Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Salt Lake City, Utah
Sunday, April 24, 2022, 12:15pm – 2:00pm

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Statistician:	**Rasha Atshan, MS, CIBMTR Statistical Center, Milwaukee, WI; E-mail: ratshan@mcw.edu.**

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1. **Introduction**
   a. Minutes and Overview Plan from February 2021 Tandem meeting (Attachment 1)
2. **Accrual summary** (Attachment 2)
3. **Presentations, published or submitted papers**
   a. **PC20-01** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing Autologous Hematopoietic Stem Cell Transplantation. (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong). Manuscript in preparation. ***Poster Presentations at 2022 Tandem meeting.***
4. **Studies in progress** (Attachment 3)
   a. **PC19-02** Does mixed peripheral blood T Cell Chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs), ***Protocol Development.***
   b. **PC19-03** The impact of pre-transplant extramedullary disease on the outcome of Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia in Children. (H Rangarajan/P Satwani/K Rao/D Chellapandian/Juliana Silva), ***Data file preparation.***
   c. **PC20-01** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing Autologous Hematopoietic Stem Cell Transplantation. (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong). **Manuscript in preparation.**
   d. **PC20-02** Germline genetics of pediatric Myelodysplastic Syndromes (MDS). (Jenny Poynter; Logan Spector), ***Sample Typing.***
5. **Future/proposed studies**
   a. **Prop 2110-19** Transplantation and Cellular Therapy for children and young adults with Down's Syndrome and Acute Leukemia. (Seth Rotz; Rabi Hanna), (Attachment 4).

b. **Prop 2110-43** Evaluation of Allogeneic Hematopoietic Cell Transplantation outcomes and prognostic factors in Acute Megakaryoblastic Leukemia. (Akshay Sharma; Neel S. Bhatt), (Attachment 5).
c. **Prop 2110-45 / 2110-81** Outcomes after post-transplant Cyclophosphamide based haploidentical Hematopoietic Cell Transplantation in pediatric patients with Acute Leukemia and Myelodysplastic Syndrome. (Akshay Sharma; Neel S. Bhatt; Hemalatha Rangarajan; Prakash Satwani), (Attachment 6).
d. **Prop 2110-165** Evaluating predictors of access and outcomes with Hematopoietic Cell Transplantation (HCT) in pediatric and adolescent patients with relapsed/refractory classical Hodgkin Lymphoma (cHL) after treatment on an initial cooperative group clinical trial. (Sharon M. Castellino; Justine Kahn), (Attachment 7).
e. **Prop 2110-211** Outcomes of children and adolescents undergoing Autologous or Allogeneic Hematopoietic Stem Cell Transplantation for first relapse or refractory non-Hodgkin Lymphoma. (Jennifer Belsky; Sarah Alexander), (Attachment 8).
f. **Prop 2110-272** Hematopoietic Stem Cell Transplant outcomes for Infant Acute Lymphoblastic Leukemia. (Nahal Rose Lalefar), (Attachment 9).
g. **Prop 2110-274** Developing a pediatric Hematopoietic Cell Transplantation-Composite Risk (pHCT-CR) Score to predict outcomes in children with Acute Leukemia undergoing Hematopoietic Cell Transplantation. (Madhavi Lakkaraja; Brian Friend), (Attachment 10).

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

h. **Prop 2110-38** Impact of Graft Versus Host Disease following Allogeneic Hematopoietic Cell Transplantation on Leukemia free survival in Hematologic Malignancies within the pediatric disease Risk Index Risk Stratification. (Andrea Bauchat; Muna Qayed), (Attachment 11).

Dropped proposed studies

a. **Prop 2109-16** Use of Thiotepa in Stem Cell Transplantation for pediatric Acute Lymphoblastic Leukemia. *Dropped due to limited availability of resources.*
b. **Prop 2110-67** Impact of Non-HLA donor characteristics in pediatric patients receiving haploidentical Stem Cell Transplantation for Malignant and Non-Malignant diseases. *Dropped due to overlapping with current study/publication.*
c. **Prop 2110-77** Outcomes of Allogeneic Hematopoietic Cell Transplantation in pediatric patients with non-remission Acute Leukemia. *Dropped due to small sample size*.
d. **Prop 2110-170 / 2110-330** Post-transplant Cyclophosphamide vs. TCR αβ depletion approaches for Haploidentical Transplant in pediatric patients with Acute Leukemias and Myelodysplastic Syndromes. (Hemalatha Rangarajan; Prakash Satwani; Amanda M. Li). *Dropped due to small sample size*
e. **Prop 2110-183** Comparison of relapse incidence following Allogeneic Hematopoietic Cell Transplantation among children with Philadelphia Positive like versus non-Philadelphia Positive like Acute Lymphoblastic Leukemia. *Dropped due to the need for supplemental data.*
f. **Prop 2110-261** Outcomes of Myeloablative Chemotherapy with Autologous Hematopoietic Cell rescue in pediatric patients with Choroid Plexus Carcinoma. *Dropped due to small sample size.*
g. **Prop 2110-282** The burden of intermediate infections in children, adolescents, and young adults with Hematologic Malignancies undergoing Allogeneic Hematopoietic Cell Transplantation. *Dropped due to the need for supplemental data.*
h. **Prop 2110-305** Outcomes of Allogenic Hematopoietic Cell Transplantation in children and young adults with Advance Stage Chronic Myeloid Leukemia. *Dropped due to small sample size.*

6. Other Business

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 for the Pediatric Cancer Working Committee

Characteristics of patients aged ≤ 18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2010 - 2019

HLA-identical sibling HCT	TED, N (%)	CRF, N (%)
Acute myeloid leukemia	820	163
Bone Marrow	640 (78)	129 (79)
Peripheral blood	161 (20)	24 (15)
Cord Blood	19 (2)	10 (6)
Acute lymphoblastic leukemia	1163	167
Bone Marrow	940 (81)	131 (78)
Peripheral blood	193 (17)	23 (14)
Cord Blood	30 (3)	13 (8)
Chronic myeloid leukemia	83	12
Bone Marrow	69 (83)	10 (83)
Peripheral blood	11 (13)	0
Cord Blood	3 (4)	2 (17)
Myelodysplastic Syndrome	201	35
Bone Marrow	170 (85)	28 (80)
Peripheral blood	27 (13)	4 (11)
Cord Blood	4 (2)	3 (9)
Hodgkin lymphoma	11	2
Bone Marrow	5 (45)	1 (50)
Peripheral blood	6 (55)	1 (50)
Non-Hodgkin lymphoma	90	22
Bone Marrow	70 (78)	17 (77)
Peripheral blood	19 (21)	5 (23)
Cord Blood	1 (1)	0

Characteristics of patients aged ≤ 18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2010 and 2019

Other related donor HCT	TED, N (%)	CRF, N (%)
Acute myeloid leukemia	480	180
Bone Marrow	235 (49)	95 (53)
Peripheral blood	240 (50)	85 (47)
Cord Blood	5 (1)	0
Acute lymphoblastic leukemia	550	232
Bone Marrow	299 (54)	132 (57)
Peripheral blood	247 (45)	97 (42)
Cord Blood	4 (1)	3 (1)
Chronic myeloid leukemia	28	15
Bone Marrow	18 (64)	10 (67)
Peripheral blood	10 (36)	5 (33)
Cord Blood	0	0
Myelodysplastic Syndrome	110	49
Bone Marrow	52 (47)	20 (41)
Peripheral blood	54 (49)	28 (57)
Cord Blood	4 (4)	1 (2)
Hodgkin lymphoma	11	5
Bone Marrow	6 (55)	3 (60)
Peripheral blood	5 (45)	2 (40)
Non-Hodgkin lymphoma	53	28
Bone Marrow	21 (40)	8 (29)
Peripheral blood	31 (58)	20 (71)
Cord Blood	1 (2)	0

Characteristics of patients aged ≤ 18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2010 and 2019

Unrelated donor HCT	TED, N (%)	CRF, N (%)
Acute myeloid leukemia	1862	730
Bone Marrow	839 (45)	189 (26)
Peripheral blood	370 (20)	76 (10)
Cord Blood	653 (35)	465 (64)
Acute lymphoblastic leukemia	2305	767
Bone Marrow	1044 (45)	148 (19)
Peripheral blood	435 (19)	70 (9)
Cord Blood	826 (36)	549 (72)
Chronic myeloid leukemia	142	33
Bone Marrow	86 (61)	18 (55)
Peripheral blood	32 (23)	4 (12)
Cord Blood	24 (17)	11 (33)
Myelodysplastic Syndrome	627	207
Bone Marrow	348 (56)	57 (28)
Peripheral blood	90 (14)	13 (6)
Cord Blood	189 (30)	137 (66)
Hodgkin lymphoma	25	11
Bone Marrow	17 (68)	8 (73)
Peripheral blood	8 (32)	3 (27)
Non-Hodgkin lymphoma	139	44
Bone Marrow	67 (48)	13 (30)
Peripheral blood	31 (22)	5 (11)
Cord Blood	41 (29)	26 (59)

Characteristics of patients aged ≤ 18 years with acute leukemia and lymphoma reported to the CIBMTR between 2010 and 2019

Autologous HCT	TED, N (%)	CRF, N (%)
Acute myeloid leukemia	49	2
Bone Marrow	0	8 (16)
Peripheral blood	2 (100)	41 (84)
Cord Blood	0	0
Acute lymphoblastic leukemia	3	0
Bone Marrow	0	0
Peripheral blood	3 (100)	0
Cord Blood	0	0
Chronic myeloid leukemia	0	0
Peripheral blood	0	0
Cord Blood	0	0
Myelodysplastic Syndrome	0	0
Peripheral blood	0	0
Hodgkin lymphoma	662	69
Bone Marrow	13 (2)	0
Peripheral blood	649 (98)	69 (100)
Non-Hodgkin lymphoma	208	42
Bone Marrow	12 (6)	3 (7)
Peripheral blood	196 (94)	39 (93)

Number of patients aged ≤ 18 years with solid tumor reported to the CIBMTR between 2010 and 2019

	Autologous		Allogeneic	
	TED	CRF	TED	CRF
Testicular	27	1	0	0
Soft tissue sarcoma (Include PNET)	27	2	2	2
Central nervous system tumors (include CNS PNET	564	55	1	0
Wilm Tumor	107	6	0	0
Neuroblastoma	2587	246	13	2
Retinoblastoma	77	7	0	0
Ewing sarcoma	177	8	9	3
Germ cell tumor, Extragonadal	137	13	0	0
Medulloblastoma	682	64	1	0
Rhabdomyosarcoma	44	3	13	3

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	4377	1184	1114
Source of data			
CRF	2727 (62)	670 (57)	724 (65)
TED	1650 (38)	514 (43)	390 (35)
Number of centers	154	119	175
Disease at transplant			
AML	1311 (30)	401 (34)	344 (31)
ALL	1915 (44)	481 (41)	480 (43)
Other leukemia	29 (1)	4 (<1)	8 (1)
CML	278 (6)	85 (7)	90 (8)
MDS	523 (12)	126 (11)	136 (12)
Other acute leukemia	103 (2)	37 (3)	18 (2)
NHL	157 (4)	33 (3)	24 (2)
Hodgkin Lymphoma	46 (1)	8 (1)	12 (1)
MPN	15 (<1)	9 (1)	2 (<1)
AML Disease status at transplant			
CR1	548 (42)	173 (43)	132 (38)
CR2	429 (33)	123 (31)	96 (28)
CR3+	38 (3)	10 (2)	12 (3)
Advanced or active disease	282 (21)	91 (23)	98 (28)
Missing	14 (1)	4 (1)	6 (2)
ALL Disease status at transplant			
CR1	579 (30)	135 (28)	124 (26)
CR2	812 (42)	216 (45)	199 (41)
CR3+	323 (17)	86 (18)	86 (18)
Advanced or active disease	181 (10)	38 (8)	54 (11)
Missing	20 (1)	6 (1)	17 (4)
MDS Disease status at transplant			
Early	177 (34)	33 (26)	26 (19)
Advanced	152 (29)	50 (40)	33 (24)
Missing	194 (37)	43 (34)	77 (57)
NHL Disease status at transplant			
CR1	30 (19)	7 (21)	8 (33)
CR2	38 (24)	16 (48)	7 (29)
CR3+	17 (11)	1 (3)	1 (4)
PR	14 (9)	2 (6)	1 (4)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced	55 (35)	7 (21)	5 (21)
Missing	3 (2)	0	2 (8)
Recipient age at transplant			
0-9 years	2099 (48)	561 (47)	530 (48)
10-19 years	2278 (52)	623 (53)	584 (52)
Median (Range)	10 (0-18)	10 (0-18)	10 (0-18)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3024 (69)	854 (72)	718 (64)
African-American, non-Hispanic	306 (7)	72 (6)	85 (8)
Asian, non-Hispanic	139 (3)	37 (3)	53 (5)
Pacific islander, non-Hispanic	10 (<1)	2 (<1)	6 (1)
Native American, non-Hispanic	30 (1)	5 (<1)	5 (<1)
Hispanic	542 (12)	127 (11)	97 (9)
Missing	326 (7)	87 (7)	150 (13)
Recipient sex			
Male	2579 (59)	697 (59)	672 (60)
Female	1798 (41)	487 (41)	442 (40)
Karnofsky score			
10-80	676 (15)	212 (18)	200 (18)
90-100	3537 (81)	926 (78)	836 (75)
Missing	164 (4)	46 (4)	78 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	4 (<1)	3 (<1)	0
4/6	65 (2)	10 (1)	12 (1)
5/6	977 (23)	224 (21)	245 (24)
6/6	3229 (76)	815 (77)	772 (75)
Unknown	102 (N/A)	132 (N/A)	85 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	213 (5)	8 (1)	13 (2)
6/8	373 (9)	28 (4)	34 (6)
7/8	1149 (27)	161 (24)	179 (31)
8/8	2444 (58)	464 (70)	344 (60)
Unknown	198 (N/A)	523 (N/A)	544 (N/A)
HLA-DPB1 Match			
Double allele mismatch	1173 (31)	46 (21)	69 (29)
Single allele mismatch	2025 (54)	122 (55)	126 (53)
Full allele matched	572 (15)	52 (24)	42 (18)
Unknown	607 (N/A)	964 (N/A)	877 (N/A)
High resolution release score			
No	595 (14)	1178 (99)	1049 (94)
Yes	3782 (86)	6 (1)	65 (6)
KIR typing available			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
No	3234 (74)	1183 (>99)	1100 (99)
Yes	1143 (26)	1 (<1)	14 (1)
Graft type			
Marrow	3499 (80)	962 (81)	857 (77)
PBSC	876 (20)	213 (18)	257 (23)
PBSC+UCB	0	5 (<1)	0
Others	2 (<1)	4 (<1)	0
Number of cord units			
Unknown	4377 (N/A)	1184 (N/A)	1114 (N/A)
Conditioning regimen			
Myeloablative	4060 (93)	1105 (93)	1025 (92)
RIC/Nonmyeloablative	296 (7)	74 (6)	71 (6)
TBD	21 (<1)	5 (<1)	18 (2)
Donor age at donation			
To Be Determined/NA	36 (1)	82 (7)	4 (<1)
0-9 years	2 (<1)	3 (<1)	0
10-19 years	100 (2)	38 (3)	15 (1)
20-29 years	1760 (40)	456 (39)	428 (38)
30-39 years	1365 (31)	375 (32)	385 (35)
40-49 years	907 (21)	183 (15)	213 (19)
50+ years	207 (5)	47 (4)	69 (6)
Median (Range)	32 (3-61)	31 (1-61)	32 (18-61)
Donor/Recipient CMV serostatus			
+/+	936 (21)	320 (27)	225 (20)
+/-	747 (17)	170 (14)	190 (17)
-/+	1195 (27)	284 (24)	296 (27)
-/-	1418 (32)	355 (30)	335 (30)
CB - recipient +	0	1 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	81 (2)	53 (4)	68 (6)
GvHD Prophylaxis			
No GvHD Prophylaxis	13 (<1)	4 (<1)	8 (1)
TDEPLETION alone	34 (1)	3 (<1)	9 (1)
TDEPLETION +- other	271 (6)	76 (6)	105 (9)
CD34 select alone	27 (1)	10 (1)	5 (<1)
CD34 select +- other	62 (1)	30 (3)	24 (2)
Cyclophosphamide alone	54 (1)	23 (2)	22 (2)
Cyclophosphamide +- others	44 (1)	23 (2)	31 (3)
FK506 + MMF +- others	221 (5)	51 (4)	32 (3)
FK506 + MTX +- others(not MMF)	1183 (27)	334 (28)	150 (13)
FK506 +- others(not MMF,MTX)	93 (2)	10 (1)	14 (1)
FK506 alone	52 (1)	12 (1)	8 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA + MMF +- others(not FK506)	216 (5)	51 (4)	44 (4)
CSA + MTX +- others(not MMF,FK506)	1607 (37)	408 (34)	486 (44)
CSA +- others(not FK506,MMF,MTX)	209 (5)	61 (5)	68 (6)
CSA alone	145 (3)	46 (4)	63 (6)
Other GVHD Prophylaxis	109 (2)	29 (2)	22 (2)
Missing	37 (1)	13 (1)	23 (2)
Donor/Recipient sex match			
Male-Male	1664 (38)	438 (37)	425 (38)
Male-Female	994 (23)	260 (22)	239 (21)
Female-Male	900 (21)	243 (21)	246 (22)
Female-Female	783 (18)	210 (18)	199 (18)
CB - recipient M	0	3 (<1)	0
CB - recipient F	0	6 (1)	0
Missing	36 (1)	24 (2)	5 (<1)
Year of transplant			
1986-1990	84 (2)	10 (1)	10 (1)
1991-1995	464 (11)	112 (9)	131 (12)
1996-2000	586 (13)	210 (18)	222 (20)
2001-2005	699 (16)	147 (12)	261 (23)
2006-2010	844 (19)	147 (12)	143 (13)
2011-2015	996 (23)	209 (18)	162 (15)
2016-2020	657 (15)	321 (27)	161 (14)
2021	47 (1)	28 (2)	24 (2)
Follow-up among survivors, Months			
N Eval	2166	585	456
Median (Range)	76 (2-385)	60 (3-327)	65 (1-335)

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	1441	439	436
Source of data			
CRF	1099 (76)	331 (75)	295 (68)
TED	342 (24)	108 (25)	141 (32)
Number of centers	88	71	102
Disease at transplant			
AML	569 (39)	155 (35)	150 (34)
ALL	610 (42)	213 (49)	193 (44)
Other leukemia	10 (1)	3 (1)	4 (1)
CML	17 (1)	5 (1)	7 (2)
MDS	144 (10)	42 (10)	52 (12)
Other acute leukemia	41 (3)	14 (3)	18 (4)
NHL	43 (3)	7 (2)	8 (2)
Hodgkin Lymphoma	5 (<1)	0	3 (1)
MPN	2 (<1)	0	1 (<1)
AML Disease status at transplant			
CR1	261 (46)	74 (48)	61 (41)
CR2	204 (36)	47 (30)	51 (34)
CR3+	12 (2)	0	3 (2)
Advanced or active disease	91 (16)	34 (22)	33 (22)
Missing	1 (<1)	0	2 (1)
ALL Disease status at transplant			
CR1	212 (15)	69 (32)	67 (35)
CR2	282 (20)	95 (45)	78 (40)
CR3+	93 (6)	34 (16)	36 (19)
Advanced or active disease	22 (2)	13 (6)	12 (6)
Missing	1 (<1)	2 (1)	0
MDS Disease status at transplant			
Early	61 (42)	14 (33)	29 (56)
Advanced	47 (33)	18 (43)	11 (21)
Missing	36 (25)	10 (24)	12 (23)
NHL Disease status at transplant			
CR1	10 (23)	1 (14)	0
CR2	18 (42)	5 (71)	6 (72)
CR3+	4 (10)	0	0
PR	3 (7)	0	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced	8 (19)	1 (14)	2 (25)
Missing	0	0	0
Recipient age at transplant			
0-9 years	927 (64)	308 (70)	276 (63)
10-19 years	514 (36)	131 (30)	160 (37)
Median (Range)	7 (0-18)	7 (0-18)	7 (0-18)
Recipient race/ethnicity			
Caucasian, non-Hispanic	688 (48)	230 (52)	233 (53)
African-American, non-Hispanic	200 (14)	59 (13)	45 (10)
Asian, non-Hispanic	63 (4)	19 (4)	28 (6)
Pacific islander, non-Hispanic	4 (<1)	2 (<1)	7 (2)
Native American, non-Hispanic	12 (1)	4 (1)	7 (2)
Hispanic	376 (26)	94 (21)	72 (17)
Missing	98 (7)	31 (7)	44 (10)
Recipient sex			
Male	838 (58)	244 (56)	246 (56)
Female	603 (42)	195 (44)	190 (44)
Karnofsky score			
10-80	229 (16)	74 (17)	70 (16)
90-100	1174 (81)	343 (78)	337 (77)
Missing	38 (3)	22 (5)	29 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	10 (1)	6 (2)	3 (1)
4/6	409 (29)	112 (30)	99 (26)
5/6	728 (52)	189 (50)	211 (55)
6/6	249 (18)	69 (18)	73 (19)
Unknown	45 (N/A)	63 (N/A)	50 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	563 (45)	114 (43)	133 (44)
6/8	351 (28)	86 (33)	81 (27)
7/8	217 (17)	36 (14)	64 (21)
8/8	123 (10)	28 (11)	26 (9)
Unknown	187 (N/A)	175 (N/A)	132 (N/A)
HLA-DPB1 Match			
Double allele mismatch	217 (38)	22 (39)	24 (36)
Single allele mismatch	294 (51)	26 (46)	30 (45)
Full allele matched	67 (12)	8 (14)	12 (18)
Unknown	863 (N/A)	383 (N/A)	370 (N/A)
High resolution release score			
No	894 (62)	394 (90)	428 (98)
Yes	547 (38)	45 (10)	8 (2)
KIR typing available			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
No	1003 (70)	434 (99)	431 (99)
Yes	438 (30)	5 (1)	5 (1)
Graft type			
UCB	1421 (99)	434 (99)	429 (98)
PBSC+UCB	8 (1)	5 (1)	5 (1)
Others	12 (1)	0	2 (<1)
Number of cord units			
1	1341 (93)	0	410 (94)
2	100 (7)	0	26 (6)
Unknown	0 (N/A)	439 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	1364 (95)	416 (95)	401 (92)
RIC/Nonmyeloablative	76 (5)	23 (5)	33 (8)
TBD	1 (<1)	0	2 (<1)
Donor age at donation			
To Be Determined/NA	58 (4)	30 (7)	43 (10)
0-9 years	1295 (90)	353 (80)	369 (85)
10-19 years	81 (6)	50 (11)	22 (5)
20-29 years	3 (<1)	1 (<1)	0
30-39 years	3 (<1)	4 (1)	1 (<1)
40-49 years	1 (<1)	1 (<1)	0
50+ years	0	0	1 (<1)
Median (Range)	4 (0-50)	4 (0-42)	3 (0-52)
Donor/Recipient CMV serostatus			
+/+	282 (20)	73 (17)	68 (16)
+/-	154 (11)	39 (9)	31 (7)
-/+	242 (17)	63 (14)	83 (19)
-/-	183 (13)	43 (10)	62 (14)
CB - recipient +	334 (23)	126 (29)	100 (23)
CB - recipient -	223 (15)	84 (19)	68 (16)
CB - recipient CMV unknown	23 (2)	11 (3)	24 (6)
GvHD Prophylaxis			
No GvHD Prophylaxis	4 (<1)	3 (1)	2 (<1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	6 (<1)	4 (1)	2 (<1)
CD34 select alone	0	1 (<1)	0
CD34 select +- other	19 (1)	7 (2)	11 (3)
Cyclophosphamide +- others	16 (1)	7 (2)	11 (3)
FK506 + MMF +- others	249 (17)	93 (21)	43 (10)
FK506 + MTX +- others(not MMF)	103 (7)	27 (6)	34 (8)
FK506 +- others(not MMF,MTX)	30 (2)	13 (3)	10 (2)
FK506 alone	9 (1)	7 (2)	3 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA + MMF +- others(not FK506)	761 (53)	188 (43)	203 (47)
CSA + MTX +- others(not MMF,FK506)	49 (3)	14 (3)	19 (4)
CSA +- others(not FK506,MMF,MTX)	161 (11)	63 (14)	77 (18)
CSA alone	23 (2)	7 (2)	16 (4)
Other GVHD Prophylaxis	8 (1)	4 (1)	3 (1)
Missing	2 (<1)	1 (<1)	2 (<1)
Donor/Recipient sex match			
CB - recipient M	838 (58)	244 (56)	245 (56)
CB - recipient F	603 (42)	195 (44)	190 (44)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	0	0	2 (<1)
2001-2005	46 (3)	58 (13)	12 (3)
2006-2010	557 (39)	121 (28)	166 (38)
2011-2015	540 (37)	123 (28)	169 (39)
2016-2020	280 (19)	127 (29)	80 (18)
2021	18 (1)	10 (2)	7 (2)
Follow-up among survivors, Months			
N Eval	815	249	237
Median (Range)	72 (1-196)	59 (3-213)	62 (1-186)

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	913	123	51
Source of data			
CRF	251 (27)	39 (32)	16 (31)
TED	662 (73)	84 (68)	35 (69)
Number of centers	52	33	28
Disease at transplant			
AML	317 (35)	39 (32)	13 (25)
ALL	412 (45)	58 (47)	33 (65)
Other leukemia	1 (<1)	0	0
CML	30 (3)	1 (1)	0
MDS	72 (8)	13 (11)	4 (8)
Other acute leukemia	33 (4)	3 (2)	1 (2)
NHL	38 (4)	7 (6)	0
Hodgkin Lymphoma	8 (1)	2 (2)	0
MPN	2 (<1)	0	0
AML Disease status at transplant			
CR1	192 (61)	23 (59)	7 (54)
CR2	77 (24)	12 (31)	3 (23)
CR3+	4 (2)	1 (3)	0
Advanced or active disease	42 (13)	1 (3)	3 (23)
Missing	2 (<1)	2 (5)	0
ALL Disease status at transplant			
CR1	161 (39)	27 (47)	11 (22)
CR2	196 (48)	25 (43)	13 (25)
CR3+	45 (11)	5 (9)	7 (14)
Advanced or active disease	10 (2)	1 (2)	2 (4)
Missing	0	0	0
MDS Disease status at transplant			
Early	16 (22)	3 (23)	1 (25)
Advanced	48 (67)	6 (46)	1 (25)
Missing	8 (11)	4 (31)	2 (50)
NHL Disease status at transplant			
CR1	10 (26)	3 (43)	0
CR2	15 (39)	1 (14)	0
CR3+	1 (3)	0	0
Advanced	11 (29)	3 (43)	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	1 (3)	0 (94)	0
Recipient age at transplant			
0-9 years	387 (42)	59 (48)	24 (47)
10-19 years	526 (58)	64 (52)	27 (53)
Median (Range)	11 (1-18)	10 (1-18)	11 (1-18)
Recipient race/ethnicity			
Caucasian, non-Hispanic	419 (46)	59 (48)	27 (53)
African-American, non-Hispanic	105 (12)	12 (10)	0
Asian, non-Hispanic	44 (5)	6 (5)	3 (6)
Pacific islander, non-Hispanic	3 (<1)	0	0
Native American, non-Hispanic	7 (1)	1 (1)	1 (2)
Hispanic	237 (26)	36 (29)	15 (29)
Missing	98 (11)	9 (7)	5 (10)
Recipient sex			
Male	526 (58)	63 (51)	33 (65)
Female	387 (42)	60 (49)	18 (35)
Karnofsky score			
10-80	160 (18)	22 (18)	11 (22)
90-100	735 (81)	96 (78)	37 (73)
Missing	18 (2)	5 (4)	3 (6)
Graft type			
Marrow	685 (75)	72 (59)	33 (65)
PBSC	206 (23)	45 (37)	16 (31)
UCB (related)	1 (<1)	4 (3)	0
BM+PBSC	0	0	1 (2)
BM+UCB	3 (<1)	2 (2)	0
PBSC+UCB	0	0	1 (2)
Others	18 (2)	0	0
Conditioning regimen			
Myeloablative	842 (92)	117 (95)	45 (88)
RIC/Nonmyeloablative	68 (7)	5 (4)	3 (6)
TBD	3 (<1)	1 (1)	3 (6)
Donor age at donation			
To Be Determined/NA	1 (<1)	0	0
0-9 years	258 (28)	32 (26)	13 (25)
10-19 years	299 (33)	43 (35)	17 (33)
20-29 years	136 (15)	16 (13)	9 (18)
30-39 years	125 (14)	22 (18)	10 (20)
40-49 years	76 (8)	7 (6)	0
50+ years	18 (2)	3 (2)	2 (4)
Median (Range)	16 (0-61)	16 (0-61)	17 (1-53)
Donor/Recipient CMV serostatus			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
+/+	338 (37)	55 (45)	18 (35)
+/-	108 (12)	7 (6)	5 (10)
-/+	241 (26)	25 (20)	16 (31)
-/-	218 (24)	33 (27)	9 (18)
CB - recipient +	0	1 (1)	0
CB - recipient -	0	0	1 (2)
Missing	8 (1)	2 (2)	2 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	41 (4)	6 (5)	2 (4)
TDEPLETION alone	24 (3)	15 (12)	3 (6)
TDEPLETION +- other	10 (1)	2 (2)	1 (2)
CD34 select alone	13 (1)	0	0
CD34 select +- other	67 (7)	8 (7)	4 (8)
Cyclophosphamide alone	23 (3)	5 (4)	3 (6)
Cyclophosphamide +- others	185 (20)	14 (11)	11 (22)
FK506 + MMF +- others	69 (8)	5 (4)	1 (2)
FK506 + MTX +- others(not MMF)	246 (27)	25 (20)	10 (20)
FK506 +- others(not MMF,MTX)	1 (<1)	1 (1)	1 (2)
FK506 alone	4 (<1)	0	1 (2)
CSA + MMF +- others(not FK506)	30 (3)	5 (4)	2 (4)
CSA + MTX +- others(not MMF,FK506)	164 (18)	24 (20)	9 (18)
CSA +- others(not FK506,MMF,MTX)	1 (<1)	2 (2)	0
CSA alone	27 (3)	6 (5)	1 (2)
Other GVHD Prophylaxis	5 (1)	1 (1)	1 (2)
Missing	3 (<1)	4 (3)	1 (2)
Donor/Recipient sex match			
Male-Male	303 (33)	33 (27)	21 (41)
Male-Female	181 (20)	31 (25)	6 (12)
Female-Male	220 (24)	27 (22)	12 (24)
Female-Female	205 (22)	26 (21)	11 (22)
CB - recipient M	3 (<1)	3 (2)	0
CB - recipient F	1 (<1)	3 (2)	1 (2)
Year of transplant			
2006-2010	35 (4)	2 (2)	0
2011-2015	274 (30)	29 (24)	11 (22)
2016-2020	540 (59)	86 (70)	33 (65)
2021	64 (7)	6 (5)	7 (14)
Follow-up among survivors, Months			
N Eval	633	98	31
Median (Range)	35 (1-147)	26 (0-103)	24 (5-97)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Pediatric Cancer Working Committee Members

FROM: Larisa Broglie, MD MS; Scientific Director for the Pediatric Cancer Working Committee

RE: Studies in Progress Summary

PC19-02: Does mixed peripheral blood T Cell Chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs).
The objectives of this study include determining the incidence of persistence of host T cells after transplant for non-T cell malignant diseases in pediatric patients. Other study objectives include exploring whether the incidence of relapse is higher in patients with persistence of host T cell populations and determining whether reactivation of CMV in patients who were CMV seropositive prior to transplant influence the incidence of host T cells after transplant.
The study protocol is being developed. The goal is to have the data file prepared for analysis by August 2022.

PC19-03: The impact of pre-transplant extramedullary disease on the outcome of Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia in children- A combined CIBMTR and EBMT analysis, (H Rangarajan/P Satwani/K Rao/D Chellapandian/B Savani/Juliana Silva).
The objective of this study is to determine whether the presence of extramedullary disease in pediatric patients with AML prior to transplant impacts post-transplant outcomes, including overall survival and disease-free survival.
This study is currently in data file preparation. The goal is to have the data file prepared for analysis by August 2022.

PC20-01 Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing Autologous Hematopoietic Stem Cell Transplantation, (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong).
The objectives of this study are to examine the association between infused CD34+ and/or TNC dose present in auto-HSCT grafts and patient outcomes following auto-HSCT performed for pediatric patients with malignant indications for transplant, specifically tumors of the central nervous system (CNS) and high-risk neuroblastoma.
The study is currently in final manuscript preparation. The goal is to publish the manuscript by June 2022.

PC20-02 Germline genetics of pediatric Myelodysplastic Syndromes, (Jenny Poynter/ Logan Spector).
The objective of this study is to identify genetic susceptibility variants for pediatric patients with MDS in an unselected cohort of pediatric patients. Genotyping will be conducted using the Illumina Global Screening array and controls will include >2000 DNA samples that have been genotyped for other childhood cancer studies. To improve power, we will focus on regions of the genome expressed in myeloid cells as determined by ATAC-seq in primary MDS cell cultures.
The study is currently in sample typing. The goal is to complete the study by December 2022

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

Transplantation and Cellular Therapy for Children and Young Adults with Down's Syndrome and Acute Leukemia

Q2. Key Words

Down's Syndrome, Acute Leukemia, ALL, AML, CAR T-Cell, treatment related mortality

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Seth Rotz, MD
Email address:	rotzs@ccf.org
Institution name:	Cleveland Clinic
Academic rank:	Assistant Professor

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):	Rabi Hanna, MD
Email address:	hannar2@ccf.org
Institution name:	Cleveland Clinic
Academic rank:	Associate Professor

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?

- 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:

Rotz

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.

Rotz- CIBMTR Proposal Task Force- working to refine overall approach to CIBMTR proposal work flow/ evaluation
Rotz/Hanna- Co-Investigators on NM20-01 (PI: Bouland)
Rotz/Hanna- contributions to various writing groups/ CIBMTR publications

Q13. PROPOSED WORKING COMMITTEE:

- Pediatric Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Broglie, Dr. Yanik

Q15. RESEARCH QUESTION:

Have outcomes for Children and Young Adults with Down's syndrome and Acute Leukemia undergoing HCT improved in recent years?
Is CAR-T cell therapy a better option for patients with Down's syndrome and ALL, compared to allogeneic HCT?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that children and adolescent and young adult (AYA) with Down's syndrome (DS) and acute leukemia will have improved hematopoietic cell transplantation (HCT) outcomes in the more recent eta. Further, we hypothesize that children and AYA with DS and relapsed/refractory Acute Lymphoblastic Leukemia (ALL) undergoing CAR T-cell therapies will have improved outcomes compared to those who underwent HCT.

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

Suggested word limit of 200 words:

Primary Objective 1: Determine if outcomes for children and AYA with DS and acute leukemia (ALL and AML) undergoing HCT have improved in more recent eras?
Secondary Objective 2: Compare outcomes of CAR T-cell therapy for children and AYA with DS and relapsed/refractory ALL to HCT.

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.

No consensus guidelines exist for the treatment of children and AYA patients with DS and relapsed/ refractory acute leukemia. Previous data has suggested a high burden of both transplant related mortality and relapse for DS patients, and poor outcomes compared to patients without DS.(Hitzler, et al 2013, Hitzler, et al 2014, Rubin, et al 1996) With improved supportive care approaches and additional attention to minimal residual disease in more recent eras, these outcomes may have improved, however they have not been recently studied. Better understanding of the risks and benefits of HCT in this population has the opportunity to improve clinical decision making and counseling of patients and families.
CAR T-Cell therapy has significantly altered the treatment landscape for children and AYA with relapsed/ refractory ALL. Although overall response rates are quite favorable, many patients will eventually relapse or require HCT. (Pasquini, et al 2020) Given the poor outcomes of HCT for DS ALL, CAR T-Cell therapy is an attractive alternative. More clearly understanding the outcomes of patients with DS ALL undergoing CAR T-cell therapies including acute toxicities, risk of relapse, and necessity to proceed to HCT will help inform clinicians about the optimal treatment approach for these patients.

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.

Historical outcomes for patients with DS and ALL undergoing HCT are dismal. The CIBMTR previously reported a 3-year disease free survival of 24% among children and AYA patients with DS ALL undergoing HCT from 2000-2009. (Hitzler, et al 2014) When children with DS ALL receive upfront conventional chemotherapy, much attention is paid to the increased risk of treatment related mortality. However, a previous analysis from the CIBMTR demonstrated relapse post-HCT was a more common cause of treatment failure than transplant toxicity.(Hitzler, et al 2014) A smaller study from Germany and Austria also demonstrated similar findings.(Meissner, et al 2007)

The CIBMTR has also previously reported on outcomes of children with DS Acute Myeloid Leukemia (AML).(Hitzler, et al 2013) Unfortunately, like their counterparts with ALL, children with DS AML undergoing HCT also have very poor outcomes with a 3-year overall survival of 19%. In contrast to patients with ALL, the previous CIBMTR report indicated both relapse and transplant toxicity were major drivers of poor outcomes. A study from Japan also demonstrated similar findings with only 2/8 patients with relapsed/refractory DS AML surviving long-term post-HCT.(Taga, et al 2012) However, given improved supportive care and closer attention to MRD status since these publications, it is unknown if outcomes for patients with DS and acute leukemia have improved in more recent years.

For patients with relapsed refractor DS ALL, cellular therapy is a promising approach to improve outcomes.(Pasquini, et al 2020) (Maude, et al 2018) In the phase II multicenter study of tisagenlecleucel, 6 patients with DS ALL were included, but outcomes for this specific group were not specifically analyzed.(Maude, et al 2018) As of January, 2020 the CIBMTR reported on 13 patients with DS ALL who underwent CAR T-Cell therapy, noting a 100% overall response rate and 100% 6-month overall survival.(Pasquini, et al 2020) However, longer-term follow-up, duration of response, and use of subsequent HCT for these patients was not reported. Given the optimistic early reports, many additional patients with DS ALL may have undergone CAR-T therapies since these publications. The opportunity to specifically study outcomes of cellular therapy in DS ALL will allow for a better understanding the longer-term outcomes of these patients, and help clinicians better understand the risk/benefits of using cellular therapy vs. HCT in this patient population.

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.

Age: <40 years (at the time of HCT)
Underlying Characteristics: Only patients with Down's syndrome
Disease: ALL, AML
Disease stage/status at transplant: Any
Year of Transplant: 2000-present
Transplant Type: Allogeneic, Cellular therapy

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.

Outcome Variables
All patients:
• Overall survival
• Event free survival
• Treatment related mortality
• Day +100 survival
• Relapse (cumulative incidence)
Outcome Variables Cellular-Therapy patients:
• CRS
• Neurotoxicity
• Underwent subsequent HCT
• Overall response rate
• Best overall response
Variables to be described
Patient and Disease Variables
• Patient age – continuous
• Patient sex: male vs. female
• Performance score (Lansky/ Karnofsky)
• Year HCT was performed (prior to 2010, 2010 and later)
• Disease: AML v. ALL
• Disease status prior to transplant/cell therapy (CR1, CR2, CR3, less than CR)
HCT-related
• Conditioning intensity: RIC v. MAC
• Conditioning regimen: Total body irradiation (TBI) vs no TBI
• Stem cell source: Bone marrow vs. Peripheral blood vs. Cord Blood
• Donor Type
• aGVHD
• cGVHD
• prior CAR-T therapies
Cellular Therapy-Related
• prior HCT
• prior blinatumomab
• MRD status

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:

Hitzler, J.K., He, W., Doyle, J., Cairo, M., Camitta, B.M., Chan, K.W., Diaz Perez, M.A., Fraser, C., Gross, T.G., Horan, J.T., Kennedy-Nasser, A.A., Kitko, C., Kurtzberg, J., Lehmann, L., O'Brien, T., Pulsipher, M.A., Smith, F.O., Zhang, M.J., Eapen, M., Carpenter, P.A. & Committee, C.P.C.W. (2013) Outcome of transplantation for acute myelogenous leukemia in children with Down syndrome. Biol Blood Marrow Transplant, 19, 893-897.

Hitzler, J.K., He, W., Doyle, J., Cairo, M., Camitta, B.M., Chan, K.W., Perez, M.A.D., Fraser, C., Gross, T.G. & Horan, J.T. (2014) Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. Pediatric blood & cancer, 61, 1126-1128.

Maude, S.L., Laetsch, T.W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., Bader, P., Verneris, M.R., Stefanski, H.E. & Myers, G.D. (2018) Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. New England Journal of Medicine, 378, 439-448.

Meissner, B., Borkhardt, A., Dilloo, D., Fuchs, D., Friedrich, W., Handgretinger, R., Peters, C., Schrauder, A., Schuster, F.R., Vormoor, J., Maecker, B., Sykora, K.W., Zintl, F., Welte, K. & Sauer, M. (2007) Relapse, not regimen-related toxicity, was the major cause of treatment failure in 11 children with Down syndrome undergoing haematopoietic stem cell transplantation for acute leukaemia. Bone Marrow Transplant, 40, 945-949.

Pasquini, M.C., Hu, Z.-H., Curran, K., Laetsch, T., Locke, F., Rouce, R., Pulsipher, M.A., Phillips, C.L., Keating, A. & Frigault, M.J. (2020) Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Advances, 4, 5414-5424.

Rubin, C.M., Mick, R. & Johnson, F.L. (1996) Bone marrow transplantation for the treatment of haematological disorders in Down's syndrome: toxicity and outcome. Bone Marrow Transplant, 18, 533-540.

Taga, T., Saito, A.M., Kudo, K., Tomizawa, D., Terui, K., Moritake, H., Kinoshita, A., Iwamoto, S., Nakayama, H., Takahashi, H., Tawa, A., Shimada, A., Taki, T., Kigasawa, H., Koh, K. & Adachi, S. (2012) Clinical characteristics and outcome of refractory/relapsed myeloid leukemia in children with Down syndrome. Blood, 120, 1810-1815.

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

Table 1A. Characteristics of Children and Young Adults with Down's Syndrome who underwent HCT for Acute Leukemia between 2000 and 2019

Characteristic	DS with ALL and HCT & CAR-T	DS with ALL and HCT	DS with ALL and CAR-T	DS with AML and HCT	Total
No. of patients	1	48	3	44	96
No. of centers	1	29	2	32	53
Age category - no. (%)					
Median (min-max)	7 (7-7)	10 (4-38)	14 (8-14)	3 (1-27)	7 (1-38)
< 10	1 (100)	24 (50)	1 (33)	39 (89)	65 (68)
10 - 17	0 (0)	13 (27)	2 (67)	1 (2)	16 (17)
18 - 29	0 (0)	9 (19)	0 (0)	4 (9)	13 (14)
30 - 39	0 (0)	2 (4)	0 (0)	0 (0)	2 (2)
Sex - no. (%)					
Male	0 (0)	29 (60)	0 (0)	25 (57)	54 (56)
Female	1 (100)	19 (40)	3 (100)	19 (43)	42 (44)
Performance score - no. (%)					
80 - 100	1 (100)	40 (83)	3 (100)	38 (86)	82 (85)
< 80	0 (0)	0 (0)	0 (0)	2 (5)	2 (2)
Not reported	0 (0)	8 (17)	0 (0)	4 (9)	12 (13)
Transplant year - no. (%)					
2000	0 (0)	5 (10)	0 (0)	2 (5)	7 (7)
2001	0 (0)	3 (6)	0 (0)	4 (9)	7 (7)
2002	0 (0)	1 (2)	0 (0)	3 (7)	4 (4)
2003	0 (0)	1 (2)	0 (0)	3 (7)	4 (4)
2004	0 (0)	2 (4)	0 (0)	3 (7)	5 (5)
2005	0 (0)	1 (2)	0 (0)	4 (9)	5 (5)
2006	0 (0)	4 (8)	0 (0)	1 (2)	5 (5)

Characteristic	DS with ALL and HCT & CAR-T	DS with ALL and HCT	DS with ALL and CAR-T	DS with AML and HCT	Total
2007	0 (0)	0 (0)	0 (0)	3 (7)	3 (3)
2008	0 (0)	7 (15)	0 (0)	2 (5)	9 (9)
2009	0 (0)	10 (21)	0 (0)	5 (11)	15 (16)
2010	0 (0)	1 (2)	0 (0)	3 (7)	4 (4)
2012	0 (0)	2 (4)	0 (0)	0 (0)	2 (2)
2013	0 (0)	0 (0)	0 (0)	3 (7)	3 (3)
2014	0 (0)	3 (6)	0 (0)	2 (5)	5 (5)
2015	0 (0)	1 (2)	0 (0)	2 (5)	3 (3)
2016	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)
2017	0 (0)	1 (2)	0 (0)	2 (5)	3 (3)
2018	1 (100)	2 (4)	2 (67)	0 (0)	5 (5)
2019	0 (0)	4 (8)	1 (33)	1 (2)	6 (6)

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

Evaluation of Allogeneic Hematopoietic Cell Transplantation Outcomes and Prognostic Factors in Acute Megakaryoblastic Leukemia

Q2. Key Words

Allogeneic Hematopoietic Cell Transplantation, Acute Megakaryoblastic Leukemia

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Akshay Sharma, MBBS
Email address:	akshay.sharma@stjude.org
Institution name:	St. Jude Children's Research Hospital, Memphis, TN
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?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Neel S. Bhatt, MBBD, MPH
Email address:	nbhatt@fredhutch.org
Institution name:	Fred Hutchinson Cancer Research Center, Seattle, WA
Academic rank:	Assistant Professor

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:

Akshay Sharma, MBBS

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.

I was the lead PI for the CIBMTR COVID outcomes study published in the Lancet Haematology. Additional analysis of this dataset and a pediatric focussed manuscript is currently under preparation.

Q13. PROPOSED WORKING COMMITTEE:

- Pediatric Cancer

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

- No

Q15. RESEARCH QUESTION:

We would like to evaluate the outcomes after allogeneic hematopoietic cell transplantation in pediatric patients with acute megakaryoblastic leukemia (AMKL).

Q16. RESEARCH HYPOTHESIS:

Allogeneic hematopoietic cell transplantation (allo-HCT) provides curative therapy for patients with acute megakaryoblastic leukemia (AMKL), with improved outcomes in those who are transplanted in first complete remission.

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

Suggested word limit of 200 words:

To determine the outcomes (OS, DFS, NRM, Relapse) of allo-HCT in AMKL patients and identify prognostic factors associated with improved outcomes.
To determine the effect of remission status (first remission, second remission, progressive/refractory disease) on outcomes (OS, DFS, NRM, Relapse) in patients receiving allo-HSCT for AMKL.
To determine the outcomes in AMKL utilizing alternative donor sources and compare them to traditional matched-related donor transplants.

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.

Acute megakaryoblastic leukemia (AMKL) has a bimodal age distribution with peaks in early childhood (younger than 3 years) and in adulthood.(1) AMKL comprises of approximately 1% of all AML cases in adults and about 10% of all AML cases in children.(2, 3) Children with Down syndrome have a much higher incidence of AMKL, but also have a more favorable prognosis compared to children without AMKL.(4)

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.

AMKL is a rare subtype of acute myeloid leukemia with dismal outcomes.(2, 5-7) Even though approximately half the patients with de novo AMKL achieve complete remission (CR) with conventional chemotherapy, 5-year event-free survival in non-Down syndrome children is only 14-49% and has not improved much in the last few decades.(2, 7-10) Median survival in adults with AMKL is even worse at less than 12 months.(11) Allogeneic hematopoietic stem cell transplantation (allo-HCT) has been suggested to improve outcomes in patients with AMKL, but the available literature is scant and inconsistent.(9, 12) A large study from the European Group for Blood and Marrow Transplantation (EBMT) suggested that allo-HCT in CR1 improves survival (3 year OS 82% in children and 43% in adults). (5) A recent single center analysis performed at our institution of 44 pediatric patients who underwent their first allo-HCT for AMKL between 1986 and 2016 revealed that AMKL continues to have poor outcomes after allo-HCT due a high rate of relapse in the first year post-transplant (3 year OS 34.1%). Two factors which were independently associated with improved OS and less cumulative incidence of relapse after allo-HCT for AMKL were being in CR at the time of transplant (Hazard Ratio=0.4, P=0.02) and non-Hispanic Caucasian race (Hazard Ratio=0.3, P=0.005).
Since AMKL is a rare disease, there is limited data on transplant outcomes in this population. A large analysis utilizing the CIBMTR database will allow the transplant community to clearly define the outcomes of allo-HCT in patients with AMKL, identify prognostic markers for improved outcomes, and help to elucidate the utility of both alternative (haploidentical and cord blood) donors against the standard matched-donor transplants. Such an assessment of favorable prognostic factors will help identify patients who have better outcomes with HCT and hence will guide clinicians to recommend HCT to that subset of patients earlier leading to improved overall outcomes.

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.

All pediatric patients who underwent HCT (allogeneic or autologous) for AMKL registered with CIBMTR between years 1990 and 2021.

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.

This proposed study will require no supplemental data to be collected. The current data is included in the CIBMTR collection forms for Pre-HSCT and Post-HSCT Acute Myelogenous Leukemia.
This study is a retrospective registry analysis of all pediatric patients who received HCT for AMKL between January 1990 and December 2021.
Baseline characteristics and known prognostic variables will be collected from CIBMTR database forms. These characteristics will include: age, sex, de novo or Down's syndrome related, Karnofsky/ Lansky performance status, presence of extra-medullary disease at diagnosis (including CNS), WBC at diagnosis, immune-phenotype at diagnosis, number of prior chemotherapy regimens if available, time from diagnosis to transplant, remission status at transplant (first remission, second or higher remission, progressive/refractory disease), conditioning therapy (chemotherapy-based or total body irradiation based, including chemotherapy type and TBI dose), GvHD prophylactic regimen, use of anti-thymocyte globulin, T-cell depletion of the graft, presence of minimal residual disease prior to transplant (molecular data or flow cytometry data) if available, donor source (peripheral blood, cord, bone marrow), transplant type (haploidentical, 1 or 2 HLA-antigen mismatch unrelated donor, MUD, HLA-identical sibling donor, cord blood), and cytogenetics at diagnosis if available.
Transplant outcomes (OS, PFS, cumulative incidence (CI) NRM, and CI Relapse) will be evaluated for all patients, patients in CR1, second remission and greater (CR2+), and those with progressive/refractory disease. Additionally, transplant outcomes will be evaluated for patients receiving haploidentical or cord-Blood transplantation versus matched unrelated donor and matched related donor transplantation.
Median overall survival, and progression-free survival will be calculated utilizing Kaplan-Meier analysis and compared utilizing the log-rank test. Cumulative incidences of NRM, Relapse, and GVHD (chronic and acute) will be performed utilizing the cumulative incidence procedure to account for competing risks, and comparison will be performed utilizing the Fine-Gray test.
Differences between groups will be evaluated utilizing the Chi-squared test or Fisher's exact test for categorical variables, two-sample test for proportions, or the Wilcoxon rank sum test for medians. For cumulative incidence, the Fine-Gray analysis will be utilized to compare variables with competing risks.
Outcomes will be compared between patients in CR1, CR2+, and no-remission/refractory disease. TBI-based conditioning will be compared to chemotherapy based conditioning. Haploidentical/cord blood transplant will be compared to matched-donor transplants normalized for preHCT risk factors.
Prognostic variables will be evaluated for their impact on OS, DFS, NRM and Relapse utilizing univariate analysis and multivariate analysis by cox proportional hazards analysis.

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

NA

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 for this study.

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.

NA

Q26. REFERENCES:

1. Gassmann W, Loffler H. Acute megakaryoblastic leukemia. Leukemia & lymphoma. 1995;18 Suppl 1:69-73.
2. Inaba H, Zhou Y, Abla O, Adachi S, Auvrignon A, Beverloo HB, et al. Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study. Blood. 2015;126(13):1575-84.
3. Lange BJ, Kobrinsky N, Barnard DR, Arthur DC, Buckley JD, Howells WB, et al. Distinctive demography, biology, and outcome of acute myeloid leukemia and myelodysplastic syndrome in children with Down syndrome: Children's Cancer Group Studies 2861 and 2891. Blood. 1998;91(2):608-15.
4. Roberts I, Izraeli S. Haematopoietic development and leukaemia in Down syndrome. British journal of haematology. 2014;167(5):587-99.
5. Garderet L, Labopin M, Gorin NC, Polge E, Baruchel A, Meloni G, et al. Hematopoietic stem cell transplantation for de novo acute megakaryocytic leukemia in first complete remission: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). Blood. 2005;105(1):405-9.
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9. Barnard DR, Alonzo TA, Gerbing RB, Lange B, Woods WG, Children's Oncology G. Comparison of childhood myelodysplastic syndrome, AML FAB M6 or M7, CCG 2891: report from the Children's Oncology Group. Pediatr Blood Cancer. 2007;49(1):17-22.
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11. Oki Y, Kantarjian HM, Zhou X, Cortes J, Faderl S, Verstovsek S, et al. Adult acute megakaryocytic leukemia: an analysis of 37 patients treated at M.D. Anderson Cancer Center. Blood. 2006;107(3):880-4.
12. de Oliveira JS, Sale GE, Bryant EM, Sanders J, Buckner CD. Acute megakaryoblastic leukemia in children: treatment with bone marrow transplantation. Bone Marrow Transplant. 1992;10(5):399-403.

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

Table 1A. Characteristics of pediatric patient who underwent transplant for AMKL between 2000 and 2019

Characteristic	AMKL with DS	AMKL without DS	Total
No. of patients	22	597	619
No. of centers	16	145	148
Age category - no. (%)			
Median (min-max)	3 (1-4)	3 (0-18)	3 (0-18)
< 10	22 (100)	542 (91)	564 (91)
10 - 17	0 (0)	55 (9)	55 (9)
Sex - no. (%)			
Male	12 (55)	305 (51)	317 (51)
Female	10 (45)	292 (49)	302 (49)
Performance score - no. (%)			
80 - 100	17 (77)	458 (77)	475 (77)
< 80	1 (5)	38 (6)	39 (6)
Not reported	4 (18)	101 (17)	105 (17)
Transplant years groups - no. (%)			
2000 - 2009	18 (82)	347 (58)	365 (59)
2010 - 2019	4 (18)	250 (42)	254 (41)
Transplant year - no. (%)			
2000	1 (5)	37 (6)	38 (6)
2001	3 (14)	26 (4)	29 (5)
2002	1 (5)	32 (5)	33 (5)
2003	2 (9)	42 (7)	44 (7)
2004	2 (9)	34 (6)	36 (6)
2005	2 (9)	44 (7)	46 (7)
2006	0 (0)	27 (5)	27 (4)
2007	2 (9)	22 (4)	24 (4)
2008	0 (0)	33 (6)	33 (5)
2009	4 (18)	31 (5)	35 (6)
2010	1 (5)	19 (3)	20 (3)
2011	0 (0)	36 (6)	36 (6)
2012	0 (0)	35 (6)	35 (6)
2013	1 (5)	34 (6)	35 (6)
2014	0 (0)	28 (5)	28 (5)
2015	0 (0)	21 (4)	21 (3)
2016	3 (14)	33 (6)	36 (6)
2017	0 (0)	30 (5)	30 (5)
2018	0 (0)	19 (3)	19 (3)
2019	0 (0)	14 (2)	14 (2)
Indicator of HCT cases in CRF retrieval - no. (%)			
No	3 (14)	346 (58)	349 (56)
Yes	19 (86)	251 (42)	270 (44)

CIBMTR Study Proposal

Study Title:

Outcomes after post-transplant cyclophosphamide based haploidentical hematopoietic cell transplantation in pediatric patients with acute leukemia and myelodysplastic syndrome

1st PI Information:
PI Name (First, Middle, Last): Akshay Sharma
Degree(s): MBBS
Academic Rank: Instructor
Junior Investigator (yes/no), *if applicable*: Yes
Junior Investigator Status (# years from fellowship), *if applicable*: 3
Email Address: Akshay.sharma@stjude.org
Institution Name: St. Jude Children's Research Hospital, Memphis, TN

2nd PI Information:
PI Name (First, Middle, Last): Neel S. Bhatt
Degree(s): MBBS, MPH
Academic Rank: Assistant Professor
Junior Investigator (yes/no), *if applicable*: Yes
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Junior Investigator Status (# years from fellowship), *if applicable*: NA
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Institution Name: Columbia University Medical Center, NY.

Research Hypothesis:
We hypothesize that haploidentical hematopoietic cell transplantation (haplo HCT) using post-transplant cyclophosphamide (PT-Cy) in pediatric patients (≤ 21 years) with acute leukemia and myelodysplastic

syndrome (MDS) is associated with a disease-free survival (DFS) that is comparable to HLA matched donor HCT and better than mismatched unrelated donor HCT. Further, haplo HCT with PT-Cy is associated with a comparable incidence of acute and chronic graft versus host disease (GVHD) to HLA matched donor HCT and the incidence is lower than mismatched unrelated donor HCT. We further hypothesize that through the CIBMTR database we will be able to identify risk factors for GVHD in pediatric patients receiving haploidentical transplantation using PT-Cy.

Specific Aims:

Primary:

1. Compare the DFS among pediatric patients (≤ 21 years) with acute leukemia and MDS who have undergone haplo HCT with PT-Cy and those undergoing HLA matched donor HCT or mismatched unrelated donor HCT.
2. Describe the incidence, characteristics, and risk factors for acute and chronic GVHD in children and adolescents undergoing PT-Cy based haploidentical HCT. The role of conditioning intensity (myeloablative versus reduced intensity) and stem cell source (bone marrow versus peripheral blood) will be evaluated.

Secondary:

The following endpoints will be compared between haplo HCT with PT-Cy and HLA matched HCT or mismatched unrelated donor HCT.

1. Evaluate time to neutrophil recovery and platelet recovery following HCT.
2. Evaluate 100 day and 1 year transplant-related mortality (TRM) and incidence of graft failure.
3. Evaluate relapse incidence (RI).
4. Evaluate incidence and severity of acute and chronic graft versus host disease.
5. Evaluate 1-year and 3-year graft-versus-host disease (GVHD)-free relapse-free survival (GRFS) (a composite end point of survival without grade III-IV acute GVHD, systemic therapy-requiring chronic GVHD, or relapse) and cGVHD-free relapse-free survival (CRFS).
6. 1-year and 3-year overall survival (OS).

Scientific Impact:

Although there are several studies in adults comparing outcomes of PT-Cy based haplo HCT with MSD and alternative donor transplants, there are none in children. Similarly, while incidence and risk factors for acute and chronic GVHD in adult patients undergoing PT-Cy based haploidentical HCT are well described, no such data exists in the pediatric population. Children are more likely to receive myeloablative (MA) conditioning regimen and bone marrow as graft source. Therefore, whether the outcomes observed in adults hold true in children remains unanswered. With increasing use of haplo HCT in children our proposed study will provide timely information to the pediatric transplant community if PTCY based haplo HCT is comparable to other matched related donor transplants in children. Also by identifying risk factors for acute and chronic GVHD in pediatric patients undergoing PT-

Cy based haploidentical HCT will allow for improved risk stratification and improved GVHD outcomes in pediatric patients

Scientific Justification:

For many patients in need of an allogeneic HCT, especially ethnic minorities and racial groups that are underrepresented in the donor registries, there is limited availability of fully matched unrelated donors.[1] For these patients, haploidentical donors may be the only available donor choice for an allogeneic HCT. In case of children, haploidentical donor is a particularly attractive donor source because parents who could serve as a haplo HCT donor are usually immediately available and highly motivated. Historically haplo HCT was associated with high transplant related mortality.[2] The use of post-transplant cyclophosphamide has been shown in adults to be a safe and effective option to reduce the burden of GVHD after an HLA mismatched donor HCT.[3-6] While there have been several reports in adults, there are few studies including specifically pediatric patients. A recent CIBMTR study revealed that 80% of haplo HCTs are being performed using PT-Cy for GVHD prophylaxis. [7] In a survey of 315 HCT physicians, 21% of respondents predicted that haploidentical donors would be the preferred donors and 55% predicated that CNI based prophylaxis will be replaced by PT-Cy in the coming years.[8]

In recent years, several groups have published their single institution experience with small cohorts of pediatric patients (N=13-40 each) undergoing haplo HCT and PT-Cy.[9-12] These studies demonstrate the safety and feasibility of haplo HCT with PT-Cy in pediatric patients. However, the patient characteristics, conditioning regimens, and the range of reported outcomes in these studies are quite diverse which makes comparisons challenging. Jaiswal et al. reported on a cohort of 20 patients aged 2-20 years who underwent haploidentical transplant with fludarabine, busulfan, and melphalan conditioning followed by PT-Cy.[10] The cohort had prompt engraftment and cumulative incidence of acute GVHD was 35%. Berger et al reported 33 patients treated across 5 Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) centers with haplo HCT and PT-Cy.[9] While some patients had fully myeloablative conditioning, others had nonmyeloablative conditioning. Acute GVHD developed in 22% of patients. Klein et al. and Katsanis et al. reported additional pediatric cohorts with acute GVHD developing in 33% and 30% respectively.[11,12] These studies suggest that while PT-Cy is an effective GVHD prevention modality in pediatric patients, there are patients who are at risk for developing GVHD and this cohort can only be delineated in a large study that combines patients with different risk factors and exposures. In a review, Shah et al summarized several published reports of PT-Cy based haplo HCT in children (n=385) from 2016 to 2020.[13] The disease-free survival (DFS) and overall survival at last follow up in these studies ranged from 33-78% and 48-84% respectively.[13]

Registry-based studies in adults HCT recipients comparing outcomes of PT-Cy based haplo HCT with HCT using other donor sources have shown comparable clinical outcomes to MUD and MSD HCT for acute leukemias and lymphomas.[14] Salvatore et al compared 122 haplo HCT with 1888 MSD HCT in adults with high-risk AML in first complete remission (CR1).[15] In these patients there were no differences between the two groups with the exception of less relapse post haplo HCT.[15] In a more recent CIBMTR study of adults with AML in CR1 (2008-2015), Rashidi et al compared 336 patients who underwent a PT-Cy based haplo HCT with 869 recipients of MSD HCT using calcineurin inhibitor–based GVHD prophylaxis.[16] The haplo HCT group included more reduced-intensity conditioning (65% vs 30%) and bone marrow grafts (62% vs 7%).[16] In multivariable analysis, haplo HCT and MSD groups were comparable with regard to OS,

LFS, NRM, relapse incidence or grade II-IV aGVHD. However, the haplo HCT group had a significantly lower rate of chronic GVHD.[16] These developments have led to consideration of haplo HCT even over a MUD or umbilical cord blood donor (UCB) at some centers.

The above data suggests that outcomes after PT-Cy based haplo HCT in adult patients with leukemia are comparable to outcomes after HCT with MUD and even MSD donors. Several risk factors have historically been identified to confer risk of acute and chronic GVHD including donor source.[17] It is unclear which of these risk factors hold true in the pediatric population undergoing haplo HCT with PT-Cy. Transplant practices differ in children whereby the latter are more likely to receive BM as a graft source, and a myeloablative conditioning regimen. Given the lack of studies we propose compare outcomes of haplo HCTs in children with leukemia with patients who received MSD and other alternative donor sources. We propose a 1:2 matching for MSD, MUD and if feasible for MMUD and UCB separately. Controls will be matched for age, sex, disease type, severity, conditioning type and graft source. We hope to investigate the impact of PT-Cy based haplo HCT and post-transplant outcomes and the potential risk factors for the development of GVHD in the pediatric population. We will focus on graft source and conditioning intensity as possible risk factors for GVHD.

Patient Eligibility Population:

Inclusion Criteria:

- Age < 21 years
- Patients receiving and allogeneic transplantation for acute leukemia or MDS.
- Underwent HCT between 2008- 2021.
- Patients who received haplo HCT using PT-Cy or HLA matched donor HCT or HLA mismatched donor HCT.
- Patients with at least one year of follow up.

Exclusion Criteria:

- Exclude patients who underwent ex-vivo T cell depletion and Cord blood recipients
- Recipients of ≥ 2nd allogeneic HCT.
- Exclude patients that received grafts from multiple donors.
- Patients missing baseline of day 100 form.

Data Requirements:

This proposed study will require no supplemental data to be collected. The current data is included TED and CRF level CIBMTR collection forms.

Patient characteristics

- Age (continuous, 0-4, 5-9, 10-14, >=15)
- Gender (male v female)
- Donor-recipient CMV status (+/+, +/-, -/+, -/-)
- HCT-CI score 0-2, ≥3
- Ethnicity (Caucasian v African American v Hispanic v Other)
- Indication (malignant v non-malignant disease)
- Performance Status (<90 v 90-100)
- Cytogenetic risk group: AML

  - Favorable: inv(16), t(16;16), t(15;17), and t(8;21) without complex abnormality
  - Poor: −5/5q, −7/7q, FLT3/internal tandem duplication with high allelic ratio, t(6;9), 3q);
  - Intermediate: all others
- Cytogenetic risk group: ALL:
  - Cytogenetic risk
  - Poor: (t9;22), iAMP21, abnormal 17p, loss of 13q, and 11q23 [infant])
  - Intermediate: (all others).
- Minimal residual disease status prior to alloHCT if available
- Presence of Extra medullary disease at diagnosis Y/N if Y specify site
- Disease ALL, AML, MDS.
- Disease status: CR1 vs. CR2+

Transplant characteristics

- Donor-recipient sex match (M-M, M-F, F-F, F-M)
- HLA matching: specify degree of matching
- Donor /Recipient ABO and Rh Typing
- Donor: Sibling/Parent/Unrelated
- Donor age (continuous and in decades)
- Graft source (Bone marrow v Peripheral blood)
- Conditioning Intensity (Myeloablative v Reduced Intensity)
- TBI (yes v no)
- Serotherapy Y/N: Alemtuzumab/ATG/none
- Year of transplant (2008-2014, 2014-2021)
- Other GVHD prophylaxis agents: PTCY alone, PTCY with Calcineurin inhibitors (CNI) ± MMF, PTCY with Sirolimus ± MMF, MTX, CNI ± MMF , none

Outcomes

- Neutrophil engraftment (yes v no), day from HCT
- Platelet engraftment (yes vs no), day from HCT
- Primary or secondary graft failure (yes v no)
- Relapse (for malignancies, yes v no), if yes time from HCT
- Grade II-IV aGVHD (yes v no)
- Grade III-IV aGVHD (yes v no)
- aGVHD organ involvement
- cGVHD (yes v no)
- Extensive cGVHD or limited cGVHD
- cGVHD severity by NIH scoring if available: mild/moderate/severe
- Follow up
  1. Alive/Died
  2. Cause of death if applicable
  3. Last follow up in months

Sample Requirements:

No biological samples are required for this study.

Study Design:

This study is a retrospective CIBMTR registry analysis of risk factors and outcomes of acute and chronic GVHD in haploidentical HCT using PT-Cy in pediatric patients. We propose a 1:2 matching for recipients

of haplo HCT with MSD, MUD and if feasible for MMUD separately. Controls will be matched for age, sex, disease type, severity, conditioning type and graft source.

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Non-CIBMTR Data Source:
Not applicable

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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

X **No**

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.

Not applicable

Table 1A. Characteristics of pediatric patients undergoing first Allogeneic HCT for Acute Leukemia and Myelodysplastic Syndrome

Characteristic	Matched related donor	Haploidentical donor	Matched unrelated donor	Mismatched Unrelated Donor	Total
No. of patients	4031	1059	1254	359	6703
No. of centers	279	182	150	85	311
Age category - no. (%)					
Median (min-max)	13 (1-21)	13 (1-21)	13 (1-21)	14 (1-21)	13 (1-21)
< 10	1443 (36)	396 (37)	466 (37)	121 (34)	2426 (36)
10 - 17	1740 (43)	429 (41)	465 (37)	145 (40)	2779 (41)
18 - 21	848 (21)	234 (22)	323 (26)	93 (26)	1498 (22)
Sex - no. (%)					
Male	2382 (59)	630 (59)	722 (58)	226 (63)	3960 (59)
Female	1649 (41)	429 (41)	532 (42)	133 (37)	2743 (41)
Performance score - no. (%)					
80 - 100	3772 (94)	998 (94)	1175 (94)	344 (96)	6289 (94)
< 80	164 (4)	51 (5)	68 (5)	12 (3)	295 (4)
Not reported	95 (2)	10 (1)	11 (1)	3 (1)	119 (2)
Disease - no. (%)					
AML	1370 (34)	407 (38)	423 (34)	120 (33)	2320 (35)
ALL	2042 (51)	510 (48)	615 (49)	173 (48)	3340 (50)
Other leukemia	138 (3)	30 (3)	44 (4)	16 (4)	228 (3)
CML	145 (4)	30 (3)	48 (4)	9 (3)	232 (3)
MDS	293 (7)	64 (6)	111 (9)	37 (10)	505 (8)
AMKL	43 (1)	18 (2)	13 (1)	4 (1)	78 (1)

Characteristic	Matched related donor	Haploidentical donor	Matched unrelated donor	Mismatched Unrelated Donor	Total
Graft (Product) type - no. (%)					
Bone marrow	2950 (73)	580 (55)	939 (75)	254 (71)	4723 (70)
Peripheral blood	1073 (27)	458 (43)	314 (25)	105 (29)	1950 (29)
BM + PB	4 (0)	3 (0)	1 (0)	0 (0)	8 (0)
PB + OTH	4 (0)	18 (2)	0 (0)	0 (0)	22 (0)
Planned GVHD prophylaxis (major) - no. (%)					
CD34 selection	16 (0)	30 (3)	18 (1)	9 (3)	73 (1)
Post-Cy	111 (3)	820 (77)	45 (4)	34 (9)	1010 (15)
Tac based	1210 (30)	68 (6)	734 (59)	143 (40)	2155 (32)
CsA based	2580 (64)	111 (10)	440 (35)	167 (47)	3298 (49)
Other	68 (2)	9 (1)	13 (1)	3 (1)	93 (1)
Missing	46 (1)	21 (2)	4 (0)	3 (1)	74 (1)
Transplant year - no. (%)					
2008	418 (10)	23 (2)	90 (7)	35 (10)	566 (8)
2009	437 (11)	50 (5)	86 (7)	34 (9)	607 (9)
2010	421 (10)	36 (3)	104 (8)	18 (5)	579 (9)
2011	345 (9)	25 (2)	85 (7)	33 (9)	488 (7)
2012	309 (8)	32 (3)	103 (8)	31 (9)	475 (7)
2013	307 (8)	62 (6)	106 (8)	34 (9)	509 (8)
2014	325 (8)	50 (5)	115 (9)	24 (7)	514 (8)
2015	276 (7)	74 (7)	93 (7)	26 (7)	469 (7)
2016	322 (8)	134 (13)	106 (8)	36 (10)	598 (9)
2017	302 (7)	178 (17)	123 (10)	31 (9)	634 (9)
2018	301 (7)	189 (18)	101 (8)	25 (7)	616 (9)
2019	268 (7)	206 (19)	142 (11)	32 (9)	648 (10)

Characteristic	Matched related donor	Haploidentical donor	Matched unrelated donor	Mismatched Unrelated Donor	Total
Indicator of HCT cases in CRF retrieval - no. (%)					
No	3405 (84)	724 (68)	959 (76)	264 (74)	5352 (80)
Yes	626 (16)	335 (32)	295 (24)	95 (26)	1351 (20)

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

Evaluating predictors of access and outcomes with hematopoietic cell transplantation (HCT) in pediatric and adolescent patients with relapsed/refractory classical Hodgkin lymphoma (cHL) after treatment on an initial cooperative group clinical trial

Q2. Key Words

pediatric, Hodgkin lymphoma, HCT

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Sharon M Castellino , MD, MSc
Email address:	sharon.castellino@choa.org
Institution name:	Emory University/Children's Healthcare of Atlanta
Academic rank:	Professor of Pediatrics

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Justine Kahn, MD, MSc
Email address:	jk2034@cumc.columbia.edu
Institution name:	Columbia University
Academic rank:	Assistant Professor, Pediatrics

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?

- 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:

Sharon M Castellino, MD, MSc

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.

none to date

Q13. PROPOSED WORKING COMMITTEE:

- Pediatric Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Muna Qayed MD, MS; Rachel Phelan MD, Larisa Broglie MD, MS

Q15. RESEARCH QUESTION:

To evaluate predictors of receipt of HCT and outcomes following receipt of HCT after up-front response-based therapy or salvage therapy for classical Hodgkin Lymphoma HL (cHL) on Children's Oncology Group (COG)Trials.

Q16. RESEARCH HYPOTHESIS:

Outcomes following relapse, including receipt of hematopoietic cell transplantation HCT, will differ by age and race/ethnicity among patients receiving up-front response-based therapy or salvage therapy for classical Hodgkin Lymphoma (cHL) on Children's Oncology Group (COG) trials.

1.1 Among patients receiving up-front or salvage therapy on Children's Oncology Group (COG) trials for newly diagnosed classical Hodgkin lymphoma (cHL), receipt of HCT will differ by age and race/ethnicity.

1.2 Patterns of failure (site of failure ; time to failure); Progression-free survival; treatment-related mortality) following first HCT for relapsed cHL will differ by race/ ethnicity (non-Hispanic black vs non-Hispanic white; Hispanic vs. non-Hispanic white) and age at initial diagnosis (> 15 vs, < 15 years)

1.3 Overall survival post-HCT will differ by race/ethnicity and age

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) *Suggested word limit of 200 words:*

Primary:

1. To evaluate the receipt of HCT in ~700 pediatric and adolescent patients with relapsed cHL using a novel data linkage between COG and the CIBMTR.

1.1 To characterize the type/source of HCT (autologous versus allogeneic), and the dose of stem cells (autoHCT)

Secondary:

2.0 To evaluate patient- and disease- and system -related predictors of receipt of HCT after HL relapse including age, race/ethnicity, insurance, location of COG treatment, initial disease (stage, B symptoms, bulk) , disease status (at completion of COG treatment and immediately prior to HCT)

3.0 To evaluate overall survival and progression-free survival after HCT, adjusting for initial COG therapy, demographics, disease and transplant factors.

4.0 To characterize transplant-related toxicities overall and by:

4.1 Race/ethnicity

4.2 Age at HCT: (< 15 vs. > 15 yrs.)

4.3 Time from HCT: early (< 100 days) versus late (> 100 days) from date of HCT

4.4 Relapse versus non-relapse toxicities

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.

Longitudinal data in children and adolescents with relapsed or refractory HL are limited: While the COG database captures relapse events and death through 10 years post enrollment, details of post relapse therapy and causes of mortality are poorly characterized. By linking the COG to the CIBMTR, we will establish the capacity to evaluate access to HCT, and importantly, to examine survival outcomes after HCT in patients with recurrent HL who were treated on COG trials for either up-front, or first salvage therapy. This linkage will enable us to fill a critical gap in the literature regarding use and outcomes of HCT in patients with recurrent HL and more broadly, will establish the premise for future longitudinal studies linking COG data to the CIBMTR.

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 use of risk-based, response-adapted approaches to treat cHL is predicated on the fact that salvage strategies, primarily, HCT, are successful in maintaining excellent overall survival (OS) rates.(1,2) Today, HCT remains definitive therapy for patients with relapsed or refractory HL.(3,4) In a cohort of pediatric patients treated for newly diagnosed HL on contemporary COG trials, we recently identified significant disparities in OS both by age and by race/ethnicity. In this pooled analysis of 1,605 children and adolescents treated on one of 3 COG trial for newly diagnosed HL between 2002 and 2012, event-free survival did not differ between non-Hispanic White and non-White patients. Despite no disparities in the risk of relapse, however, non-Hispanic Black and Hispanic (vs. non-Hispanic White) patients had 3.5-fold and 2.7-fold increased risk of post-relapse mortality, respectively.(5) Further, in preliminary analyses of survival outcomes by age in this cohort, similar patterns of post-relapse disparities are observed in patients who are 15 years and older, vs. younger at diagnosis (manuscript in review Lancet Haematology). (6) A recently assembled cohort of patients receiving salvage chemotherapy regimens (n=188) on COG trial shows 5- yr survival of 57% for non-white patients compared to 71% for white patients p=0.08) (COG data- not published yet).

The limitations of extant datasets are highlighted in our inability to systematically study longitudinal care and outcomes of COG patients with cHL in the post-relapse setting once they are off study. These limitations are exacerbated by the fact that cHL is a disease of adolescents and young adults and the fact that many patients may transfer from pediatric/COG treating center to adult care, often during a period or relapse.(7) As a result, there remains an urgent gap in our understanding of post-relapse care and outcomes in pediatric and adolescent patients treated for cHL on contemporary COG trials. While autologous (auto)-HCT is standard therapy for relapsed HL, there remain questions about which patients actually undergo auto-HCT, which undergo allogeneic HCT, what toxicities patients have during HCT, and whether racial/ethnic and age-related survival disparities persist in patients who do undergo HCT.

In a CIBMTR analysis of 836 patients >15 years treated for HL between 1990 and 2008, Myers et al. reported that older age, male sex, Karnofsky status < 90, total body irradiation, and higher numbers of prior chemotherapy regimens were risk factors for overall mortality.(8) In a separate CIBMTR analysis limited to 606 children and adolescents undergoing auto-HCT for HL between 1995 and 2010, performance status < 90, extra nodal disease at HCT and time from diagnosis to first relapse (<12 months) were risk factors of progression-free survival post-transplant.(9) While race and age at transplant (< or >/= 21 years) were tested and did not emerge as significant independent predictors in this analysis, the data was limited in terms of details related to initial therapy (disease factors, treatment, response and system factors) and importantly was limited to those children and adolescents who actually make it to auto HCT.

Our current proposal builds on these studies in HL by analyzing a clinical trials cohort in whom we have already identified post-relapse survival disparities that remain unexplained. (5,6) The COG cohort includes patients treated with risk-based, response-adapted therapy on contemporary clinical trials (2002-2019). By linking these patients to the CIBMTR, we will be able to examine longitudinal patterns of care and outcomes of patients from the time of up-front therapy, through transplant and into post-transplant follow-up. This novel linkage of a COG HL cohort to the CIBMTR will allow us to examine outcomes while adjusting for systematically collected treatment and toxicity data from both the COG and the CIBMTR (i.e. post infusion), and will identify drivers of post-relapse outcomes in children and adolescents with recurrent HL.

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 who develop relapsed or refractory disease after undergoing up-front therapy for de novo cHL on one of four COG trials (2002 – 2018): AHOD 0431, 0031 or 0831 or 1331 trials: (N ~ 450)
2. Patients with recurrent cHL who received salvage therapy on one of five COG trials between 2001 and 2017: AHOD00P1, AHOD0431, AHOD0121, AHOD0321, AHOD0521 and AHOD1221 (N=188)
3. Age: < 30 years at initial diagnosis of cHL
4. Exclude: patients with HCT prior to a COG trial

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.

CIBMTR data requested will include: TED level (to address Aim 1) and CRF level (to facilitate multivariable analyses and predictors relevant to aims 2, 3, 4,)
1 Patient :
Age at transplant: continuous and categorical
Age at last follow up
Sex: male vs. female
Race/ethnicity: Non-Hispanic White; Non-Hispanic Black; Asian/Hawaiian/Pacific Islander; Hispanic; Other
Country: US vs. Canada vs. other
Insurance status and type (will be categorized for non-US as previously)
Neighborhood socioeconomic status (zip code based - for US patients)
2. Disease-related (at initial presentation, at time of relapse)
HL stage (Ann Arbor)
Histology
Bulk disease
B-symptoms
Was a FDG PET or PET-CT done prior to diagnosis (2018 Lym pre inf Q69/70)
Remission status prior to HCT
3. Initial Treatment-related
COG study
Therapy: chemotherapy (agents and cumulative doses); date of start and stop
Radiation therapy : dose and sites; dates
Dose-limiting toxicities (CTCAE > grade 3 events)
Location of care (institution size, zip code, comprehensive cancer center, NCORP)
4. Transplant/HCT -related
Transplant center (zip code, CIBMTR center: TED versus CRF track; cancer center)
Year of transplant (date)
Karnofsky/Lansky performance score: ≥90% vs. <90%
Pre-transplant salvage therapy (drugs and number of regimen)
Response status prior to prep for HCT (PET status; CR, PR SD)
Type of cell source: autologous; allogeneic
Conditioning regimen (agents and cumulative doses)
TBI dose if applicable
Radiation therapy at time of or post transplantation (dose and sites)
Additional maintenance therapy post transplantation (ie. Brentuximab vedotin or PD1 inhibitors)
Time from relapse diagnosis to transplant
Graft source: bone marrow vs. peripheral blood vs. cord blood
Cell dose for HCT
Organ toxicities and grade: Cardiovascular, pulmonary, hepatic, renal, infectious, GVHD-related
Subsequent HCT (type: autologous ; allogeneic)
Second or subsequent malignancy
Cause of death

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

not applicable

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.

1. The CIBMTR data will be linked to two pooled COG cohorts:
a. Patients enrolled on the COG trials for de novo disease (AHOD0031, AHOD0431, AHOD0831, AHOD1331), who develop disease recurrence. The data set for AHOD0031, 0431 and 0831 has been assembled and cleaned 5 . Data on relapse events on AHOD1331 (Study Chair: S. Castellino) is expected to be released pending DSMC review in March 2022.
b. Patients enrolled on salvage trials after relapse or recurrence- this data set has preliminary assembly and is in process of being analyzed
Methodology to link data: Data will be linked using direct identifiers following a data sharing honest broker agreement between COG and the CIBMTR. The COG dataset will be the data set of patients enrolled on trial. Linking variables will include patient name, date of birth, and sex. Confirmatory variables will include month and year of initial diagnosis.
The assembled investigator team is committed to the feasibility and execution of the data sets, as several of the investigators are members of the COG Hodgkin lymphoma committee: S. Castellino- Steering, Initial therapeutic, Disparities ; Kahn -Disparities, AYA; Kelly - Discipline Chair, COG HL Committee; Cole- Vice Chair HL, Relapse/Retrieval therapies; Parsons: Steering; Health related quality of life, Discipline Chair – Cancer Care Delivery; Pei: COG Statistician for HL committee.
The feasibility of this approach to linkage has been discussed with COG Statistical Cahir (Todd Alonzo, PhD). Linkage will be arranged in a manner respective of PHI.

Q26. REFERENCES:

1. Castellino SM, Parsons SK, Kelly KM. Closing the survivorship gap in children and adolescents with Hodgkin lymphoma. Br J Haematol. 2019;187(5):573-587.
2. Kelly KM. Hodgkin lymphoma in children and adolescents: improving the therapeutic index. Hematology Am Soc Hematol Educ Program. 2015;2015:514-521.
3. Horton TM, Drachtman RA, Chen L, et al. A phase 2 study of bortezomib in combination with ifosfamide/vinorelbine in paediatric patients and young adults with refractory/recurrent Hodgkin lymphoma: a Children's Oncology Group study. Br J Haematol. 2015;170(1):118-122.
4. Harker-Murray PD, Drachtman RA, Hodgson DC, Chauvenet AR, Kelly KM, Cole PD. Stratification of treatment intensity in relapsed pediatric Hodgkin lymphoma. Pediatr Blood Cancer. 2014;61(4):579-586.
5. Kahn JM, Kelly KM, Pei Q, ...Castellino SM. et al. Survival by Race and Ethnicity in Pediatric and Adolescent Patients With Hodgkin Lymphoma: A Children's Oncology Group Study. J Clin Oncol. 2019;37(32):3009-3017.
6. Kahn JM, Kelly KM, Pei Q, Friedman D, Keller FG, Bhatia S, Henderson TO, Schwartz C, Castellino SM. Outcomes by age in pediatric and adolescent patients treated for de novo Hodgkin lymphoma on contemporary Children's Oncology Group trials. S-X-04 Klinische Pädiatrie 2020; 232:112
7. Kahn JM, Kelly KM. Adolescent and young adult Hodgkin lymphoma: Raising the bar through collaborative science and multidisciplinary care. Pediatr Blood Cancer. 2018;65(7):e27033.
8. Myers RM, Hill BT, Shaw BE, et al. Long-term outcomes among 2-year survivors of autologous hematopoietic cell transplantation for Hodgkin and diffuse large b-cell lymphoma. Cancer. 2018;124(4):816-825.
9. Satwani P, Jin Z, Martin PL, et al. Sequential myeloablative autologous stem cell transplantation and reduced intensity allogeneic hematopoietic cell transplantation is safe and feasible in children, adolescents and young adults with poor-risk refractory or recurrent Hodgkin and non-Hodgkin lymphoma. Leukemia. 2015;29(2):448-455.
10. Satwani P. Ahn KW, Carreras, J etal. A prognostic model predicting autologous transplantation outcomes in children, adolescents and young adults with Hodgkin lymphoma Bone Marrow Transplant. 2015; 50

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

Table 1A. Characteristics of pediatric patients undergoing HCT with relapsed/refractory for Hodgkin lymphoma (cHL) by patients age at diagnosis

Characteristic	< 15	15 - 29	Total
No. of patients	327	3474	3801
No. of centers	126	316	334
Patient age, at diagnosis, years - median (min-max)	13 (0-15)	23 (15-30)	23 (0-30)
Sex - no. (%)			
Male	202 (62)	1851 (53)	2053 (54)
Female	125 (38)	1623 (47)	1748 (46)
Disease status prior to HCT (NHL/HD) - no. (%)			
PR	252 (77)	2568 (74)	2820 (74)
Chemoresistant	55 (17)	750 (22)	805 (21)
Untreated	3 (1)	44 (1)	47 (1)
Unknown	17 (5)	112 (3)	129 (3)
Performance score - no. (%)			
80 - 100	304 (93)	3151 (91)	3455 (91)
< 80	11 (3)	191 (5)	202 (5)
Not reported	12 (4)	132 (4)	144 (4)
Transplant type - no. (%)			
Allogeneic	69 (21)	840 (24)	909 (24)
Autologous	258 (79)	2634 (76)	2892 (76)
Race-Ethnicity Category - no. (%)			
Non-Hispanic White	96 (29)	1734 (50)	1830 (48)
Non-Hispanic Non-White	44 (13)	457 (13)	501 (13)
Hispanic White	42 (13)	378 (11)	420 (11)
Hispanic Non-White	5 (2)	26 (1)	31 (1)
Not reported	140 (43)	879 (25)	1019 (27)
Age category at diagnosis - no. (%)			
< 15	327 (100)	0 (0)	327 (9)
15 - 17	0 (0)	443 (13)	443 (12)
18 - 29	0 (0)	3031 (87)	3031 (80)
Transplant year - no. (%)			
2008	34 (10)	391 (11)	425 (11)
2009	35 (11)	366 (11)	401 (11)
2010	28 (9)	366 (11)	394 (10)
2011	31 (9)	328 (9)	359 (9)
2012	21 (6)	302 (9)	323 (8)
2013	24 (7)	300 (9)	324 (9)
2014	19 (6)	272 (8)	291 (8)
2015	24 (7)	251 (7)	275 (7)
2016	28 (9)	216 (6)	244 (6)
2017	31 (9)	285 (8)	316 (8)

Characteristic	**< 15**	**15 - 29**	**Total**
2018	28 (9)	198 (6)	226 (6)
2019	24 (7)	199 (6)	223 (6)
Indicator of HCT cases in CRF retrieval - no. (%)			
No	310 (95)	3224 (93)	3534 (93)
Yes	17 (5)	250 (7)	267 (7)

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

Outcomes of children and adolescents undergoing autologous or allogeneic hematopoietic stem cell transplantation for first relapse or refractory non-Hodgkin lymphoma

Q2. Key Words

Non-Hodgkin lymphoma, relapsed, refractory, children, adolescents

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Jennifer Belsky, DO, MS
Email address:	jbelsky@iu.edu
Institution name:	Riley Children's Hospital/ Indiana University
Academic rank:	Assistant Professor

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):	Sarah Alexander, MD
Email address:	sarah.alexander@sickkids.ca
Institution name:	The Hospital for Sick Children/ University of Toronto
Academic rank:	Professor

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:

Jennifer Belsky

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.

none

Q13. PROPOSED WORKING COMMITTEE:

- Pediatric Cancer

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

- No

Q15. RESEARCH QUESTION:

In children and adolescents treated for first relapse or refractory non-Hodgkin lymphoma (excluding lymphoblastic lymphoma) does transplant type impact one year event free survival when accounting for disease subtype, time in first remission and disease status at time of transplant?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that pediatric patients with first relapse or refractory (R/R) non-Hodgkin lymphoma (NHL), excluding lymphoblastic lymphoma (LL), who have undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT) had a superior event free survival (EFS) than those who received autologous hematopoietic stem cell transplantation (auto-HSCT), when accounting for disease subtype, time in first remission and disease status at time of transplant.

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

Suggested word limit of 200 words:

The primary aim is to compare event free survival (EFS) at one year for children and adolescents who have undergone allo-HSCT or auto-HSCT for R/R NHL, excluding LL and accounting for disease subtype, time in first remission and disease status at the time of transplant. Disease subtypes include a) Burkitt/Burkitt like, b) diffuse large B cell (DLBCL), c) anaplastic large cell (ALCL), and d) other.

Secondary aims:

1. To compare overall survival (OS) at 5 years for those who have undergone allo-HSCT or auto-HSCT for R/R NHL, excluding LL, accounting for disease subtype, time in first remission and disease status at the time of transplant.
2. To compare treatment related mortality at 100 days for children and adolescents who have undergone allo-HSCT or auto-HSCT for R/R NHL, excluding LL.

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 standard of care for most children and adolescents with relapsed or R/R NHL includes disease re-induction followed by HSCT. Except for those patients with lymphoblastic lymphoma, the choice of appropriate donor type in this setting remains unclear. Data to inform the choice of allogeneic or autologous HSCT based on disease subtype, time in first remission, and disease status at time of transplant will be of critical importance.

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.

EFS for children and adolescents with NHL continues to improve, while outcomes for those with R/R disease remain poor.

NHL is a heterogenous group of neoplasms accounting for 7% of all pediatric malignancies, originating from immature or mature B, T, or natural killer cells. In children and adolescents four subtypes (Burkitt, DLBCL, ALCL and LL) account for the majority of cases with rare lymphomas accounting for the remainder. Children and adolescents treated for NHL in resource intensive settings have excellent outcomes with the modern therapeutic regimens (1). Outcomes for children and adolescents with R/R NHL remain poor especially for those with Burkitt lymphoma, those with early relapse, and those with poor disease control at the time of transplant (2,3 4,5).

The optimal type of HSCT in the therapy of pediatric patients with R/R NHL on patient remains unclear.

HSCT is considered a core component of most curative regimens for children with R/R NHL. The treatment for patients with R/R NHL consists of aggressive chemotherapy, which may include targeted agents or immunotherapies, followed by consolidation with HSCT. Except in those children with R/R lymphoblastic lymphoma where existing evidence suggests that undergoing allo-HSCT is associated with a superior EFS, the choice of transplant type remains unclear (6 7,8).

In children and adolescents with mature B-NHL, data has not demonstrated superiority of allo-HSCT. Data from a CIBMTR cohort who were transplant between 1990 and 2005 showed no significant difference in EFS or OS between those who received allo versus auto HSCT (7). Similar results were reported in a French study from 2015 (9). A study from Japan's national HSCT database including 31 auto-HSCT and 48 allo-HSCT recipients between 1990-2013 demonstrated the 5-year survival was significantly lower for patients receiving allo-SCT compared to auto-SCT (32% vs 55% p=0.036), with the difference attributed to treatment related mortality (TRM)(10).

In patients with R/R ALCL, retrospective studies have described both allo- and auto-HSCT as curative therapy (4,11-13). In the 2010 CIBMTR study there was a trend towards lower probability of disease recurrence in those who received allo-HSCT, but this was not statistically significant (7). An international, prospective trial allocated patients to transplant type based on risk (time to relapse and CD3 expression) demonstrated superior EFS for those who received allo-HSCT in patients with intermediate and high-risk disease when analyzed by actual HSCT type received(5).

CIBMTR data for pediatric patients with R/R NHL.

Gross et al. reported outcomes for children and adolescents with R/R from CIBMTR data in 2010 (7). The 182 patients included in this study were those transplanted between from 1990-2005. The justification for re-evaluation of a more contemporary cohort of patients is two-fold. Therapy for children with NHL pre-HSCT has been intensified, including the addition of rituximab to upfront therapy in children and adolescents with mature B-NHL and the availability of effective targeted therapy, most applied at the time of relapse, for those with ALCL including ALK inhibitors and CD30+ directed immunotherapies. Intensification of therapy pre-HSCT may impact outcomes and may impact efficacy based on transplant type. Secondly, supportive care through the HSCT period has improved dramatically in the last several decades impacting the risks of TRM. For both reasons a reassessment of CIBMTR data in a contemporary cohort will provide important data in the design of future cooperative group prospective trials in the field.

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.

Participant selection criteria

Inclusion Criteria

• Patients undergoing allo- or auto-HSCT for first relapse or refractory disease for any NHL subtype, except lymphoblastic lymphoma.

• Age less than ≤18 years at the time of HSCT.

• Transplant performed between the years of 2000-2020.

Exclusion Criteria

• Lymphoblastic lymphoma subtype

• Patients receiving second or subsequent SCT

• Patients receiving CART cell therapy

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.

1. Patient variables-
a. Demographics: age, gender
2. Disease variables
a. NHL subtype
b. For ALCL only, presence of CD3 expression and/or small cell variant from primary tumor, and ALK expression
c. Date of first diagnosis
d. Date of relapse
e. Time to relapse
f. Frontline therapy
g. Stage of disease at relapse, including any CNS involvement
h. Disease status at time of HSCT
3. Transplant variables
a. Preparative regimen
b. HSCT type
c. Allo - Donor match and cell source
d. Allo - Graft manipulation
e. HSCT infusion date
f. HSCT prep regimen
g. Post-transplant therapy
4. Outcome variables
a. Post HSCT date of recurrence or progression, if any
b. Post HSCT date of death, if any
c. Post HSCT cause of death, if any

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

none

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

none

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.

none

Q26. REFERENCES:

1. Buhtoiarov IN. Pediatric Lymphoma. Pediatr Rev 2017;38:410-23.
2. Osumi T, Mori T, Fujita N, et al. Relapsed/refractory pediatric B-cell non-Hodgkin lymphoma treated with rituximab combination therapy: A report from the Japanese Pediatric Leukemia/Lymphoma Study Group. Pediatr Blood Cancer 2016;63:1794-9.
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4. Woessmann W, Zimmermann M, Lenhard M, et al. Relapsed or refractory anaplastic large-cell lymphoma in children and adolescents after Berlin-Frankfurt-Muenster (BFM)-type first-line therapy: a BFM-group study. J Clin Oncol 2011;29:3065-71.
5. Knörr F, Brugières L, Pillon M, et al. Stem Cell Transplantation and Vinblastine Monotherapy for Relapsed Pediatric Anaplastic Large Cell Lymphoma: Results of the International, Prospective ALCL-Relapse Trial. J Clin Oncol 2020;38:3999-4009.
6. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. Pediatr Clin North Am 2015;62:139-65.
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11. Mori T, Takimoto T, Katano N, et al. Recurrent childhood anaplastic large cell lymphoma: a retrospective analysis of registered cases in Japan. Br J Haematol 2006;132:594-7.
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13. Strullu M, Thomas C, Le Deley MC, et al. Hematopoietic stem cell transplantation in relapsed ALK+ anaplastic large cell lymphoma in children and adolescents: a study on behalf of the SFCE and SFGM-TC. Bone Marrow Transplant 2015;50:795-801.

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

Table 1A. Characteristics of pediatric patients undergoing first HCT for Non-Hodgkin Lymphoma

Characteristic	Allogeneic	Autologous	Total
No. of patients	776	560	1336
No. of centers	189	183	258
Age category - no. (%)			
Median (min-max)	12 (0-18)	14 (0-18)	13 (0-18)
< 10	299 (39)	163 (29)	462 (35)
10 - 17	477 (61)	397 (71)	874 (65)
Sex - no. (%)			
Male	516 (66)	367 (66)	883 (66)
Female	260 (34)	192 (34)	452 (34)
Not Answer	0 (0)	1 (0)	1 (0)
Performance score - no. (%)			
80 - 100	574 (74)	434 (78)	1008 (75)
< 80	50 (6)	24 (4)	74 (6)
Not reported	152 (20)	102 (18)	254 (19)
Transplant year - no. (%)			
2000	49 (6)	38 (7)	87 (7)
2001	44 (6)	29 (5)	73 (5)
2002	48 (6)	43 (8)	91 (7)
2003	53 (7)	35 (6)	88 (7)
2004	48 (6)	33 (6)	81 (6)
2005	48 (6)	36 (6)	84 (6)
2006	41 (5)	36 (6)	77 (6)
2007	39 (5)	32 (6)	71 (5)
2008	38 (5)	30 (5)	68 (5)
2009	53 (7)	30 (5)	83 (6)

Characteristic	Allogeneic	Autologous	Total
2010	31 (4)	35 (6)	66 (5)
2011	40 (5)	27 (5)	67 (5)
2012	17 (2)	18 (3)	35 (3)
2013	33 (4)	23 (4)	56 (4)
2014	48 (6)	15 (3)	63 (5)
2015	37 (5)	22 (4)	59 (4)
2016	26 (3)	25 (4)	51 (4)
2017	25 (3)	16 (3)	41 (3)
2018	31 (4)	26 (5)	57 (4)
2019	27 (3)	11 (2)	38 (3)
Indicator of HCT cases in CRF retrieval - no. (%)			
No	491 (63)	560 (100)	1051 (79)
Yes	285 (37)	0 (0)	285 (21)

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

Hematopoietic Stem Cell Transplant Outcomes for Infant Acute Lymphoblastic leukemia

Q2. Key Words

Infant leukemia, HSCT

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nahal Rose Lalefar, MD
Email address:	nahal.lalefar@ucsf.edu
Institution name:	UCSF Benioff Children's Hospital Oakland
Academic rank:	Assistant Professor of Pediatrics

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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

N/A

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:

N/A

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:

- Pediatric Cancer

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

- No

Q15. RESEARCH QUESTION:

What is the leukemia free survival and overall survival for infants with B-lymphoblastic leukemia who undergo stem cell transplantation and has survival improved for this patient population over the last 10 years?

Q16. RESEARCH HYPOTHESIS:

Disease free survival and overall survival for infant B-cell ALL will be higher for infants who undergo hematopoietic stem cell transplant (HSCT) in complete remission (CR1) compared to historical controls if they received their transplant within the last decade.

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

Suggested word limit of 200 words:

1. Determine the leukemia free survival at 1yr and 3yr for infants with acute B-lymphoblastic leukemia (CR1 vs other) who under HSCT between 2008-2018
2. Determine the overall survival at 1yr and 3yr for infants with acute B-lymphoblastic leukemia.(CR1 vs other) between 2008-2018

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.

Traditionally, HSCT has not provided clear survival benefit for infant ALL. Treatment of infant ALL remains very challenging. The comparisons between HSCT versus chemotherapy alone are based mostly on cooperative studies such as CCG/POG and Interfant-99. We know that this patient population is at high risk for relapse. As supportive care measures improve and we have expanded donor options, we may be able to demonstrate that the HSCT may be beneficial consolidative therapy to not only high risk patients but other infant ALL patients who achieve CR1.

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.

Infant ALL prognosis is poor compared to that of older children, particularly those with KMT2A rearrangement. The 4-year event-free survival (EFS) in Interfant-99, one of the largest trials of infant ALL, was 47% (Pieters, Schrappe et al. 2007). The 4 year disease free survival for those who received SCT in that trial was 44%. Pediatric leukemia trials from a similar time period report long-term EFS above 85% (Brown, Pieters et al. 2019). Outcomes were not significantly improved between Interfant-99 and Interfant-06 and other cooperative groups such as COG (Pieters, De Lorenzo et al. 2019). However, only 46% of high risk infant leukemia patients in Interfant-06 went on to receive stem cell transplants due to early events (most of which were relapses).

Older studies did show benefit of HSCT over chemotherapy for patients with infant leukemia. CCG1953 and POG 9407, which enrolled patients between1996-2000, showed a 5-year EFS/OS of 48.8%/59.36% (those who received HSCT) versus 48.7%/53.08% (those who received chemotherapy alone) (Dreyer, Dinndorf et al. 2011). However, these outcomes were limited by small patient numbers and differences in overall survival was not statistically significant. The interfant-99 study suggests that there does appear to be a small minority of KMT2A-r patients at high risk of relapse (very young age, very high WBCs, and persistence of MRD) who may benefit from HSCT in first remission (Mann, Attarbaschi et al. 2010). However, we now know there are other prognostic factors that may further impact response to treatment such as RAS mutations, which in the presence of KMT2A rearrangements, may serve as an independent predictor for a poor outcomes (Driessen, van Roon et al. 2013).

The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) MLL-10 trial, which recruited patients between 2011-2015, showed that 38 of 56 high risk infant ALL patients underwent HSCT in CR1. Twenty-five patients (66%) were alive at the time of publication in 2020 (Tomizawa, Miyamura et al. 2020).

With expanded treatment options such as immunotherapy, wider donor selection (to include haplo-identical donors), broader genetic testing to assess additional prognostic factors (e.g. RAS mutations), and incorporation of next generation minimal residual disease testing, we can evaluate recent CIBMTR outcome data to see if HSCT may benefit infant B-ALL patients in CR1 beyond what has been described in each cooperative trial.

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.

Inclusion:
Age 0-12 months of age at diagnosis
Acute lymphoblastic leukemia (B-cell)
Exclusion:
T-cell ALL, T-cell/myeloid MPAL, mature B-cell ALL, or Philadelphia chromosome–positive ALL

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.

Variables to be analyzed: 2008-2018
Age at diagnosis (0-6 months, 7-9 months, 10-12months)
Gender
Primary diagnosis: ALL (MLL germline line vs rearrangement)
Dates of transplant
Disease status at time of HSCT
Donor Type
Graft
Conditioning Regimen with intensity
GVHD prophylaxis
Acute GVHD grade I and II versus grade III and IV versus no aGVHD
EFS/DFS at 1 yr, 3 yr (compare to survival rates pre 2008)
OS at 1, 3 yr (compare to survival rates pre 2008)
Limited data previous requested (INFOREQ#2106-06)

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

DATA only

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:

Brown, P., R. Pieters and A. Biondi (2019). "How I treat infant leukemia." Blood 133(3): 205-214.

Dreyer, Z. E., P. A. Dinndorf, B. Camitta, H. Sather, M. K. La, M. Devidas, J. M. Hilden, N. A. Heerema, J. E. Sanders, R. McGlennen, C. L. Willman, A. J. Carroll, F. Behm, F. O. Smith, W. G. Woods, K. Godder and G. H. Reaman (2011). "Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: a report from the Children's Oncology Group." J Clin Oncol 29(2): 214-222.

Driessen, E. M., E. H. van Roon, J. A. Spijkers-Hagelstein, P. Schneider, P. de Lorenzo, M. G. Valsecchi, R. Pieters and R. W. Stam (2013). "Frequencies and prognostic impact of RAS mutations in MLL-rearranged acute lymphoblastic leukemia in infants." Haematologica 98(6): 937-944.

Mann, G., A. Attarbaschi, M. Schrappe, P. De Lorenzo, C. Peters, I. Hann, G. De Rossi, M. Felice, B. Lausen, T. Leblanc, T. Szczepanski, A. Ferster, G. Janka-Schaub, J. Rubnitz, L. B. Silverman, J. Stary, M. Campbell, C. K. Li, R. Suppiah, A. Biondi, A. Vora, M. G. Valsecchi, R. Pieters and G. Interfant-99 Study (2010). "Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study." Blood 116(15): 2644-2650.

Pieters, R., P. De Lorenzo, P. Ancliffe, L. A. Aversa, B. Brethon, A. Biondi, M. Campbell, G. Escherich, A. Ferster, R. A. Gardner, R. S. Kotecha, B. Lausen, C. K. Li, F. Locatelli, A. Attarbaschi, C. Peters, J. E. Rubnitz, L. B. Silverman, J. Stary, T. Szczepanski, A. Vora, M. Schrappe and M. G. Valsecchi (2019). "Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study." J Clin Oncol 37(25): 2246-2256.

Pieters, R., M. Schrappe, P. De Lorenzo, I. Hann, G. De Rossi, M. Felice, L. Hovi, T. LeBlanc, T. Szczepanski, A. Ferster, G. Janka, J. Rubnitz, L. Silverman, J. Stary, M. Campbell, C. K. Li, G. Mann, R. Suppiah, A. Biondi, A. Vora and M. G. Valsecchi (2007). "A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial." Lancet 370(9583): 240-250.

Tomizawa, D., T. Miyamura, T. Imamura, T. Watanabe, A. Moriya Saito, A. Ogawa, Y. Takahashi, M. Hirayama, T. Taki, T. Deguchi, T. Hori, M. Sanada, S. Ohmori, M. Haba, A. Iguchi, Y. Arakawa, Y. Koga, A. Manabe, K. Horibe, E. Ishii and K. Koh (2020). "A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial." Blood 136(16): 1813-1823.

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

Table 1A. Characteristics of pediatric patients undergoing HCT for Infant ALL

Characteristic	ALL
No. of patients	352
No. of centers	103
Patient age, at diagnosis, years - median (min-max)	0 (0-1)
Sex - no. (%)	
Male	176 (50)
Female	176 (50)
Performance score - no. (%)	
80 - 100	316 (90)
< 80	14 (4)
Not reported	22 (6)
Transplant year - no. (%)	
2008	42 (12)
2009	24 (7)
2010	13 (4)
2011	33 (9)
2012	39 (11)
2013	32 (9)
2014	23 (7)
2015	22 (6)
2016	28 (8)
2017	30 (9)
2018	36 (10)
2019	30 (9)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	228 (65)
Yes	124 (35)

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

Developing a Pediatric Hematopoietic Cell Transplantation-Composite Risk (pHCT-CR) Score to Predict Outcomes in Children with Acute Leukemia Undergoing Hematopoietic Cell Transplantation

Q2. Key Words

Hematopoietic Cell Transplantation- Comorbidity Index (HCT-CI), Disease Related Index (DRI), Children, Hematopoietic Cell Transplantation (HCT)

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Madhavi Lakkaraja MD, MPH
Email address:	madhavi.lakkaraja@bcm.edu
Institution name:	Texas Children's Hospital/ Baylor College of Medicine/Center for Cell and Gene Therapy
Academic rank:	Fellow, Pediatric Stem Transplant

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?

N/A

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Brian Friend, MD, MS
Email address:	brian.friend@bcm.edu
Institution name:	Texas Children's Hospital/ Baylor College of Medicine/Center for Cell and Gene Therapy
Academic rank:	Assistant Professor, Pediatric Stem Cell Transplant

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?

N/A

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:

Madhavi Lakkaraja and Brian Friend
madhavi.lakkaraja@bcm.edu, brian.friend@bcm.edu

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.

Madhavi Lakkaraja: CIBMTR proposal approved for data from BMT 1202 study looking at personalizing ATG for improving outcomes.
Brian Friend: Worked on PC19-01, IN17-01, LK18-02, Currently working on RT18-01

Q13. PROPOSED WORKING COMMITTEE:

- Pediatric Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Larisa Broglie, MD MS

Q15. RESEARCH QUESTION:

Can a composite risk score based on simplified malignant hematopoietic stem cell transplantation – comorbidity index (smHCT-CI) and pediatric disease related index (DRI) predict outcomes in children with acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) undergoing their first allogeneic HCT?

Q16. RESEARCH HYPOTHESIS:

A novel, prognostic tool termed the pediatric hematopoietic cell transplantation-composite risk (pHCT-CR) score will be able to predict overall survival in children undergoing first allogeneic HCT with acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL).

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

Suggested word limit of 200 words:

Objectives :
1) To develop and validate a pHCT-CR score in children with ALL and AML who underwent their first allogeneic HCT.
2) To compare performance of pHCT-CR score to previously described risk scores including pediatric DRI and original HCT-CI.
Outcomes to be investigated:
Primary endpoint
Overall survival (OS): Time to death from any cause. Patients who are alive will be censored at the time of last contact.
Secondary endpoints
Leukemia-free survival (LFS): Time to relapse/progression of leukemia or death from any cause
Non- relapse mortality (NRM): Time to death from any cause without relapse/progression. NRM will be summarized as a cumulative incidence estimate with competing risk being relapse/disease progression.
Relapse: Time to relapse/progression of leukemia
GVHD-free/relapse-free survival (GRFS): Time to grade III-IV acute GVHD, extensive chronic GVHD, or relapse/progression of leukemia

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 goal of our study is to develop a novel, prognostic tool termed the pHCT-CR score for children with acute leukemia that can better predict HCT outcomes than previous models. This tool would be increasingly used to characterize pre-transplant risk in children undergoing their first allogeneic HCT, that may help guide patient counseling, influence transplant approaches, and may even prove useful as an eligibility criterion for clinical trials.
Perhaps the greatest impact for a new risk score for children undergoing allogeneic HCT is that its use may lead to the development of risk-based, personalized strategies aimed at reducing toxicity and improving outcomes. Uniquely, the pHCT-CR score should be able to distinguish whether the mortality in each risk group is primarily due to NRM or relapse. This would allow for the testing of targeted, prophylactic and treatment approaches, such as modifying conditioning regimens or planning a fast wean of immunosuppression in order to improve outcomes.

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.

Allogeneic HCT is a curative treatment modality for patients with hematologic malignancies, yet it is associated with a significant risk of non-relapse mortality. Pretransplant risk assessment is increasingly becoming an important measure to optimize transplant outcomes. Hematopoietic stem cell transplantation comorbidity index (HCT-CI) is a composite score based on seventeen comorbidities that is a commonly used tool to predict transplant outcomes.1,2 As this model accounts for organ function and prior comorbidities but not disease characteristics, this risk score has most utility in discriminating risk of non-relapse mortality.1,2

In contrast, the disease risk index (DRI) and the refined-DRI (DRI-R) are risk scores based on disease specific characteristics and remission status prior to transplant, that can effectively predict leukemia-free survival.3,4 These models also attempts to diminish the heterogeneity of the study population when outcomes of several diseases are reported together. However, DRI and DRI-R does not account for patient characteristics, and therefore, is potentially less useful in predicting overall survival.3,4 Given the unique strengths of each risk score, the MD Anderson group combined the DRI-R and HCT-CI/Age to develop and validate a composite risk score that could better predict outcomes through a single site, retrospective analysis. This tool, named the hematopoietic cell transplant-composite risk (HCT-CR), stratified patients with hematologic malignancies into four risk groups, and was shown to be prognostic for overall survival, progression-free survival, and GVHD/relapse-free survival (Figure 1). More importantly, the HCT-CR not only better predicted transplant outcomes than previous models, but also provided improved utility in determining which patients should be considered for post-transplant clinical trials.5,6

However, since these models were developed in adults, they appear to be less applicable and relevant in children. Previous studies demonstrated HCT-CI scores of 0 in 50-60% of patients 20 years old.7,8 Further, a recent survey of transplant physicians found that 71% of adult providers used the HCT-CI in assessment of nearly all of their patients (75-100% of the time), compared to only 12% among pediatric providers.9 Therefore, we used expanded comorbidity definitions to develop a modified HCT-CI (i.e. simplified malignant HCT-CI) in a pediatric and young adult population, that better quantifies comorbidity burden in this younger population and predicts NRM.10 Similarly, when utilized in a pediatric population, the DRI did not discriminate risk in intermediate and high-risk disease groups.11 Due to this failure, a pediatric DRI was designed that incorporated age, cytogenetics, and disease status including minimal residual disease, and was shown to be predictive of leukemia-free survival and overall survival in patients <18 years old.12

While both of these models perform well in younger patients, each risk score has its limitations, similar to the adult models. Therefore, the goal of this study is to combine the simplified malignant HCT-CI and pediatric DRI to develop a novel pHCT-CR score that can better predict transplant outcomes in children with acute leukemia.

We are currently performing a retrospective study at Texas Children's Hospital with the aim of analyzing preliminary data at our single site to serve as further justification for this project. Our center annually performs about 125 transplants each year (Nearly 90 allogeneic) HCT in children. We have identified 313 patients transplanted between 2008 and 2019 that met the study eligibility criteria (Table 1). We look forward to the results of our analysis and intend to submit an abstract to the upcoming 2022 European Society for Blood and Marrow Transplantation meeting.

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

[Click here]

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

Inclusion Criteria:

1.Children (<18 years) with ALL or AML

2.Underwent their first allogenic HCT

3.Donor was HLA-matched related (MRD), HLA-matched unrelated (MUD), one antigen mismatched related (MMRD), haploidentical (HAPLO) donor, or HLA-matched or mismatched (at least 4/6 HLA-matched) umbilical cord blood donor

4.HCT occurred between January 2008 to December 2020.

Exclusion Criteria:

1.Embargoed centers and those with completeness index of <85% follow-up

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:
Age - continuous and categorical (0-2y, 3-10y, 11-14y, 15-18y)
Recipient gender (male, female)
Race (Caucasian, African American, Asian, Pacific Islander, Native American, multiple races)
Ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino, Non-resident of U.S., unknown/missing)
Performance status (90-100, <90)
HCT-CI (0, 1-2, ≥3)
Co-morbidities (yes, no)
Arrhythmia, cardiac disease, cerebrovascular disease, diabetes, heart valve disease, hepatic disease, peptic ulcer disease, infection, IBD, obesity, psychiatric disease, pulmonary disease, rheumatologic disease, solid tumor
History of mechanical ventilation (Yes vs. No)
History of Fungal Infection (Yes vs. No)
BMI (CRF only)
Age-adjusted BMI based on weight-for-age for 0-2y, BMI percentile for ages 2-18y (<5%ile, 5-95%ile, >95%ile)
Estimated GFR (CRF only)
Using Bedside Schwartz calculation (eGFR <40, 40-60, >60)
Disease related:
Primary disease: AML, ALL
Remission status: CR1, CR2, Not in remission
Minimal residual disease status: MRD positive, MRD negative, MRD unknown
Cytogenetics: Favorable, Intermediate, Poor, Not reported
Transplant related:
Donor (HLA-identical sibling, other relative, 8/8 matched unrelated, 7/8 matched unrelated, <7/8 matched unrelated, cord)
Graft source (PBSC, BM, cord)
Donor gender (male, female, cord)
Donor-recipient sex match (M-M, F-M, M-F, F-F, cord)
Conditioning regimen intensity (Myeloablative, reduced intensity, non-myeloablative)
Donor-recipient CMV status (-/- vs. -/+ vs. +/- vs. +/+)
Graft-versus-host disease (GVHD) prophylaxis (Ex-vivo t-cell depletion vs. CD34 selection vs. Post-Cy +- others vs. TAC + MMF vs. TAC + MTX vs. CsA + MMF vs. CsA + MTX vs. TAC + others vs. TAC alone vs. CSA + others vs. CSA alone vs. Others vs. missing
In vivo T-cell depletion (ATG/Campath vs none)
Year of transplant
Time dependent:
Neutrophil engraftment (Yes vs. No)
Acute GVHD (Yes vs. No)
o Grade II-IV
Chronic GVHD (Yes vs. No)
o Limited vs. extensive
Non-relapse mortality (Yes vs. No)
Relapse (Yes vs. No)
Death (Yes vs. No)

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:

1. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–2919.
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11. Qayed M, Gillespie S, Merli P, et al. Disease Risk Index Predicts Relapse in Children Undergoing Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2019;25:S109-S110.
12. Qayed M, Kitko CL, Ahn KW, et al. A validated pediatric disease risk index for allogeneic hematopoietic cell transplantation. Blood. 2021;137:983-993.

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

Table 1A. Characteristics of pediatric patients with Acute Leukemia Undergoing between 2008 and 2017

Characteristic	AML	ALL	Total
No. of patients	1224	1345	2569
No. of centers	81	83	84
Patient age at HCT, years - median (min-max)	8 (0-17)	9 (0-17)	9 (0-17)
Sex - no. (%)			
Male	649 (53)	835 (62)	1484 (58)
Female	575 (47)	510 (38)	1085 (42)
Karnofsky performance pre-Preparative Regimen - no. (%)			
≥ 90	1044 (85)	1116 (83)	2160 (84)
< 90	169 (14)	208 (15)	377 (15)
Missing	11 (1)	21 (2)	32 (1)
Risk group assignment - no. (%)			
Low	63 (5)	465 (35)	528 (21)
Intermediate	599 (49)	743 (55)	1342 (52)
High	282 (23)	72 (5)	354 (14)
Very High	185 (15)	0 (0)	185 (7)
Missing	95 (8)	65 (5)	160 (6)
HCT-CI - no. (%)			
0-2	1012 (83)	1121 (83)	2133 (83)
3+	210 (17)	223 (17)	433 (17)
Missing	2 (0)	1 (0)	3 (0)
Transplant year - no. (%)			
2008	104 (8)	108 (8)	212 (8)
2009	122 (10)	107 (8)	229 (9)
2010	118 (10)	73 (5)	191 (7)
2011	39 (3)	49 (4)	88 (3)

Characteristic	AML	ALL	Total
2012	61 (5)	44 (3)	105 (4)
2013	72 (6)	71 (5)	143 (6)
2014	166 (14)	215 (16)	381 (15)
2015	168 (14)	228 (17)	396 (15)
2016	193 (16)	215 (16)	408 (16)
2017	181 (15)	235 (17)	416 (16)

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 Graft Versus Host Disease Following Allogeneic Hematopoietic Cell Transplantation on Leukemia Free survival in Hematologic Malignancies within the Pediatric Disease Risk Index Risk Stratification

Q2. Key Words

Graft Versus Host Disease, Allogeneic Hematopoietic Cell Transplantation, Pediatric Leukemia, Leukemia Free survival, Pediatric Disease Risk Index Risk Stratification

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Andrea Bauchat, DO
Email address:	andrea.bauchat@duke.edu
Institution name:	Duke University Medical Center
Academic rank:	Medical Instructor

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):	Muna Qayed, MD, MSc
Email address:	mqayed@emory.edu
Institution name:	Emory University School of Medicine
Academic rank:	Associate Professor

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?

N/A

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:

Andrea Bauchat, DO

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:

- Pediatric Cancer

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

- No

Q15. RESEARCH QUESTION:

Does the presence of graft versus host disease influence leukemia free survival in pediatric patients with hematologic malignancies?

Q16. RESEARCH HYPOTHESIS:

Mild to moderate acute graft versus host disease following hematopoietic stem cell transplant is associated with improved leukemia-free survival in children with favorable risk disease by pediatric DRI classification.

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

Suggested word limit of 200 words:

Primary Objective: To determine the impact of development of grade I and II acute graft versus host disease (aGVHD) on relapse and leukemia-free survival in children undergoing hematopoietic cell transplant (HCT) for ALL and AML;
Secondary Objectives: 1. To assess the impact of development of severe (grade III-IV) aGVHD on relapse and LFS in children undergoing HCT for ALL and AML;
2. To determine whether the impact of GVHD on relapse and LFS is influenced by disease risk prior to HCT

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.

In this study, we will test the hypothesis that development of aGVHD grades I and II has a favorable impact on LFS in a subset of children undergoing HCT for hematologic malignancy. This focus is significant as current methods of immunosuppression hinders the effects of GVL, which could potentially increase the risk of disease relapse. Completion of this study's aims may provide objective support to identify specific patient populations who would benefit from tailoring GVHD prophylaxis. Early withdrawal or decreased immunosuppression may benefit these patients to balance allowance of GVL and GVHD to improve LFS.
Pre-HCT PDRI risk stratification in combination with understanding the impacts of aGVHD within each risk category may reveal patient populations who would benefit from increased GVL.

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.

Relapse of disease remains one of the main etiologies of mortality in pediatric patients after HCT for hematologic malignancies. Predictors of leukemia-free survival (LFS) outcomes post-HCT include disease status prior to HCT, disease characteristics, and cytogenetics.1,2 A recent analysis by Qayed et al validated the disease risk index (DRI) tool for pediatrics to categorize patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) based on risk factors for prognostication. This report evaluated 1228 ALL patients and 1135 AML patients identifying 3 and 4 risk groups, respectively, with the primary outcome focus on LFS. The 3 risk groups for ALL include good, intermediate, and high risk whereas the 4 risk groups of AML were good, intermediate, high, and very high risk.3

An additional variable to consider in risk stratification is the presence or absence of GVHD post-HCT. GVHD has been reported as protective against relapse in hematologic malignancies since it has been associated with an increased graft versus leukemia (GVL) effect.4-7 The biology of this phenomenon consists of the donor T cells recognizing histocompatibility antigens on recipient leukemia cells resulting in one of the therapeutic benefits of HCT in this disease group.4 Current literature suggests that development of acute GVHD grades I-II decreases relapse risk and improves overall survival. In a CIBMTR registry study reported by Yeshurun et al, 5215 patients with ALL were evaluated in 3 cohorts based on disease stratifications to determine the effects of GVHD on disease-free survival (DFS), non-relapse mortality (NRM), and overall survival (OS). Development of GVHD in children or adults with ALL in CR1/CR2 was associated with an improved DFS compared to those without GVHD. Specifically, patients in CR1/CR2 had significantly improved DFS with isolated grades I and II compared to no GVHD with HR 0.74 for adults (95% CI, 0.61-0.89) and HR 0.74 (95% CI, 0.61-0.89) for pediatrics.8 The development of grade I-II aGVHD without cGVHD was associated with improved OS compared to those without any form of GVHD with 17-24% lower risk of overall mortality. Although relapse was decreased in patients who developed aGVHD grades III or IV, non-relapse mortality was higher resulting in inferior OS regardless of cohort group.8 In this analysis, patients in CR1 and CR2 were grouped together whereas our study will control for difference by utilizing the PDRI for risk stratification. Another study by Bader et al evaluated peri-HCT risk factors in pediatric and young adult patients with ALL. aGVHD was associated with decreased incidence regardless of pre-transplant MRD status with a threefold decrease in relapse.9 Similar relapse rates were noted in patients with post-HCT MRD who developed aGVHD and MRD negative patients who did not develop aGVHD.9

In another study, Pulsipher et al (PBMTC ONC051) examined the association of risk factors including aGVHD on the risk of relapse in pediatric patients transplanted for ALL on the Children's Oncology Group (COG) ASWCT0431 Trial. The study was conducted from 2007–2011 and results were presented after multivariate analysis. A marked difference was noted in relapse rate of patients who had pre-HCT MRD <0.1% and developed aGVHD compared to those without aGVHD (13% vs. 40%; p= 0.008). Patients with pre-HCT MRD < 0.1% and aGVHD by day +55 had a decrease rate of relapse with improved event free survival compared to those with pre-HCT MRD ≥ 0.1% in the absence of aGVHD (CI of relapse 73% vs 13%; p=<0.0001; 2yr EFS 71 vs. 18%; p=0.001).10 Furthermore, a notable difference in 2 year OS in these two groups was statistically significant at 74% versus 46% respectively (p=0.04). 10 There was no statistical differences between those with pre-HCT MRD ≥ 0.1% with aGVHD and any other group potentially due to the low patient numbers (n=5). Grade IV aGVHD decreased disease relapse, however, as noted in similar studies, the OS was decreased due to transplant related mortality.10 Notably, these analyses focus solely on ALL without AML. Currently, there is paucity of data evaluating GVHD impacts on patients with AML. Kato et al examined GVHD in both ALL (n=1030) and AML (n=496) pediatric patients in CR1/CR2. Between both leukemia groups, aGVHD grades II-IV demonstrated decreased relapse compared to patients with aGVHD grades 0-I at 3 years post-HCT. Specifically in ALL, developing grade II aGVHD was associated with a decreased relapse risk of 18.2% (95% CI 13.9–23.6) compared to 26.0% (95% CI 21.3–31.5) in grade 0 and 26.2% (95% CI 21.1–32.3) in grade I. Regarding AML, relapse risk reduction between grade I and grade II aGVHD was not significant at 20.7% (95% CI 14.6–28.9) and 20.5% (95% CI 14.1–29.3) respectively. OS was comparable in all patients with aGVHD grade 0-I at 79.0% and 79.5%, respectively and similar to patients with grade II GVHD (76.3%). Although those with grade III-IV aGVHD demonstrated lower relapse rate, the OS was significantly inferior at 66.9% and 42.5% respectively.11 cGVHD decreased risk of relapse more in the patients with AML compared to the ALL disease group where results were not significant. Relapse risk in AML patients without cGVHD was 24.0% (95% CI 19.5–29.2; p = 0.02) compared to 11.0% (95% CI 6.8–17.6) in those with cGVHD. Although cGVHD provided some reductive effect on relapse, no survival advantage was observed.11 Neudorf et all reported on the effects of GVL in DFS for AML pediatric patients in the Children's Cancer Group (CCG) study 2891. The data illustrated that grade I and 2 aGVHD were associated with improved DFS of 65% (95% CI 49-78%) compared to those without at 58% (95% CI, 46-68%).12

In this study, we will test the hypothesis that development of aGVHD grades I and II has a favorable impact on LFS in a subset of children undergoing HCT for hematologic malignancy. This focus on aGVHD is significant as current methods of prophylactic immunosuppression impedes the effects of GVL, which could potentially increase the risk of disease relapse. Pre-HCT PDRI risk stratification in combination with understanding the impacts of aGVHD within each risk category may reveal patient populations who would benefit from increased GVL. The results of this protocol may provide objective support to further tailor GVHD prophylaxis with early withdrawal of immunosuppression to balance allowance of GVL and GVHD to improve LFS.

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

[Click here]

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

We propose using the existing dataset from protocol PC19-01 for this analysis.
Inclusion Criteria:
-Children < 18 years of age who received their first HCT for ALL or AML
-Must be the patient's first allogeneic transplantation
-Transplant period: 2008-2017
-Any donor type
-Any stem cell source
-Presence or absence of GVHD

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.

We propose using the existing dataset from protocol PC19-01 for this analysis. The new variable for data collection is GVHD.
No other supplementary data should be requires.
Below are our VARIABLES TO BE ANALYZED:
Patient
-Age at transplant: included in PDRI
-Sex: Male, Female
-Karnofsky/Lansky performance score: 90 – 100 versus < 90
-HCT CI 0-2 versus ≥ 3
-Recipient CMV serostatus: seropositive versus seronegative
Disease
–Primary diagnosis: ALL, AML
–Pediatric disease risk index classification: ALL (good, intermediate, and high risk), AML (good, intermediate, high, and very high risk)
–Cytogenetic risk (ALL): Good versus intermediate versus poor/high risk, AML included in PDRI
–Disease status: first CR MRD negative versus first CR MRD positive versus first CR MRD unknown versus second CR MRD negative versus second CR MRD positive versus second CR MRD unknown versus relapse/primary induction failure
Donor
-HLA matched sibling versus Mismatched relative versus unrelated donor
Graft versus host disease
-Acute GVHD grade I and II versus grade III and IV versus no aGVHD
-Chronic GVHD mild versus cGVHD moderate-severe (limited versus extensive depending on available data)
-aGVHD and cGVHD versus aGVHD alone versus cGVHD alone

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

NA

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

NA

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.

NA

Q26. REFERENCES:

1. Bitan M, Ahn KW, Millard HR, Pulsipher MA, Abdel-Azim H, Auletta JJ, Brown V, Chan KW, Diaz MA, Dietz A, Vincent MG, Guilcher G, Hale GA, Hayashi RJ, Keating A, Mehta P, Myers K, Page K, Prestidge T, Shah NN, Smith AR, Woolfrey A, Thiel E, Davies SM, Eapen M. Personalized Prognostic Risk Score for Long-Term Survival for Children with Acute Leukemia after Allogeneic Transplantation. Biol Blood Marrow Transplant. 2017 Sep;23(9):1523-1530. doi: 10.1016/j.bbmt.2017.05.011. Epub 2017 May 17. PMID: 28527984; PMCID: PMC5683075.
2. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, Ritz J, Sorror ML, Lee SJ, Deeg HJ, Storer BE, Appelbaum FR, Antin JH, Soiffer RJ, Kim HT. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012 Jul 26;120(4):905-13. doi: 10.1182/blood-2012-03-418202. Epub 2012 Jun 18. PMID: 22709687; PMCID: PMC3412351.
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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)?

- Yes, I have 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.

Muna Qayed - Honoraria: Novartis, Mesoblast
(Andrea Bauchat: none)

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

Table 1 and Table 2 describe the cohort used for PC19-01 analysis (without inclusion of GVHD data)

Table 1. Acute lymphoblastic leukemia: Patient, Disease and Transplant Characteristics

Variable	
Number	1345
Age at transplant♯	
<2 years	68 (5%)
≥2 years	1277 (95%)
Sex	
Male	835 (62%)
Female	510 (38%)
Hematopoietic co-morbidity index score	
≤2	1121 (83%)
≥3	223 (17%)
Not reported	1 (<1%)
Performance Score	
90-100	1116 (83%)
≤80	208 (15%)
Not reported	21 (2%)
Cytomegalovirus serostatus	
Negative	512 (38%)
Positive	821 (61%)
Not reported	12 (1%)
Cytogenetic risk	
Intermediate	770 (57%)
Poor	497 (37%)
Not reported	78 (6%)
Disease status	
1st complete remission MRD (+)	171 (13%)
1st complete remission MRD (-)	338 (25%)
1st complete remission	21 (2%)
2nd complete remission MRD (+)	156 (12%)
3rd complete remission MRD (+)	33 (2**%)
2nd complete remission MRD (-)	435 (32%)
3rd complete remission MRD (-)	94 (7%)
≥2nd complete remission	44 (3%)
Not in remission	53 (4%)
Donor	
HLA-matched sibling	255 (19%)

HLA-mismatched relative	117 (9%)
HLA-matched unrelated	335 (25%)
1-locus mismatched unrelated	133 (10%)
6-8/8 HLA-matched cord blood	297 (22%)
≤5/8 HLA-matched cord blood	208 (15%)
Conditioning regimen	
TBI/cyclophosphamide	478 (36%)
TBI/cyclophosphamide/fludarabine	334 (25%)
TBI/cyclophosphamide + other	330 (25%)
TBI + other	126 (9%)
Busulfan/cyclophosphamide	26 (2%)
Busulfan/melphalan	18 (1%)
Fludarabine/busulfan/thiotepa	33 (2%)
GVHD prophylaxis	
Ex vivo T-cell depletion/CD34 selection	75 (6%)
Post-CY ± other(s)	57 (4%)
Calcineurin inhibitor + mycophenolate	485 (36%)
Calcineurin inhibitor + methotrexate	610 (45%)
Calcineurin inhibitor ± other	93 (7%)
Other	25 (2%)
Transplant period	
2008-2012	381 (28%)
2013-2017	964 (72%)
Disease Risk Index Group	
Low	465 (34%)
Intermediate	743 (55%)
High	72 (5%)

Abbreviation: MRD = minimal residual disease; TBI = total body irradiation

*Cytogenetic risk: poor ((t9;22), iAMP21, abnormal 17p, loss of 13q, 11q23 (infant); intermediate (all others)

Table 2. Acute myeloid leukemia: Patient, Disease and Transplant characteristics

Variable	
Number	1224
Age at transplant♯	
<3 years	325 (26%)
≥3 years	909 (74%)
Sex	
Male	649 (53%)
Female	575 (47%)
Hematopoietic co-morbidity index score	
≤2	1012 (83%)
≥3	210 (17%)
Not reported	2 (<1%)
Performance Score	
90-100	1044 (85%)
≤80	169 (14%)
Not reported	11 (1%)
Cytomegalovirus serostatus	
Negative	446 (36%)
Positive	760 (62%)
Not reported	18 (2%)
Cytogenetic risk*	
Favorable	100 (8%)
Intermediate	778 (64%)
Poor	317 (26%)
Not reported	29 (2%)
Disease status	
1st complete remission MRD (+)	175 (14%)
1st complete remission MRD (-)	428 (35%)
1st complete remission	48 (4%)
2nd complete remission MRD (+)	84 (7%)
2nd complete remission MRD (-)	269 (22%)
2nd complete remission	28 (2%)
Not in remission	188 (15%)
Donor	
HLA-matched sibling	257 (21%)
HLA-mismatched relative	89 (7%)
HLA-matched unrelated	344 (28%)
1-locus mismatched unrelated	126 (10%)

6-8/8 HLA-matched cord blood	238 (19%)
≤5/8 HLA-matched cord blood	170 (14%)
Conditioning regimen	
TBI/cyclophosphamide	92 (8%)
TBI/cyclophosphamide/fludarabine	143 (12%)
TBI/cyclophosphamide + other	46 (4%)
TBI + other	53 (4%)
Busulfan/cyclophosphamide	537 (44%)
Busulfan/melphalan	75 (6%)
Fludarabine/busulfan/thiotepa	278 (23%)
GVHD prophylaxis	
Ex vivo T-cell depletion/CD34 selection	66 (5%)
Post-CY ± other(s)	51 (4%)
Calcineurin inhibitor + mycophenolate	427 (35%)
Calcineurin inhibitor + methotrexate	549 (45%)
Calcineurin inhibitor ± other	100 (8%)
Other	31 (3%)
Transplant period	
2008-2012	444 (36%)
2013-2017	780 (64%)
Disease Risk Index Group	
Low	63 (5%)
Intermediate	599 (49%)
High	282 (23%)
Very high	185 (15%)

Abbreviation: MRD = minimal residual disease; TBI = total body irradiation

*Cytogenetic risk: favorable (inv(16), t(16;16), t(15;17), t(8;21) without complex abnormality; poor (-5/5q, -7/7q, FLT3 ITD with high allelic ratio, t(6;9), 3q); intermediate (all others)

Table 1A. Characteristics of pediatric patients with Acute Leukemia Undergoing between 2008 and 2017

Characteristic	AML	ALL	Total
No. of patients	1224	1345	2569
No. of centers	81	83	84
Patient age at HCT, years - median (min-max)	8 (0-17)	9 (0-17)	9 (0-17)
Sex - no. (%)			
Male	649 (53)	835 (62)	1484 (58)
Female	575 (47)	510 (38)	1085 (42)
Karnofsky performance pre-Preparative Regimen - no. (%)			
≥ 90	1044 (85)	1116 (83)	2160 (84)
< 90	169 (14)	208 (15)	377 (15)
Missing	11 (1)	21 (2)	32 (1)
Risk group assignment - no. (%)			
Low	63 (5)	465 (35)	528 (21)
Intermediate	599 (49)	743 (55)	1342 (52)
High	282 (23)	72 (5)	354 (14)
Very High	185 (15)	0 (0)	185 (7)
Missing	95 (8)	65 (5)	160 (6)
HCT-CI - no. (%)			
0-2	1012 (83)	1121 (83)	2133 (83)
3+	210 (17)	223 (17)	433 (17)
Missing	2 (0)	1 (0)	3 (0)
Transplant year - no. (%)			
2008	104 (8)	108 (8)	212 (8)
2009	122 (10)	107 (8)	229 (9)
2010	118 (10)	73 (5)	191 (7)
2011	39 (3)	49 (4)	88 (3)

Characteristic	AML	ALL	Total
2012	61 (5)	44 (3)	105 (4)
2013	72 (6)	71 (5)	143 (6)
2014	166 (14)	215 (16)	381 (15)
2015	168 (14)	228 (17)	396 (15)
2016	193 (16)	215 (16)	408 (16)
2017	181 (15)	235 (17)	416 (16)