	658 (9)	85 (10)
CML	161 (3)	34 (4)	183 (3)	23 (3)
MDS	1453 (30)	232 (27)	2356 (34)	268 (32)
Recipient / 1st donor allele level matching at HLA-DPB1 - no. (%)				
0	1 (0)	1 (0)	1393 (20)	200 (24)
1	13 (0)	79 (9)	2927 (42)	318 (38)
2	426 (9)	21 (2)	1287 (18)	87 (10)
Missing	4354 (91)	772 (88)	1363 (20)	240 (28)
Graft Source - no. (%)				
Bone marrow	216 (5)	240 (27)	854 (12)	126 (15)
Peripheral blood	4578 (95)	633 (73)	6116 (88)	719 (85)
Planned GVHD prophylaxis - no. (%)				
Cyclophosphamide alone	40 (1)	3 (0)	40 (1)	1 (0)
Cyclophosphamide + others	282 (6)	846 (97)	609 (9)	239 (28)
FK506 + MMF ± others	530 (11)	21 (2)	996 (14)	71 (8)
FK506 + MTX ± others	2603 (54)	1 (0)	3954 (57)	360 (43)
FK506 ± others	426 (9)	0 (0)	622 (9)	51 (6)
FK506 alone	110 (2)	1 (0)	167 (2)	16 (2)
CSA + MMF ± others	346 (7)	1 (0)	344 (5)	64 (8)
CSA + MTX ± others	395 (8)	0 (0)	202 (3)	40 (5)
CSA + others	17 (0)	0 (0)	21 (0)	1 (0)
CSA alone	45 (1)	0 (0)	15 (0)	2 (0)

Characteristic	HLA-identical sibling	Haploidentical	HLA-Matched Unrelated	HLA-Mismatched Unrelated
Indicator of HCT cases in CRF retrieval - no. (%)				
No	3232 (67)	475 (54)	4496 (65)	533 (63)
Yes	1562 (33)	398 (46)	2474 (35)	312 (37)
Year of Transplant - no. (%)				
2013	489 (10)	19 (2)	734 (11)	107 (13)
2014	786 (16)	56 (6)	841 (12)	121 (14)
2015	753 (16)	89 (10)	883 (13)	124 (15)
2016	739 (15)	125 (14)	968 (14)	114 (13)
2017	692 (14)	155 (18)	1040 (15)	111 (13)
2018	731 (15)	219 (25)	1199 (17)	136 (16)
2019	604 (13)	210 (24)	1305 (19)	132 (16)
Follow-up - median (range)	48 (3-101)	34 (6-96)	43 (3-101)	46 (3-97)