Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Orlando, FL
Friday, February 17th, 2023, 12 p.m. – 2 p.m. (EST)

Co-Chair:	**Gregory Yanik, MD, The University of Michigan, Ann Arbor, MI** **Phone: 734-647-8902; E-mail: gyanik@med.umich.edu.**
Co-Chair:	**Kirk Schultz, MD, The University of British Columbia, Vancouver, BC, Canada** **Phone: 604-875-3168; E-mail: kschultz@mail.ubc.ca.**
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1. **Introduction**
   a. **Minutes and overview plan from April 2022 meeting** (Attachment 1)
   b. **Instructions for signing-in and voting**
   c. **Introduction of incoming Co-Chair**:
   Akshay Sharma MBBS; St. Jude Children's Research Hospital, Memphis TN
   E-mail: Akshay.Sharma@STJUDE.ORG

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. (Knight T/ Wall D/ Chiengthong K), **Submitted.**

4. **Studies in Progress** (Attachment 3)

   a. **PC19-02:** Does mixed peripheral blood T Cell Chimerism predict relapse? (Prockop S/Boelens J/Peggs K), **Protocol Development/ Data File Preparation.**
   b. **PC19-03:** The impact of pre-transplant extramedullary disease on the outcome of Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia in Children. (Rangarajan H/ Satwani P/Chellapandian D), **Protocol Development/ Data File Preparation.**
   c. **PC20-02:** Germline genetics of pediatric Myelodysplastic Syndromes (MDS). (Poynter J/ Spector L), **Sample Typing/ Data File Preparation.**

d. **PC22-01:** 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. (Bauchat A/Qayed M), **Protocol Development.**
e. **PC22-02:** Evaluating predictors of access and outcomes with hematopoietic cell transplantation in pediatric and adolescent patients with relapsed/refractory classical Hodgkin lymphoma after treatment on an initial cooperative group clinical trial. (Castellino S/Kahn J), **Protocol Development.**
f. **SC21-08:** Optimizing Haploidentical Donor Selection for Pediatric HCT. (Liberio N/ Broglie L), **Manuscript Preparation.**

5. Future/Proposed Studies

a. **PROP 2210-104:** Post-transplant Cyclophosphamide vs. TCR αβ/CD19+ deplete approaches for Haploidentical Transplant in pediatric patients with Acute Leukemias and Myelodysplastic Syndrome: A CIBMTR/EBMT collaborative study. (Li A/Rangarajan H/Satwani P, Attachment 4)
b. **PROP 2210-120:** Comparison of myeloablative conditioning regimens for acute myeloid leukemia in children and young adults. (Pfeiffer T/Shenoy S, Attachment 5)
c. **PROP 2210-217:** Outcomes of children who receive an allogeneic hematopoietic cell transplantation for Juvenile Myelomonocytic Leukemia. (Sharma A/Bhatt N, Attachment 6)

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

d. **PROP 2210-276:** Comparison of bone marrow and peripheral blood stem cells as graft source in Children undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematological malignancies with unmanipulated haploidentical grafts utilizing post-transplant Cyclophosphamide as GvHD prophylaxis. (Srinivasan A/ Krueger J) (Attachment 7)

Dropped Proposed Studies

a. **Prop 2209-10:** Feasibility and Outcomes of Third Allogeneic Hematopoietic Cell Transplantation in Individuals with Relapsed or Refractory Acute Leukemia. *Dropped due to overlap with ongoing study.*
b. **PROP 2210-47:** Outcomes of Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) after Blinatumomab Salvage Therapy in Pediatric Patients with Relapsed/Refractory B-cell Lineage Acute Lymphoblastic Leukemia (BL-ALL). *Dropped due to overlap with an ongoing corporate study.*
c. **PROP 2210-102:** Determinants of Outcome for Children with Acute Leukemia or MDS Who Receive a Third or Subsequent Allogeneic Hematopoietic Cell Transplant. *Dropped due to overlap with ongoing study.*
d. **PROP 2210-144:** Determining the Optimal CD34+ Cell Dose and TNC Content in Pediatric Allogeneic Hematopoietic Cell Transplantation Performed for Malignant Diseases. *Dropped due to heterogeneous population.*
e. **PROP 2210-166:** Post-Transplant Clinical Outcomes and Neoplastic Risk in Fanconi Anemia. *Dropped due to overlap with ongoing study.*
f. **PROP 2210-167:** Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies. *Dropped due to feasibility, data not collected by CIBMTR.*

g. **PROP 2210-216:** Prognostic Impact of Cytogenetic and Molecular Risk Classification in AML after Hematopoietic Stem Cell Transplant in Pediatrics, Adolescents, and Young Adults. *Dropped due to overlap with a published study.*
h. **PROP 2210-243:** Impact of Sorafenib after Allo-HSCT as prevention of AML relapse in children. *Dropped due to feasibility, data not reliably reported to CIBMTR.*
i. **PROP 2210-281:** Comparison of umbilical cord blood transplants and unmanipulated haploidentical stem cell transplants in children undergoing allogeneic transplant for hematological malignancies. *Dropped due to Overlap with a published study.*

CIBMTR®
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MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Salt Lake City, UT
Sunday, April 24, 2022, 12:15 p.m. – 2:00 p.m.

Co-Chair:	**Gregory Yanik, MD, The University of Michigan**
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Co-Chair:	**Kirk Schultz, MD, The University of British Columbia**
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1. Introduction

The Pediatric Cancer Working Committee (PCWC) met on Sunday, April 24, 2022, at 12:18 p.m. The chairs, scientific director, and statistical team were all presented at the meeting. Dr. Greg Yanik attended the meeting virtually. Attendees were asked to have their name badges scanned at the front gate for attendance purposes and to maintain the committee membership roster.

Dr. Larisa Broglie introduced herself as the new Scientific director and the PCWC leadership, then she introduced the new master's level statistician Rasha Atshan.

Dr. Broglie proceeded to take the attendees through the committee's goals, expectations, and limitations. Dr. Broglie announced that the WC leadership is looking forward to WC members' engagement in all stages of a study's process. Dr. Broglie provided an overview of the CIBMTR, the data sources available for future study proposals, and public datasets that are available on the CIBMTR website. Dr. Broglie informed the attendees of the Information Request service that is available on the CIBMTR website. Then, she informed the attendees that the WC leadership is going to provide updates on ongoing studies and present the new studies proposals. Finally, Dr. Broglie introduced Dr. Yanik to the attendees as the next speaker to provide an overview of the Pediatric Cancer Accruals report summary.

2. Accrual summary

Dr. Yanik introduced himself to the attendees then he directed the attendees' attention to the accrual summaries included in the meeting materials. Dr. Yanik provided a concise summary of the numbers of pediatric patients available in the CIBMTR database.

3. Presentations, Published or Submitted Papers

Dr. Broglie introduced Dr. Schultz to the attendees. Dr. Schultz directed the attendee's attention to the working committee materials for information regarding the abstract presentation and to presentation that are accepted at various conferences:

Dr. Schultz introduced Dr. Tristan Knight to attendees and requested Dr. Knight to present the progress of his study. Dr. Knight introduced himself and thanked the WC chairs and statistical team for their leadership and work to complete the following study. Then, Dr. Knight provided an overview of the study and the corresponding findings. Dr. Broglie announced Dr. Knight's poster presentation date, time, and location.

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

Dr. Schultz provided a brief overview of the committee's portfolio of active studies. He began with PC19-03, a collaboration study between CIBMTR and EBMT, this study requires merging North America and European databases. Dr. Schultz emphasized the difficulties of merging two databases that are collected differently. Dr. Schultz also emphasized that PC19-03 will be used as template for future collaboration between CIBMTR and EBMT to study uncommon diseases and answer uncommon scientific questions.

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. PCWC Logistics

Dr. Schultz provided an overview of WC membership then he encouraged young investigators to engage in research with CIBMTR. He also encouraged senior investigators to collaborate and develop future study proposals with young investigators. Then, Dr. Schultz reminded the attendees of PCWC goals, expectations, and limitations. Dr. Schultz provided an overview of the rules of authorship at CIBMTR, and he reminded the attendees of the proposals' voting process.

6. Future/Proposed Studies

Dr. Muna Qayed announced the Collaborative Session that present a highlight proposal from each working committee. Dr. Qayed announced the collaborative session proposal from PCWC then she added the Collaborative Session date, time, and location. Dr. Qayed reminded the attendees of the scoring logistics. She also reminded the presenters that each presentation duration is five minutes followed by five minutes for the Questions & Answers session. Dr. Qayed introduced each proposal title and the presenters to the audience in the following order.

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).
Dr. Rotz presented the proposal on behalf of the group. The proposal hypothesizes that children and adolescents & young adults (AYA) with Down's syndrome (DS) and acute leukemia will have improved hematopoietic cell transplantation (HCT) outcomes in the more recent era. Further, the proposal hypothesizes 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. The objectives of the study are to determine if outcomes for children and AYA with DS and acute leukemia (ALL and AML) undergoing HCT have improved in more recent eras. And to Compare outcomes of CAR T-cell therapy for children and AYA with DS and relapsed/refractory ALL to HCT.
Comments from discussion:

i. A comment regarding the outcomes of the study. Will there be a fundamental difference between the patients who are receiving CAR-T therapy compared to patients who receive HCT (in demographics, biology, outcomes, etc). Dr. Rotz replied that he doesn't know if the characteristics of CAR-T and HCT patients will be an exact match, and this could be a limitation of the study regarding relapse risk. However, he noted that focusing on the overall survival will not have such a limitation. Dr. Yanik added that a recent world data show that there is an increase in the number of patients with Down's syndrome and ALL who have received CART with an outstanding overall survival.
ii. A couple of attendees expressed enthusiasm for the study and express that the study presents a good question by looking at Down's syndrome and HCT outcomes, while comparing CAR-T and HCT can be complicated since there are confounding factors in deciding between CAR-T and HCT such as parental or legal guardian preferences.
iii. Another comment was made regarding the study years between 2000-2020, it is a large time span for the study and the field had changed in the past ten years. The attendee asked if Dr. Rotz considered focusing on comparing CAR-T and HCT between 2010-2020?
iv. An attendee noted that the Down's syndrome with AML is interesting, but children with Down's syndrome are more likely to develop M7 AML and asked how many cases have M7 AML. M7 may be difficult to combine with other AML subtypes. Dr. Rotz replied that the data collection forms need to be reviewed to see what type of data are collected for the different AML subtypes. Dr. Rotz added that considering the different subtypes of AML is a good point but there is different way to view the data for examples age and therapy type.
v. A question was asked whether if biological samples are considered as a part of the study analysis since recent Down's syndrome and Chromosome 21 data showed that there are four of six interferon receptors. Dr. Rotz replied that he wasn't aware of these factors and Dr. Qayed added that CIBMT needs to investigate the biological samples inventory for patients with Down's syndrome before answering the question.

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).
Dr. Sharma presented the proposal on behalf of the group. The proposal hypothesizes that 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. The objectives of this proposal are: 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, and to determine the outcomes in AMKL utilizing alternative donor sources and compare them to traditional matched-related donor transplants.
Comments from discussion:
An attendee suggested combining Dr. Rotz proposal 2110-19 with Dr. Sharma proposal 2110-43. Dr. Sharma agreed with the suggestion, and he acknowledge the positive impact of combining the two proposals.

c. **PROP 2110-45/2110-81** Combined proposal: 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).

Dr. Sharma presented this proposal on behalf of the group. The proposal hypothesizes 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. Further, the proposal hypothesizes that through the CIBMTR database, risk factors for GVHD in pediatric patients receiving haploidentical transplantation using PT-Cy can be identified. The objectives of the proposal are: to 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 sibling donor HCT, matched unrelated donor HCT, or mismatched unrelated donor HCT, and to describe the incidence, characteristics, and risk factors for acute and chronic GVHD in children and adolescents undergoing PT-Cy based haploidentical HCT.

Comments from discussion:

i. A question was raised regarding excluding mismatch Cord Blood as comparative group, Dr. Sharma replied that including Mismatch CB is great suggestion and if the proposal is selected to move forward as PCWC study, he will consider looking into mismatch CB group.

ii. The next comment addressed using PT-Cy for matched unrelated and mismatched unrelated donors in adult patients, which had good results in preventing GVHD. Since the pediatric data is outdated in comparison to the adult data regarding PT-Cy, Dr. Sharma agreed with the attendee, and he added that there is enough adults data that compares the matched unrelated and mismatched unrelated donors, while not the same volume of data is available for pediatrics data.

iii. Another comment suggested investigating the possible outcomes from using PT-Cy such as overall survival, relapse free survival, and non-relapse mortality; and investigating the connection between viral infections and HCT when using a haploidentical donor.

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).

Dr. Kahn presented the proposal virtually on behalf of the group. This proposal hypothesizes that outcomes following relapse of Hodgkin Lymphoma, 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. The objectives of this proposal are: to compare outcomes by histologic category, to compare outcomes by donor platform and conditioning intensity and finally to develop a predictive model for survival post-AlloHCT for MDS/MPN's.

Comments from discussion:

i. Dr. Schultz added a comment that this will be the first study merge the CIBMTR and COG data. Dr. Broglie added that the CIBMTR and COG data has been linked to complete clinical trials but combining the two datasets to complete a study has not been done previously. Dr. Qayed asked if the patient's population will based on patient enrolled in COG trials, linking the patient's data to the follow up data from CIBMTR database. Dr. Kahn replied that the study will use patients'

data whose disease relapsed from the COG trials adding transplant and outcome data from CIBMTR database.

ii. A Question was asked about the difficulties of linking the COG trials and CIBMTR databases? Dr. Broglie replied that linking the databases can be performed but will require time and collaboration. Dr. Kahn added that linking the databases has not been done previously, and she added that cHL is a rare disease and the population consist of pediatric patients. Dr. Broglie added that the logistic of data sharing & combining are time consuming but linking the two databases is feasible.

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).
Dr. Belsky presented this proposal virtually on behalf of the group. This proposal hypothesizes 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. The objectives of this proposal are: 1) 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; 2) to compare overall survival (OS) at 5 years for those who have undergone Allo-HSCT or Auto-HSCT for R/R NHL, time in first remission and disease status at the time of transplant, and 3) to compare treatment related mortality at 100 days for children and adolescents who have undergone Allo-HSCT or Auto-HSCT.
<u>Comments from discussion:</u>
A question was asked about whether patients who receive both Allo and Auto transplant will be considered in the study population. Dr. Belsky replied that the study team is considering including the patients who received multiple transplants in the study population. Dr. Alexander added that the number of patients who received multiple transplants is small, and those patients will not be included in the primary analysis, but the descriptive analysis results could potentially be examined.

f. **Prop 2110-272** Hematopoietic Stem Cell Transplant outcomes for Infant Acute Lymphoblastic Leukemia. (Nahal Rose Lalefar), (Attachment 9).
Dr. Lalefar presented this proposal. This proposal hypothesizes that 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. The objectives of this proposal are: to determine the Leukemia free survival and overall survival at 1yr and 3yr for infants with Acute B-Lymphoblastic Leukemia (CR1 vs other) who received HSCT between 2008-2018.
<u>Comments from discussion:</u>

i. An attendee made a comment about expanding the year of transplant up to 2020 or 2021 to increase the number of cases in the study. Dr. Schultz added that some investigators debate that transplant don't improve the outcomes of two types of ALL, and AMKL is one of them. Dr. Schultz added that if this study can answer the scientific question that will be an important contribution to this debate.

ii. An attendee added this is a good scientific question specially if the MRD are included in the study's population.

iii. A virtual attendee asked since in the past ten years only very high-risk patients had BMT, how is the study team going to consider them in the population? Dr. Lalefar replied that after investigating the AMKL patients who had transplant, and she found that not only high-risk patients had a transplant.

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).
Dr. Lakkaraja presented this proposal on behalf of the group. This proposal hypothesizes that 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). The objectives of this proposal are: to develop and validate a pHCT-CR score in children with ALL and AML who underwent their first allogeneic HCT, and to compare performance of pHCT-CR score to previously described risk scores including pediatric DRI and original HCT-CI.
Comments from discussion:
An attendee asked how is MRD will be defined? Dr. Lakkaraja clarified that the MRD will be defined according to the CIBMTR definition of MRD to stay consistent with CIBMTR database.

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

Dr. Larisa reminded the attendees that proposal "**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." was selected to be presented at the Collaborative Session.

7. Dropped proposed studies

The committee received the following additional studies proposal, but these proposals were not selected for presentation at the Tandem meeting, for the reason outlined below.

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. *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.*

8. Concluding Notes

The meeting was adjourned at **2:00** p.m. After the new proposals were presented, each attendee had the opportunity to vote using the Tandem mobile application or Tandem website. Based on the voting results, current scientific merit, and impact of the studies on the field, the PCWC leadership will determine which studies will move forward as the committee's research portfolio for the upcoming year.

Working Committee Overview Plan 2022-2023		
Study number and title	**Status**	**Chairs priority**
PC19-02: Does mixed peripheral blood T cell chimerism predict relapse?	Protocol development	2
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	Datafile preparation	2
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	Manuscript preparation	3
PC20-02: Germline genetics of pediatric myelodysplastic syndromes.	Sample Typing	3
PC22-01: 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	Protocol Pending	2
PC22-02: 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.	Protocol Pending	3

Working Assignments for Working Committee Leadership (May 2022)	
Muna Qayed	**PC19-02:** Does mixed peripheral blood T cell chimerism predict relapse?
	PC22-01: 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.
Gregory Yanik	**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.
	PC22-02: 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.
Kirk Schultz	**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.
	PC20-02: Germline genetics of pediatric myelodysplastic syndromes.

Accrual Summary for the Pediatric Cancer Working Committee

Overall Characteristics of patients aged < 18 years reported to the CIBMTR between 2010 – 2019

Characteristic	TED, N (%)	CRF, N (%)	Total
Disease - no. (%)			
AML	2170 (18.1)	1029 (39.0)	3199 (21.9)
ALL	2922 (24.4)	1090 (41.3)	4012 (27.4)
Other Leukemia	230 (1.9)	76 (2.9)	306 (2.1)
CML	197 (1.6)	57 (2.2)	254 (1.7)
MDS	655 (5.5)	269 (10.2)	924 (6.3)
NHL	398 (3.3)	89 (3.4)	487 (3.3)
HD	676 (5.6)	17 (0.6)	693 (4.7)
MM-PCD	5 (0.0)	1 (0.0)	6 (0.0)
Others/Solid tumors	4747 (39.6)	9 (0.3)	4756 (32.5)
Donor type - no. (%)			
Autologous	5621 (46.8)	0 (0.0)	5621 (38.4)
HLA-identical sibling	2028 (16.9)	360 (13.7)	2388 (16.3)
Twin	6 (0.1)	8 (0.3)	14 (0.1)
Other related	804 (6.7)	455 (17.3)	1259 (8.6)
Well-matched unrelated (8/8)	1619 (13.5)	404 (15.3)	2023 (13.8)
Partially-matched unrelated (7/8)	598 (5.0)	154 (5.8)	752 (5.1)
Mis-matched unrelated (<= 6/8)	63 (0.5)	20 (0.8)	83 (0.6)
Multi-donor	31 (0.3)	16 (0.6)	47 (0.3)
Unrelated (matching TBD)	586 (4.9)	5 (0.2)	591 (4.0)
Cord blood	629 (5.2)	1215 (46.1)	1844 (12.6)
Not reported	15 (0.1)	0 (0.0)	15 (0.1)
Graft type - no. (%)			
Bone marrow	4273 (35.6)	997 (37.8)	5270 (36.0)
Peripheral blood	7098 (59.2)	425 (16.1)	7523 (51.4)
Umbilical cord blood	629 (5.2)	1215 (46.1)	1844 (12.6)

Characteristics of patients aged ≤ 18 years who received HLA-identical sibling HCT (2010 - 2019)

Characteristic	TED, N (%)	CRF, N (%)	Total
Acute myelogenous leukemia	657	155	812
Bone marrow	509 (77.5)	123 (79.4)	632 (77.8)
Peripheral blood	139 (21.2)	22 (14.2)	161 (19.8)
Umbilical cord blood	9 (1.4)	10 (6.5)	19 (2.3)
Acute lymphoblastic leukemia	1006	156	1162
Bone marrow	810 (80.5)	129 (82.7)	939 (80.8)
Peripheral blood	175 (17.4)	17 (10.9)	192 (16.5)
Umbilical cord blood	21 (2.1)	10 (6.4)	31 (2.7)
Chronic myelogenous leukemia	70	12	82
Bone marrow	58 (82.9)	10 (83.3)	68 (82.9)
Peripheral blood	11 (15.7)	0 (0.0)	11 (13.4)
Umbilical cord blood	1 (1.4)	2 (16.7)	3 (3.7)
Myelodysplastic Syndrome	168	30	198
Bone marrow	143 (85.1)	25 (83.3)	168 (84.8)
Peripheral blood	24 (14.3)	2 (6.7)	26 (13.1)
Umbilical cord blood	1 (0.6)	3 (10.0)	4 (2.0)
Non-Hodgkin lymphoma	68	21	89
Bone marrow	53 (77.9)	16 (76.2)	69 (77.5)
Peripheral blood	14 (20.6)	5 (23.8)	19 (21.3)
Umbilical cord blood	1 (1.5)	0 (0.0)	1 (1.1)
Hodgkin lymphoma	9	2	11
Bone marrow	4 (44.4)	1 (50.0)	5 (45.5)
Peripheral blood	5 (55.6)	1 (50.0)	6 (54.5)
Umbilical cord blood	0	0	0

Characteristics of patients aged ≤ 18 years who received other related donor HCT (2010 - 2019)

Characteristic	TED, N (%)	CRF, N (%)	Total
Acute myelogenous leukemia	315	159	474
Bone marrow	139 (44.1)	92 (57.9)	231 (48.7)
Peripheral blood	171 (54.3)	67 (42.1)	238 (50.2)
Umbilical cord blood	5 (1.6)	0 (0.0)	5 (1.1)
Acute lymphoblastic leukemia	349	211	560
Bone marrow	174 (49.9)	123 (58.3)	297 (53.0)
Peripheral blood	173 (49.6)	86 (40.8)	259 (46.3)
Umbilical cord blood	2 (0.6)	2 (0.9)	4 (0.7)
Chronic myelogenous leukemia	17	13	30
Bone marrow	10 (58.8)	8 (61.5)	18 (60.0)
Peripheral blood	7 (41.2)	5 (38.5)	12 (40.0)
Umbilical cord blood	0	0	0
Myelodysplastic Syndrome	66	48	114
Bone marrow	32 (48.5)	20 (41.7)	52 (45.6)
Peripheral blood	31 (47.0)	27 (56.3)	58 (50.9)
Umbilical cord blood	3 (4.5)	1 (2.1)	4 (3.5)
Non-Hodgkin lymphoma	27	26	53
Bone marrow	13 (48.1)	8 (30.8)	21 (39.6)
Peripheral blood	13 (48.1)	18 (69.2)	31 (58.5)
Umbilical cord blood	1 (3.7)	0 (0.0)	1 (1.9)
Hodgkin lymphoma	6	5	11
Bone marrow	3 (50.0)	3 (60.0)	6 (54.5)
Peripheral blood	3 (50.0)	2 (40.00)	5 (45.5)
Umbilical cord blood	0	0	0

Characteristics of patients aged ≤ 18 years who received unrelated donor HCT (2010 - 2019)

Characteristic	TED, N (%)	CRF, N (%)	Total
Acute myelogenous leukemia	1142	713	1855
Bone marrow	652 (57.1)	188 (26.4)	840 (45.3)
Peripheral blood	294 (25.7)	75 (10.5)	369 (19.9)
Umbilical cord blood	196 (17.2)	450 (63.1)	646 (34.8)
Acute lymphoblastic leukemia	1552	723	2275
Bone marrow	893 (57.5)	138 (19.1)	1031 (45.3)
Peripheral blood	375 (24.2)	62 (8.6)	437 (19.2)
Umbilical cord blood	284 (18.3)	523 (72.3)	807 (35.5)
Chronic myelogenous leukemia	110	32	142
Bone marrow	69 (62.7)	18 (56.3)	87 (61.3)
Peripheral blood	28 (25.5)	4 (12.5)	32 (22.5)
Umbilical cord blood	13 (11.8)	10 (31.3)	23 (16.2)
Myelodysplastic Syndrome	425	193	618
Bone marrow	295 (69.4)	47 (24.4)	342 (55.3)
Peripheral blood	77 (18.1)	12 (6.2)	89 (14.4)
Umbilical cord blood	53 (12.5)	134 (69.4)	187 (30.3)
Non-Hodgkin lymphoma	98	42	140
Bone marrow	55 (56.1)	11 (26.2)	66 (47.1)
Peripheral blood	27 (27.6)	5 (11.9)	32 (22.9)
Umbilical cord blood	16 (16.3)	26 (61.9)	42 (30.0)
Hodgkin lymphoma	15	10	25
Bone marrow	9 (60.0)	8 (80.0)	17 (68.0)
Peripheral blood	6 (40.0)	2 (20.0)	8 (32.0)
Umbilical cord blood	0	0	0

Characteristics of patients aged ≤ 18 years who received autologous HCT (2010 - 2019)

Characteristic	TED, N (%)
Acute myelogenous leukemia	49
Bone marrow	8 (16.3)
Peripheral blood	41 (83.7)
Umbilical cord blood	0
Acute lymphoblastic leukemia	3
Bone marrow	0
Peripheral blood	3 (100)
Umbilical cord blood	0
Non-Hodgkin lymphoma	205
Bone marrow	12 (5.9)
Peripheral blood	193 (94.1)
Umbilical cord blood	0
Hodgkin lymphoma	646
Bone marrow	13 (2.0)
Peripheral blood	633(98.0)
Umbilical cord blood	0

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

	Autologous	Allogeneic		
	TED	TED	CRF	Total
Testicular	29	0	0	0
Soft tissue sarcoma (Include PNET)	27	0	2	2
Central nervous system tumors (include CNS PNET	561	1	0	1
Wilm Tumor	107	0	0	0
Neuroblastoma	2596	11	1	12
Retinoblastoma	77	0	0	0
Ewing sarcoma	174	7	3	10
Germ cell tumor, Extragonadal	132	0	0	0
Medulloblastoma	684	1	0	1
Rhabdomyosarcoma	44	11	3	14

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants with biospecimens available through the CIBMTR Repository

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	4501	1287	1610
Source of data			
CRF	2713 (60)	675 (52)	1007 (63)
TED	1788 (40)	612 (48)	603 (37)
Number of centers	162	123	197
Disease at transplant			
AML	1348 (30)	442 (34)	489 (30)
ALL	1966 (44)	519 (40)	706 (44)
Other leukemia	29 (1)	5 (<1)	10 (1)
CML	276 (6)	87 (7)	130 (8)
MDS	551 (12)	135 (10)	199 (12)
Other acute leukemia	106 (2)	41 (3)	24 (1)
NHL	166 (4)	39 (3)	35 (2)
Hodgkin Lymphoma	45 (1)	9 (1)	13 (1)
MPN	14 (<1)	10 (1)	4 (<1)
Recipient age at transplant			
0-9 years	2165 (48)	613 (48)	778 (48)
10-17 years	2336 (52)	674 (52)	832 (52)
Median (Range)	10 (0-18)	10 (0-18)	10 (0-18)
Year of transplant			
1986-1990	73 (2)	10 (1)	30 (2)
1991-1995	437 (10)	107 (8)	204 (13)
1996-2000	581 (13)	210 (16)	332 (21)
2001-2005	707 (16)	154 (12)	321 (20)
2006-2010	856 (19)	154 (12)	186 (12)
2011-2015	1019 (23)	215 (17)	228 (14)
2016-2020	678 (15)	338 (26)	229 (14)
2021-2022	150 (3)	99 (8)	80 (5)
Follow-up among survivors, Months			
N Eval	2277	643	775
Median (Range)	73 (0-385)	59 (2-295)	63 (0-372)

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.

Unrelated cord Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants with biospecimens available through the CIBMTR Repository

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	1505	458	576
Source of data			
CRF	1129 (75)	326 (71)	332 (58)
TED	376 (25)	132 (29)	244 (42)
Number of centers	90	75	117
Disease at transplant			
AML	595 (40)	166 (36)	205 (36)
ALL	636 (42)	223 (49)	258 (45)
Other leukemia	10 (1)	1 (<1)	4 (1)
CML	17 (1)	5 (1)	8 (1)
MDS	152 (10)	43 (9)	64 (11)
Other acute leukemia	43 (3)	12 (3)	21 (4)
NHL	45 (3)	8 (2)	11 (2)
Hodgkin Lymphoma	5 (<1)	0	4 (1)
MPN	2 (<1)	0	1 (<1)
Recipient age at transplant			
0-9 years	971 (65)	319 (70)	360 (63)
10-17 years	534 (35)	139 (30)	216 (38)
Median (Range)	7 (0-18)	7 (0-18)	8 (0-18)
Year of transplant			
1996-2000	0	0	2 (<1)
2001-2005	46 (3)	40 (9)	14 (2)
2006-2010	562 (37)	125 (27)	200 (35)
2011-2015	552 (37)	126 (28)	226 (39)
2016-2020	287 (19)	131 (29)	102 (18)
2021-2022	58 (4)	36 (8)	32 (6)
Follow-up among survivors, Months			
N Eval	847	265	303
Median (Range)	71 (0-196)	56 (0-213)	54 (0-186)

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.

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants with biospecimens available through the CIBMTR Repository

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	1080	164	73
Source of data			
CRF	253 (23)	39 (24)	17 (23)
TED	827 (77)	125 (76)	56 (77)
Number of centers	54	40	35
Disease at transplant			
AML	376 (35)	53 (32)	23 (32)
ALL	491 (45)	75 (46)	39 (53)
Other leukemia	1 (<1)	0	0
CML	31 (3)	1 (1)	2 (3)
MDS	86 (8)	18 (11)	6 (8)
Other acute leukemia	41 (4)	3 (2)	2 (3)
NHL	43 (4)	12 (7)	1 (1)
Hodgkin Lymphoma	8 (1)	2 (1)	0
MPN	3 (<1)	0	0
Recipient age at transplant			
0-9 years	451 (42)	83 (51)	30 (41)
10-17 years	629 (58)	81 (49)	43 (59)
Median (Range)	12 (0-18)	10 (1-18)	12 (1-18)
Year of transplant			
2006-2010	34 (3)	2 (1)	2 (3)
2011-2015	272 (25)	32 (20)	13 (18)
2016-2020	550 (51)	88 (54)	35 (48)
2021-2022	224 (21)	42 (26)	23 (32)
Follow-up among survivors, Months			
N Eval	752	118	41
Median (Range)	25 (2-147)	24 (0-117)	15 (0-122)

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.

CELEBRATING 50 YEARS 1972-2022 CIBMTR® 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: 2021-2022 Studies in Progress Summary

PC19-02: Does mixed peripheral blood T Cell Chimerism predict relapse?
(Prockop S/Boelens J/Peggs K).
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 with particular focus on reviewing chimerism data and categorizing chimerism based on the data and timepoints available. The goal is to have the data file prepared for analysis by August 2023.

PC19-03: The impact of pre-transplant extramedullary disease on the outcome of Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia in children,
(Rangarajan H/ Satwani P/Chellapandian D).
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 study protocol was recently updated, and years expanded to include more recent data and disease characteristics like the pediatric DRI. The goal is to have the data file prepared for analysis by August 2023.

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,
(Knight T / Wall D/ Chiengthong K).
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 two manuscripts were submitted to *Transplantation and Cellular Therapy,* and we are awaiting response from reviewers.

PC20-02: Germline genetics of pediatric Myelodysplastic Syndromes,
(Poynter J/ Spector L).
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 and accompanying data file is being prepared. The goal is to have the accompanying CIBMTR data file sent by June 2023, with the remaining study finalized once sample testing has been completed.

PC22-01: 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,
(Bauchat A/Qayed M).
The primary objective of this study is 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, with the hypothesis that mild to moderate aGVHD is associated with improved Leukaemia-free survival in children with favourable risk disease by pediatric DRI classification.
The study protocol is being developed. The goal is to finalize the protocol and begin data analysis by August 2023.

PC22-02: Evaluating predictors of access and outcomes with hematopoietic cell transplantation in pediatric and adolescent patients with relapsed/refractory classical Hodgkin lymphoma after treatment on an initial cooperative group clinical trial,
(Castellino S/Kahn J).
The objective of this study is primary to use a novel data linkage between the Children's Oncology Group (COG) and the CIBMTR to:

1. To evaluate the receipt of HCT in a contemporary cohort of children and adolescents with r/r HL; to determine patient- and disease-related factors associated with receipt of HCT including age at initial diagnosis, race/ethnicity, insurance type, and location of care during COG therapy.
2. To evaluate post-transplant survival outcomes (PFS, TRM, OS) in the above transplanted cohort.

The study protocol is being developed, approach to data linkage being evaluated, and data use agreement being developed. The goal is to develop the protocol by August 2023.

SC21-08: Optimizing Haploidentical Donor Selection for Pediatric HCT,
(Liberio N/ Broglie L).
The primary objective of this study is to determine the effect of donor age and donor relationship on the outcomes of related Haploidentical HCT. Outcomes include acute and chronic GVHD, relapse, graft failure, and overall survival. The study analysis has been completed and the study is in manuscript preparation.
This study is being performed by a pediatric hematology/oncology fellow at the Medical College of Wisconsin as part of a Master's Degree Thesis and is supported by additional funding. The study is being developed and all statistical analysis performed by the fellow. This study falls outside traditional working committee practices but is of interest to the pediatric community and so results will be shared with the committee. The goal is to publish the manuscript by June 2023.

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

Post-transplant cyclophosphamide vs. TCR αβ/CD19+ deplete approaches for Haploidentical Transplant in pediatric patients with acute leukemias and myelodysplastic syndrome: A CIBMTR/EBMT collaborative study

Q2. Key Words

Haploidentical transplant, PTCY vs TCR αβ/CD19+ deplete, outcomes, pediatrics

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Amanda M. Li MD
Email address:	ali3@cw.bc.ca
Institution name:	British Columbia Children's Hospital
Academic rank:	Clinical 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):	Hemalatha Rangarajan MD and Prakash Satwani MD
Email address:	Hemalatha.Rangarajan@nationwidechildrens.org
Institution name:	Nationwide Children's Hospital
Academic rank:	Clinical Associate Professor of Pediatrics

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:

Hemalatha Rangarajan

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.

Hemalatha Rangarajan
I have completed the following study with CIBMTR
IB17-02: Outcomes of Pediatric patients with JMML following unrelated donor transplant: The impact of Donor KIR Gene Content and KIR Ligand Matching
Manuscript Published. Transplantation and Cellular Therapy. PMID: 34407489. Role : Principal investigator
The following proposals that I have submitted have been accepted and are at varying stages of development. I am one of the co-principal investigators on all these protocols.
1. IN20-01: Incidence, Risk Factors, and Outcomes of Infections post CD19 CAR T therapies. February 2020. Data analysis is ongoing.
2. CT20-02: Resource utilization in patients receiving CAR-T Therapy. February 2020. Data analysis ongoing
3. PC19-03: Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with AML and CNS involvement. February 2019. Data analysis is ongoing.
4. NM22-01:Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis: Protocol development
5. RRT: 2110-80:Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database: Protocol Development

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. Larisa Broglie . This proposal was submitted in 2021, but was it was felt that the CIBMTR registry lacked the participant numbers to arrive at statistically meaningful outcomes. However, it was felt that those numbers could potentially be achieved in collaboration with the European Bone Marrow Transplant (EBMT) group, and hence a re-submission was proposed as a joint CIBMTR/EBMT collaboration.

Q15. RESEARCH QUESTION:

Are the outcomes in pediatric patients with acute leukemias and myelodysplastic syndrome undergoing haploidentical hematopoietic stem cell transplants (haploHCT) comparable between alpha-beta T cell receptor deplete (TCR αβ/CD19+) and post-transplant cyclophosphamide (PTCY) transplant approaches.

Q16. RESEARCH HYPOTHESIS:

Outcomes in pediatric patients with acute leukemias and myelodysplastic syndrome undergoing haploidentical hematopoietic stem cell transplants (haploHCT) will be comparable between alpha-beta T cell receptor deplete (TCR αβ/CD19+) and post-transplant cyclophosphamide (PTCY) transplant approaches.

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

Suggested word limit of 200 words:

Specific Aim: We will compare the following transplant outcomes between pediatric patients with hematological malignancies receiving a TCR αβ/CD19+ deplete vs PTCY haploHCT.
Primary endpoint
2-year Leukemia Free Survival (LFS) in pediatric patients
Secondary endpoints
1) 2-year Overall Survival (OS), graft-versus-host disease (GvHD)-free, relapse-free survival (GRFS), and chronic GvHD-free, relapse-free survival (CRFS)
2) Transplant related mortality (TRM) at 100 days
3) Incidence of graft failure.
4) Latency of neutrophil and platelet engraftment
5) Incidence of acute GvHD (aGvHD) and severity of aGvHD (grades I-II versus III-IV).
6) Incidence and severity of chronic GvHD
Other exploratory endpoints
1) Length of first hospitalization
2) Incidence of fungal and bacterial infections during the first 100 days post-HCT, and the incidence of viral reactivation in first 100 days post-HCT (CMV, EBV, HHV6 and adenovirus)
3) Incidence of organ toxicity during first 100 days post-HCT (VOD, pulmonary toxicity, renal toxicity including hemorrhagic cystitis, Cardiac toxicity and CNS toxicity)
4) Immune reconstitution by day 100 post HCT (minimum at least absolute CD4 count and IVIG data if available)

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.

Use of haploidentical donors has expanded the donor pool for patients in need of life saving allogeneic hematopoietic stem cell transplants (alloHCT) with an increasing number being performed in both malignant as well as nonmalignant disorders [1]. Common strategies for haploidentical HCTs (HaploHCT) include ex vivo T cell depletion by T cell receptor (TCR) αβ /CD19 depletion and use of post-transplant cyclophosphamide (PTCY). However, there are only isolated reports that have directly compared both approaches. Therefore, we propose comparing both approaches for various transplant outcomes in a contemporary cohort of patients. Our study will provide vital data to the transplant community regarding equivalence or superiority of one approach over the other. This will enable transplant centers to prioritize and adopt a strategy in keeping with the availability of their local resources.

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.

HaploHCTs are now increasingly being performed in both malignant as well as nonmalignant disorders when a suitable matched sibling (MSD) or fully matched unrelated donor (MUD) are unavailable [1]. However, human leukocyte antigen (HLA)-mismatched transplants are associated with increased risks of graft rejection and graft-versus-host disease (GvHD), and therefore haploHCTs require T-cell depletion strategies to safely and successfully overcome the HLA-disparity. Common strategies include the use of post-transplant cyclophosphamide (PTCY) given 3-4 days after graft infusion, to decrease the expanded population of alloreactive T-cells, or ex-vivo depletion of alpha-beta T-cells (TCR αβ/CD19+ depletion) by immunomagnetic columns prior to graft infusion. CD19+ B-cells are typically also depleted to decrease the risk of EBV reactivation in the setting of a T-cell deplete transplant. A recent CIBMTR study revealed that 80% of haploHCTs are being performed using PTCY for GVHD prophylaxis [2]. In a survey of 315 HCT physicians [2], 21% of respondents predicted that haploidentical donors would be the preferred donors and 55% predicated that calcineurin inhibitor (CNI) based GvHD prophylaxis will be replaced by PTCY in the coming years.

Single center studies using haploHCTs in hematological malignancies have shown rates of leukemia-free survival (LFS), overall survival (OS) and acute graft versus host disease (aGvHD) and chronic GvHD comparable to MUD [3-6]. Registry-based studies in adults have also shown outcomes of haploHCT similar to that of MUD transplants and even MSD transplants in acute leukemias and lymphomas [7]. The role of haploidentical related donors is being considered by some centers to be nearly equivocal to matched unrelated or umbilical cord donor sources. In a recent CIBMTR study of adults with acute myeloid leukemia in first complete remission, CR1, Rashidi et al [8] compared 336 patients who underwent a PTCY based haploHCT with 869 MSD using CNI-based GvHD prophylaxis. The haploHCT group included more reduced-intensity conditioning (65% vs 30%) and bone marrow grafts (62% vs 7%). In multivariable analysis, haplo-HCT and MSD did not significantly differ with regards to OS, LFS, non-relapse mortality, relapse incidence or grade II-IV aGvHD. However, the haploHCT group had a significantly lower rate of chronic GvHD.

Shah et al. elegantly summarized all relevant studies (n=12) that have reported outcomes of PTCY based haploHCT in children (n=385) from 2016 to 2020 [9]. Myeloablative conditioning (MAC) regimens were used in 70% (n=273) and reduced intensity conditioning (RIC) regimens were used in the remaining 30% (n=112). Four studies used only bone marrow (BM) as the graft source, one study used BM and peripheral blood stem cells (PBSC) grafts, two studies used either BM or PBSC, and five studies used only PBSC grafts. Collectively, the reported incidence of graft failure was 0-13%, acute GvHD (grade II-IV) was 17-47%, incidence of chronic GvHD was 4-53%, incidence of non-relapse mortality (NRM) was 2.9 - 36%, and rate of relapse was 17.6 to 52%. The disease-free survival (DFS) and overall survival at last follow up in these studies ranged from 33-78% and 48-84%, respectively.

The outcomes of ex vivo T cell depleted haploHCT using TCR αβ/CD19+ depletion also appears to be promising in children with acute leukemia. In a prospective study [10] evaluating the outcome of children with acute leukemia that received TCR αβ/CD19+ deplete depleted grafts, the 5-year probability of GvHD and Relapse Free Survival (GRFS) was 71%. In another multicenter retrospective study by Bertaina et al [11] comparing MUD, mismatched unrelated donor (MMUD) and TCR αβ/CD19+ transplants in acute leukemia, the GvHD rates were remarkably low in TCR αβ/CD19+ depleted transplants (grade II-IV 16%, grade III-IV 0%), with comparable LFS across all types of transplant.

In our review of literature, we identified only one study from Spain [12] that compared both approaches in children. In this study, there were total of 192 patients with a median age of 8.6 years with high-risk hematological malignancies (ALL, AML, JMML, CML, MDS, JMML). This included 41 recipients of PTCY haploHCT and 151 recipients of various ex vivo T cell depletion strategies. The latter included CD3-depletion either by CD34+ selection or CD3+CD19+ depletion, TCRαβ+CD19+ depletion or CD45RA+ depletion with CD34+ addback. With the exception of 9 patients who received PTCY and bone marrow grafts, all other patients received PBSC grafts. The 2-year OS was 55%, DFS was 49% and relapse rate 30%, aGvHD grade III-IV: 18%, 2-year cGvHD 32%, 2-year GRFS of 40%; graft failure rate of 28% and TRM of 21% with no difference between both platforms. The authors concluded that both platforms of haploHCT were equally effective.

In conclusion, haploidentical donors are increasingly being used in pediatric stem cell transplantation, and the scope of diseases which are being considered for this type of transplant is widening. A direct comparison of the two most common T-cell depletion strategies in this population will help inform how to optimally proceed with haploidentical transplants in children with hematologic malignancies, balancing therapeutic efficacy, toxicity, and accessibility.

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:
• All patients undergoing first allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia or lymphoblastic lymphoma, acute myeloid leukemia, myelodysplastic syndrome (MDS) with a haploidentical related donor (≥2 antigen mismatch) and either post-transplant cyclophosphamide or ex-vivo αβ T cell depletion
• Age ≤ 21 years at the time of allogeneic HCT
• Years: 2010-2021, with at least 2 year of follow up
Exclusion
• Patients receiving haploidentical transplants without ex-vivo αβ T cell depletion or post-transplant cyclophosphamide.
• Recipients of 2nd or more allogeneic HCT
• Patients missing baseline of day 100 form
• Patients receiving grafts from multiple donors

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 included
Patient Related
• Age ≤ 21 years
• Sex, Race
• Performance score; 80 vs ≥ 80
• HCT comorbidity index
• CMV status Negative/Positive/Not reported
• ABO/RH
• Disease AML/ALL/MDS
• Disease status: CR1, CR2, active disease
• AML
• With prior MDS Y/N
• Therapy related Y/N
• Prior history of EMD Y/N
• Cytogenetic risk group:
• 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
• ALL:
• Prior blinatumomab, inotuzumab , or CAR T (Specify CART)
• 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 for both AML and ALL
Donor Related
• Age
• Sex
• Donor CMV status Negative/Positive/Not reported
• Donor Relation: Offspring/parent/sibling
• Donor ABO Rh
• HLA matching: 5/10, 6/10, 7/10, 8/10
Transplant related
• Conditioning regimen and intensity Myeloablative/Reduced toxicity
• Serotherapy Y/N Campath/ATG/both/none
• Rituximab Y/N as part of conditioning
• Cell source: PB/BM/GCSF primed BM
• T cell depletion strategy: PTCY vs. αβ T cell depletion
• GVHD prophylaxis in addition to above: Tacrolimus/Cyclosporine only, Sirolimus only, Tacrolimus/Cyclosporine+ MMF, Sirolimus+ MMF vs others.
Outcomes
• Day of Neutrophil and platelet engraftment
• Graft failure
• Relapse Y/N if Y months from HCT
• Acute GVHD Y/N with Grade I-II vs II-IV
• Chronic GVHD Y/N with NIH scoring
• Alive or dead at last follow up Y/N
• If death cause of death
• Infections withing first 100 days post HCT: Viral, Bacterial and Fungal
• Immune reconstitution data at day 100 and IVIG use if available.
• Organ toxicity data (VOD, Pulmonary toxicity, renal toxicity including hemorrhagic cystitis, cardiac toxicity and CNS toxicity)

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.

Not applicable

Q26. REFERENCES:

REFERENCES:
1. D'Souza, A., et al., Current Use and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant, 2017. 23(9): p. 1417-1421.
2. Farhadfar, N., et al., Hematopoietic Cell Transplantation (HCT) Predictions for the Year 2023. Biology of Blood and Marrow Transplantation, 2020. 26(3, Supplement): p. S201.
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9. Shah, R.M., Contemporary haploidentical stem cell transplant strategies in children with hematological malignancies. Bone Marrow Transplant, 2021. 56(7): p. 1518-1534.
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12. Pérez-Martínez, A., et al., Haploidentical transplantation in high-risk pediatric leukemia: A retrospective comparative analysis on behalf of the Spanish working Group for bone marrow transplantation in children (GETMON) and the Spanish Grupo for hematopoietic transplantation (GETH). Am J Hematol, 2020. 95(1): p. 28-37.

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

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Table 1A. Characteristics of pediatric and young adults who underwent first Allo HCT for ALL, AML, or MDS using PT-CY or T-Cell Depletion as GVHD Prophylaxis between 2010 and 2019

Characteristic	T-cell depletion	Post-CY	Total
No. of patients	254	645	899
No. of centers	42	134	157
Age category - no. (%)			
Median (min-max)	11 (1-21)	13 (1-21)	12 (1-21)
< 10	116 (46)	261 (40)	377 (42)
10 - 17	106 (42)	250 (39)	356 (40)
18 - 29	32 (13)	134 (21)	166 (18)
Sex of recipient - no. (%)			
Male	139 (55)	398 (62)	537 (60)
Female	115 (45)	247 (38)	362 (40)
Performance score - no. (%)			
80 - 100	208 (82)	531 (82)	739 (82)
< 80	40 (16)	104 (16)	144 (16)
Not reported	6 (2)	10 (2)	16 (2)
Disease - no. (%)			
AML	113 (44)	279 (43)	392 (44)
ALL	110 (43)	320 (50)	430 (48)
MDS	31 (12)	46 (7)	77 (9)
Graft type - no. (%)			
Bone marrow	5 (2)	404 (63)	409 (45)
Peripheral blood	237 (93)	241 (37)	478 (53)
Umbilical cord blood	12 (5)	0 (0)	12 (1)
GVHD Prophylaxis - no. (%)			
Ex-vivo T-Cell Depletion	138 (54)	0 (0)	138 (15)
CD34 selection	96 (38)	0 (0)	96 (11)
Post-CY + other(s)	0 (0)	645 (100)	645 (72)
αβ T-cell depletion	20 (8)	0 (0)	20 (2)
Reported planned conditioning intensity - no. (%)			
RIC/NMA	52 (20)	81 (13)	133 (15)
Myeloablative	196 (77)	559 (87)	755 (84)
TBD after review	6 (2)	5 (1)	11 (1)
Transplant year - no. (%)			

Characteristic	T-cell depletion	Post-CY	Total
2010	14 (6)	0 (0)	14 (2)
2011	12 (5)	0 (0)	12 (1)
2012	15 (6)	2 (0)	17 (2)
2013	18 (7)	13 (2)	31 (3)
2014	23 (9)	37 (6)	60 (7)
2015	28 (11)	55 (9)	83 (9)
2016	24 (9)	93 (14)	117 (13)
2017	37 (15)	138 (21)	175 (19)
2018	29 (11)	147 (23)	176 (20)
2019	54 (21)	160 (25)	214 (24)
Indicator of HCT cases in CRF retrieval - no. (%)			
No	168 (66)	357 (55)	525 (58)
Yes	86 (34)	288 (45)	374 (42)

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

Comparison of myeloablative conditioning regimens for acute myeloid leukemia in children and young adults. A CIBMTR Analysis.

Q2. Key Words

Acute myeloid leukemia, Allogeneic Hematopoietic Cell Transplantation, Conditioning

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Thomas Pfeiffer, MD
Email address:	pthomas@wustl.edu
Institution name:	Washington University School of Medicine
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):	Shalini Shenoy, MD
Email address:	shalinishenoy@wustl.edu
Institution name:	Washington University School of Medicine
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:

Thomas Pfeiffer

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:

This study intends to evaluate the impact of conditioning regimens correlated with disease status on outcomes in children with acute myeloid leukemia undergoing first allo-HCT, and to identify prognostic factors impacting outcomes.

Q16. RESEARCH HYPOTHESIS:

The optimal conditioning regimen for children with AML undergoing allogeneic hematopoietic cell transplantation (allo-HCT) is subject of ongoing debate. Clinical trials prospectively evaluating different conditioning regimens are lacking. Registry data suggest similar non-relapse mortality (NRM), overall (OS) and relapse-free survival (RFS) for pediatric AML patients receiving busulfan either with cyclophosphamide (Bu/Cy) or fludarabine (Bu/Flu) (1). Total body irradiation (TBI) based regimens were recently shown to result in similar outcomes despite increased toxicity (2). Further improvement of disease control may be achieved through the addition of melphalan and the resultant increase in (leukemic) stem cell toxicity. Indeed, recent European data demonstrate superior outcomes with Bu/Cy/Mel conditioning compared to Bu/Flu and Bu/Cy (3). Additional validation of these data is now needed. We hypothesize that OS and RFS rates may be improved with Bu/Cy/Mel conditioning compared to other Busulfan based myeloablative regimens.

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

Suggested word limit of 200 words:

Primary Objective:
1. Evaluate OS, RFS, and NRM in AML patients undergoing first allo-HCT receiving either Bu/Cy/Mel, Bu/Flu or Bu/Cy conditioning.

Secondary Objectives:
1. Report the timing of hematopoietic recovery
2. Assess the incidence of acute and chronic GVHD
3. Evaluate infection rates.
4. Explore additional patient and transplant related factors for their impact on outcomes, including age (<12 and > 12 years), donor choice, graft source, transplant period, remission status, genetic markers and risk category, and ATG use.

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

Allogeneic hematopoietic cell transplant is the accepted standard of care for the treatment of children and young adults with high-risk AML as defined by cytogenetic and molecular features, and/or response to up-front therapy (4). Disease relapse is the most common type of transplant failure in AML, occurring in up to 40-50% of patients (5,6). The prognosis for children who relapse after allo-HCT is unfortunately dismal, with a probability of long-term survival of less than 20% (7). Thus, there is a desperate need to make allo-HCT more effective without compromising safety.

The type of conditioning may play a crucial role in preventing relapse following allo-HCT. The most commonly used conditioning regimens for pediatric AML in North America have either been TBI based or non-TBI based with busulfan / cyclophosphamide (Bu/Cy) and busulfan / fludarabine (Bu/Flu) utilized most prominently (8). This is in contrast to several European study groups that have historically favored the addition of a third alkylator (Bu/Cy/Mel) (9–11). Such a regimen may theoretically exert enhanced stem cell toxicity and improved targeting of residual leukemic progenitor cells. Despite the important role of the conditioning regimen in allo-HCT, no consensus exists regarding the optimal choice of drugs. Randomized, prospective studies are lacking, and decision-making is largely based on retrospective analysis and registry data. Recent data suggest that the combination of Bu/Cy/Mel may favorably impact post-HCT relapse rates with comparable safety and NRM (12). Further validation of these data along with an in-depth analysis of influencing factors is now needed.

The proposed analysis of AML conditioning regimens and their impact on key transplant outcomes will inform the transplant community which treatment strategy strikes the best balance between preventing relapse and minimizing toxicity. It will further allow for the identification of additional prognostic factors to guide transplant decisions for physicians and families. Ultimately, this knowledge may then lead to improved outcomes for these patients. If our CIBMTR proposal is approved, we will seek collaboration with EBMT to obtain a larger dataset if feasible.

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.

Myeloablative conditioning for AML in North America has historically relied on TBI, Bu/Cy or Bu/Flu with similar outcomes observed between these options (1,2). A recent report by EBMT demonstrated markedly improved 5-year RFS in pediatric AML patients in CR1 conditioned with Bu/Cy/Mel (75%) compared to Bu/Cy (58%) and TBI/Cy (62%). Non-relapse mortality and rates of severe GVHD were comparable between the groups (12). These promising outcomes for patients receiving Bu/Cy/Mel conditioning are consistent with earlier results from the AIEOP 2002/01 trial (8-year RFS of 73%) (9). Bu/Cy/Mel was also used as the standard myeloablative regimen on the recently completed BFM 2007 trial. This study demonstrated encouraging 4-year EFS for children with AML transplanted in CR1: 76% and 84% for the entire cohort and for children less than 12 years, respectively. In contrast, recent CIBMTR data suggest a 3-year RFS of about 60% for pediatric AML patients undergoing allo-HCT in CR1 and receiving Bu/Cy or Bu/Flu conditioning (1).

A recent report by the NOPHO-DBH consortium also demonstrated superior 5-year RFS for Bu/Cy/Mel (59%) compared to Bu/Cy (43%) in pediatric AML patients in CR1 or CR2 receiving similar upfront therapy (13). Dandoy et al. retrospectively analyzed a similar cohort of pediatric AML patients in CR1 or CR2 and demonstrated a 5-year RFS of 55% and 52% in patients receiving TBI-based and non-TBI based (Bu/Cy, Bu/Flu) conditioning, respectively (2). While the outcomes with Bu/Cy/Mel conditioning are promising, the addition of a third alkylator may increase toxicity. In fact, busulfan and melphalan are both metabolized through the GSH/GST system in the liver, thus there is a potential for pharmacological interactions (14). This can largely be mitigated through careful therapeutic drug monitoring (TDM) of busulfan, which is now standard practice at most centers. In the only study to date demonstrating increased toxicity of Bu/Cy/Mel, TDM was not performed. Toxicity in this study appeared to be clearly age dependent, with unexpectedly high rates of NRM only observed in adolescent patients: the 4-year NRM was 9% and 31% in children younger or older than 12 years, respectively (11).

In sum, the promising role of Bu/Cy/Mel conditioning in allo-HCT for pediatric and young adult patients with AML demonstrated in recent European studies warrants further investigation through the large data set provided by CIBMTR. While Bu/Cy/Mel conditioning appears to favorably impact relapse rates, the use of three alkylators may be associated with increased toxicity. Currently available data do not provide a satisfactory answer to this question. A comprehensive comparison of Bu/Cy/Mel, Bu/Cy and Bu/Flu may help identify an optimal myeloablative regimen. This would in turn increase a clinician's confidence in choosing the best possible treatment strategy to prevent relapse and improve 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.

Patients with de novo AML in first or second remission, aged <30 years and undergoing first allogeneic HCT with myeloablative busulfan dosing. Patients with antecedent hematological disorders or secondary AML will be excluded.

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 standard CIBMTR collection forms and Acute Myelogenous Leukemia pre- and -post HCT forms.

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.**

If our CIBMTR proposal is approved, we will seek collaboration with EBMT to have a larger dataset. No data linkage will be needed between CIBMTR and EBMT records.

Q26. REFERENCES:

1. Harris AC, Boelens JJ, Ahn KW, et al. Comparison of pediatric allogeneic transplant outcomes using myeloablative busulfan with cyclophosphamide or fludarabine. Blood Adv. 2018;2(11):1198.
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3. Lucchini G, Labopin M, Beohou E, et al. Impact of Conditioning Regimen on Outcomes for Children with Acute Myeloid Leukemia Undergoing Transplantation in First Complete Remission. An Analysis on Behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2017;23(3):467–474.
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9. Locatelli F, Masetti R, Rondelli R, et al. Outcome of children with high-risk acute myeloid leukemia given autologous or allogeneic hematopoietic cell transplantation in the aieop AML-2002/01 study. Bone Marrow Transplant. 2015;50(2):181–188.
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12. Lucchini G, Labopin M, Beohou E, et al. Impact of Conditioning Regimen on Outcomes for Children with Acute Myeloid Leukemia Undergoing Transplantation in First Complete Remission. An Analysis on Behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2017;23(3):467–474.
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14. Dirven HA, van Ommen B, van Bladeren PJ. Glutathione conjugation of alkylating cytostatic drugs with a nitrogen mustard group and the role of glutathione S-transferases. Chem Res Toxicol. 1996;9(2):351-60.

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

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Table 1A. Characteristics of pediatric and young adults who underwent first Allo HCT for AML using Myeloablative conditioning regimen between 2010 and 2019

Characteristic	N (%)
No. of patients	2152
No. of centers	158
Age category - no. (%)	
Median (min-max)	17 (0-30)
< 10	658 (31)
10 - 17	515 (24)
18 - 29	979 (45)
Sex of recipient - no. (%)	
Male	1121 (52)
Female	1031 (48)
Performance score - no. (%)	
80 - 100	1744 (81)
< 80	385 (18)
Not reported	23 (1)
Graft type - no. (%)	
Bone marrow	1014 (47)
Peripheral blood	866 (40)
Umbilical cord blood	272 (13)
Conditioning regimen - no. (%)	
Bu/Cy/Mel	38 (2)
Bu/Cy	1191 (55)
Bu/Mel	112 (5)
Flu/Bu/TT	78 (4)
Flu/Bu	733 (34)
Donor type - no. (%)	
HLA-identical sibling	574 (27)
Other related	231 (11)
Well-matched unrelated (8/8)	807 (38)
Partially-matched unrelated (7/8)	228 (11)
Mis-matched unrelated (<= 6/8)	28 (1)
Multi-donor	4 (0)
Unrelated (matching TBD)	8 (0)
Cord blood	272 (13)

Characteristic	**N (%)**
Transplant year - no. (%)	
2010	149 (7)
2011	175 (8)
2012	159 (7)
2013	181 (8)
2014	227 (11)
2015	236 (11)
2016	264 (12)
2017	250 (12)
2018	244 (11)
2019	267 (12)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	1479 (69)
Yes	673 (31)

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 who receive an allogeneic hematopoietic cell transplantation for juvenile myelomonocytic leukemia

Q2. Key Words

juvenile myelomonocytic leukemia, children, allogeneic hematopoietic cell transplantation

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 Bhatt, MD
Email address:	nbhatt@fredhutch.org
Institution name:	Fred Hutchinson Cancer Center, Seattle, WA
Academic rank:	Assistant Member

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

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.

CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies

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 (Scientific Director, Pediatric Cancer Working Committee and Non Malignant Working Committee)

Q15. RESEARCH QUESTION:

What are the short- and long-term outcomes of children with juvenile myelomonocytic leukemia (JMML) who receive an allogeneic hematopoietic cell transplantation (HCT)?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the overall and disease-free survival of patients with JMML who undergo allogeneic HCT, especially with HLA-matched sibling donor and myeloablative conditioning with busulfan, cyclophosphamide, and melphalan has improved over time. However, the burden of short-term toxicities and late effects among HCT recipients remains high due to the conditioning intensity.

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

Suggested word limit of 200 words:

1. Compare the overall survival, disease-free survival, and non-relapse mortality of children with JMML who receive an allogeneic HCT by donor type, conditioning regimens, and year of transplant and with historically published data.
2. Describe the burden of late effects in the survivors of HCT for JMML.

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.

JMML is a rare disorder and there are no large studies evaluating the outcomes of patients undergoing HCT for JMML using different conditioning regimens or graft/donor sources in the contemporary era. There are even fewer reports of late effects in these patients. A large study exploring outcomes of patients with JMML undergoing HCT from different graft sources/donors and receiving a variety of conditioning regimens would help elucidate the predictors of improved outcomes and help clinicians select best conditioning regimens, or researchers to develop better conditioning regimens for patients. Additionally, to our knowledge, there has not been a comprehensive analysis of the burden of late effects in this patient population. Given their unique exposures, receiving HCT at an early age and having several genetic predispositions may put these patients at a high risk of late effects. A comprehensive description of these may help clinicians identify and address these late effects in their 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.

JMML is a rare pediatric cancer with an incidence of approximately 1/million/year. It is most commonly seem among children 0-14 years of age, with a median age of presentation being around 2 years. JMML is an aggressive disease for most children with a median survival of 12 months or less, and allogeneic HCT remains the only curative treatment. Allogeneic HCT is recommended for all children with JMML associated with NF1 mutation, somatic PTPN11 and KRAS mutations, and for most children with somatic NRAS mutations. Female sex and older age at diagnosis have been associated with poor outcomes, even after HCT for JMML. There is insufficient data to infer the association of genetic mutations on post-HCT outcomes.

In published literature, outcomes from allogeneic HCT for JMML are comparable between various donor and graft sources, with greater degrees of HLA mismatch associated with worse outcomes. In the largest prospective trial of allogeneic HCT for JMML conducted by the EWOG-MDS/European Blood and Marrow Transplantation (EBMT) group which included 100 recipients, overall survival (OS) was 64% at 5-years with 13% experiencing transplant related mortality (Locatelli F, et al. Blood. 2005;105(1):410.) It is important to note that this study included patients transplanted between 1993-2002. In another Japanese study (N=27), OS was a little lower at 58% at 4 years (Manabe A et al. Leukemia. 2002;16(4):645.) Chemotherapy-based (busulfan-cyclophosphamide-melphalan) approaches are preferred over radiation-based conditioning (Locatelli F, et al. J Clin Oncol. 1997;15(2):566.) Busulfan-fludarabine-melphalan conditioning has been used as an alternative to busulfan-cyclophosphamide-melphalan with inferior outcomes in a small study (N=30) (Yabe M, et al. Int J Hematol. 2015;101(2):184.) but 13 recipients in this study received grafts from mismatched donors which may have confounded the results. Additionally, busulfan and fludarabine conditioning has been considered inferior compared to busulfan-cyclophosphamide-melphalan (Dvorak CC et al. Pediatr Blood Cancer. 2018 Jul;65(7):e27034). Haploidentical HCT using T cell-depleted grafts or post-transplant cyclophosphamide has also been used for children without a suitable matched donor, but remains an investigational approach.

Thus, a large study exploring outcomes of patients with JMML undergoing HCT from different graft sources/donors and receiving a variety of conditioning regimens would help elucidate the predictors of improved outcomes. Additionally, to our knowledge, there has not been a comprehensive analysis of the burden of late effects in this patient population. Given their unique exposures, receiving HCT at an early age and having several genetic predispositions may put these patients at a high risk of late effects. A comprehensive description of these may help clinicians identify and address these late effects in their patients.

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 patients who underwent allogeneic HCT for JMML reported to the CIBMTR between years 2000 and 2022 will be included in this study. All graft/donor sources and all conditioning regimens will be included.
This proposed study will require no supplemental data to be collected. The current data is included in the CIBMTR collection forms.
This study is a retrospective registry analysis of all patients who received an allogeneic HCT for JMML between January 2000 and January 2022.
Baseline characteristics and known prognostic variables will be collected from CIBMTR database forms. These characteristics will include: age, sex, performance status, WBC at diagnosis, genetic mutations, number of prior chemotherapy regimens, time from diagnosis to transplant, disease status at transplant, 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, donor source (peripheral blood, cord, bone marrow), transplant type (haploidentical, 1 or 2 HLA-antigen mismatch, MUD, sibling donor, cord blood), hematopoietic cell transplantation-co-morbidity index (HCT-CI), and cytogenetics at diagnosis.
Transplant outcomes (overall survival, disease free survival, cumulative incidence of non relapse mortality, and relapse) will be described and compared by key patient, disease, and HCT-related factors. Additionally, exploratory analysis will be pursued to compare outcomes by the molecular markers, presence of fetal hemoglobin, type of pre-HCT therapy, and history of splenectomy if feasible among those with available disease-specific form (Form 2015). Incidence of late effects (Avascular necrosis, Cataracts, Congestive heart failure, Diabetes mellitus, Gonadal dysfunction/ infertility requiring hormone replacement, Growth hormone deficiency/ disturbance, Hemorrhagic cystitis, Hypothyroidism, Myocardial infarction, Pancreatitis, Thrombotic thrombocytopenic purpura/ Hemolytic uremic syndrome, Renal failure warranting dialysis, Stroke/ Seizures, Bronchiolitis obliterans, Pulmonary hemorrhage, Cryptogenic organizing pneumonia, Interstitial pneumonitis/ Idiopathic pneumonia syndrome, Non-infectious liver toxicity (Cirrhosis), New malignancy, Psychiatric (depression, anxiety, PTSD) will be evaluated for all patients with CRF level data and described.

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. No biological samples are required for this study.

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

No PROs required.

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:

Locatelli F, Nöllke P, Zecca M, Korthof E, Lanino E, Peters C, Pession A, Kabisch H, Uderzo C, Bonfim CS, Bader P, Dilloo D, Stary J, Fischer A, Révész T, Führer M, Hasle H, Trebo M, van den Heuvel-Eibrink MM, Fenu S, Strahm B, Giorgiani G, Bonora MR, Duffner U, Niemeyer CM; European Working Group on Childhood MDS; European Blood and Marrow Transplantation Group. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood. 2005 Jan 1;105(1):410-9. doi: 10.1182/blood-2004-05-1944. Epub 2004 Sep 7. PMID: 15353481.

Manabe A, Okamura J, Yumura-Yagi K, Akiyama Y, Sako M, Uchiyama H, Kojima S, Koike K, Saito T, Nakahata T; MDS Committee of the Japanese Society of Pediatric Hematology. Allogeneic hematopoietic stem cell transplantation for 27 children with juvenile myelomonocytic leukemia diagnosed based on the criteria of the International JMML Working Group. Leukemia. 2002 Apr;16(4):645-9. doi: 10.1038/sj.leu.2402407. PMID: 11960345.

Locatelli F, Niemeyer C, Angelucci E, Bender-Götze C, Burdach S, Ebell W, Friedrich W, Hasle H, Hermann J, Jacobsen N, Klingebiel T, Kremens B, Mann G, Pession A, Peters C, Schmid HJ, Stary J, Suttorp M, Uderzo C, van't Veer-Korthof ET, Vossen J, Zecca M, Zimmermann M. Allogeneic bone marrow transplantation for chronic myelomonocytic leukemia in childhood: a report from the European Working Group on Myelodysplastic Syndrome in Childhood. J Clin Oncol. 1997 Feb;15(2):566-73. doi: 10.1200/JCO.1997.15.2.566. PMID: 9053478.

Yabe M, Ohtsuka Y, Watanabe K, Inagaki J, Yoshida N, Sakashita K, Kakuda H, Yabe H, Kurosawa H, Kudo K, Manabe A; Japanese Pediatric Myelodysplastic Syndrome Study Group. Transplantation for juvenile myelomonocytic leukemia: a retrospective study of 30 children treated with a regimen of busulfan, fludarabine, and melphalan. Int J Hematol. 2015 Feb;101(2):184-90. doi: 10.1007/s12185-014-1715-7. Epub 2014 Dec 11. PMID: 25504334.

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

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Table 1A. Characteristics of pediatrics patients who underwent Allo for JMML HCT between 2000 and 2019

Characteristic	N (%)
No. of patients	626
No. of centers	124
Age category - no. (%)	
Median (min-max)	2 (0-17)
< 10	615 (98)
10 - 17	11 (2)
Sex of recipient - no. (%)	
Male	422 (67)
Female	202 (32)
Not answered	2 (0)
Performance score - no. (%)	
80 - 100	421 (67)
< 80	104 (17)
Not reported	101 (16)
Graft type - no. (%)	
Bone marrow	301 (48)
Peripheral blood	137 (22)
Umbilical cord blood	182 (29)
Other	1 (0)
Missing	5 (1)
Reported planned conditioning intensity - no. (%)	
RIC/NMA	46 (7)
Myeloablative	543 (87)
TBD after review	37 (6)
Conditioning regimen - no. (%)	
TBI-based	109 (17)
Bu/Cy/Mel	249 (40)
Bu + others	177 (28)
Others	52 (8)
None	13 (2)
Missing	26 (4)
Donor type - no. (%)	
HLA-identical sibling	112 (18)
Other related	67 (11)

Characteristic	**N (%)**
Well-matched unrelated (8/8)	128 (20)
Partially-matched unrelated (7/8)	45 (7)
Mis-matched unrelated (<= 6/8)	15 (2)
Multi-donor	2 (0)
Unrelated (matching TBD)	69 (11)
Cord blood	182 (29)
Missing	6 (1)
Center Region - no. (%)	
US centers	362 (58)
Non-US centers	264 (42)
Transplant year - no. (%)	
2000	27 (4)
2001	26 (4)
2002	34 (5)
2003	45 (7)
2004	32 (5)
2005	28 (4)
2006	26 (4)
2007	26 (4)
2008	41 (7)
2009	29 (5)
2010	42 (7)
2011	28 (4)
2012	36 (6)
2013	34 (5)
2014	28 (4)
2015	29 (5)
2016	25 (4)
2017	35 (6)
2018	23 (4)
2019	32 (5)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	334 (53)
Yes	292 (47)

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

Comparison of Bone Marrow and Peripheral Blood Stem Cells as graft source in Children undergoing allogeneic Hematopoietic Stem Cell Transplantation for Hematological malignancies with unmanipulated haploidentical grafts utilizing post-transplant cyclophosphamide as GvHD prophylaxis.

Q2. Key Words

Haploidentical transplant, post-transplant cyclophosphamide, pediatric leukemias

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Anand Srinivasan
Email address:	anand-srinivasan@ouhsc.edu
Institution name:	University of Oklahoma Health Sciences Center
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):	Joerg Krueger
Email address:	joerg.krueger@sickkids.ca
Institution name:	The Hospital for Sick Children
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?

- 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:

Anand Srinivasan

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/

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 undergoing unmanipulated haploidentical allogeneic transplants for hematological malignancies with post-transplantation cyclophosphamide platform, does the source of stem cells matter?

Q16. RESEARCH HYPOTHESIS:

Bone marrow has remained the preferred graft source in many pediatric hematopoietic stem cell transplant centers due to concerns about graft-versus-host disease (GvHD) when utilizing peripheral blood stem cells. Data regarding the ideal graft source for children receiving a haploidentical graft with PT-Cy is scarce.
Based on our single institution experience, we hypothesize that children undergoing HSCT for hematological malignancies from a haploidentical donor have comparable outcomes with peripheral blood stem cell grafts compared to bone marrow grafts.

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

Suggested word limit of 200 words:

Aim 1: To analyze and compare incidence of graft-versus-host disease free relapse free survival (GRFS) between recipients of peripheral blood stem cells versus bone marrow as a stem cell source among recipients of haploidentical transplants using the PT-Cy platform. Other clinically relevant outcomes between the two graft sources will be studied including overall survival, relapse free survival, incidence of grade 2-4 aGVHD, incidence of grade 3-4 aGVHD, incidence of cGVHD requiring systemic treatment and incidence graft failure.
Aim 2: To analyze factors that affect outcome among haploidentical recipients including donor age, donor type (sibling vs parent), non-inherited maternal antigens (NIMA) vs non-inherited paternal antigens (NIPA), ABO status and CMV status in patients receiving PBSC vs a BM graft.

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.

A fully matched sibling donor (MSD) bone marrow graft remains the preferred donor for children with hematological malignancies who have an indication for an allogeneic HSCT. For patients who don't have a MSD, unrelated living donors or cord grafts from the registry can be utilized. The availability of such a fully matched donor can be as low as 16%, for patients with diverse racial/ethnic backgrounds (Gragert et al. 2014; Allan et al. 2009). For those without a suitable donor in the registry and depending on center preference, a haploidentical family donor has become standard of care in many adult and pediatric centers. Multiple approaches have been utilized including ex vivo T cell depletion (Aversa et al. 2005), GCSF use (Rossetti, Gregori, and Roncarolo 2010), post-transplant cyclophosphamide (Symons et al. 2019; Srinivasan et al. 2022) and pre and post-transplant anti-thymocyte globulin (Mohty 2007). Post-transplant cyclophosphamide (PT-Cy) has been the most common approach in North America.
Bone marrow (BM) has been the stem cell source of choice in pediatrics due to the increased risk of aGVHD and cGVHD noted with the use of peripheral blood stem cells (PBSC) (Keesler et al. 2018). However, in a PTCTC consortium study, the use of bone marrow in haploidentical transplants led to a relatively high graft failure rate (Symons et al. 2019). We have previously shown (in a retrospective setting) that haploidentical transplants using a peripheral blood stem cell source has a low graft failure rate with an acceptable incidence of aGVHD and cGVHD (Srinivasan et al. 2022). Mayumi et al and Luznik et al postulated that PTCy targets and eliminates early proliferating alloreactive donor and recipient T cells selectively, followed by an increase in T regulatory cells that counterbalances the effect of any remaining alloreactive cells; thymic clonal deletion of anti-host T cells also may contribute to the lower incidence of cGVHD (Mayumi, Umesue, and Nomoto 1996; Luznik, O'Donnell, and Fuchs 2012). Given this different mechanism of action of PT-Cy, data comparing outcomes amongst the two stem cell sources in the pediatric haploidentical setting is lacking.
Furthermore, what characteristics are important when selecting a haploidentical donor with the two available stem cell sources. Numerous studies have suggested the importance of donor age in other haplo platforms such as T cell depleted graft and Beijing platform (Wang et al. 2014; González-Vicent et al. 2017). This was also confirmed in adult patients undergoing haplo transplant with PT Cy platform that donor age plays a significant impact on the outcomes (Canaani et al. 2018). In children undergoing haplo transplants with the PT-Cy platform, data comparing impact of these factors in pediatric patients receiving PBSC grafts vs BM grafts remain sparse. Other factors could affect outcomes differently such as donor type (sibling vs parent), non-inherited maternal antigens (NIMA) vs non-inherited paternal antigens (NIPA), ABO status and CMV status. It remains to be seen what effects these factors have on the outcomes based on the stem cell source.
There is sufficient knowledge gap among practitioners in regards to these questions that warrants a study of the CIBMTR registry experience.

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.

Haploidentical transplants using PT-Cy platform has expanded donor options in pediatrics

Haploidentical transplantation with a T cell-replete graft followed by post-transplantation cyclophosphamide (PT-Cy) has shown comparable outcomes in adult patients with malignant and nonmalignant diseases (Solomon 2016; Luznik et al. 2008; Klein et al. 2016; Dietrich et al. 2016; DeZern et al. 2017; Grunwald et al. 2021; Bolaños-Meade et al. 2019; Wieduwilt et al. 2022). Pediatric data on T cell-replete haplo peripheral blood stem cell (PBSC) transplantation are limited and are mostly on patients receiving nonmyeloablative conditioning (Saglio et al. 2020; Trujillo et al. 2021; Sharma et al. 2020; Hong et al. 2018).

The CIBMTR is presently doing an analysis to compare the disease-free survival among pediatric patients with acute Leukemia and MDS who have undergone haploidentical transplant with PT-Cy and those undergoing HLA matched sibling donor (MSD), matched unrelated donor (MUD), or mismatched unrelated donor transplants (MMUD). We have also previously reported a single institution experience comparing the outcomes of haploidentical peripheral blood transplants with matched sibling and matched unrelated donor transplants (Srinivasan et al. 2022) after a fully myeloablative conditioning. Our analysis showed a comparable outcome between haplo transplants, MSD transplants and MUD transplants with a slightly higher incidence of cGVHD among recipients of MUD transplants, compared to haplo recipients. This further support growing evidence that haplo transplants with PT-Cy is a good alternative donor option for patients without suitable donors.

Does the source of haploidentical stem cells matter?

Mobilized peripheral blood stem cells (PBSC) grafts can be quickly obtained and has lesser long term discomfort on the donor (Pulsipher et al. 2009). It also removes all anesthetic risks for the donor, especially for an older donor, who can be collected with a peripheral IV. A CIBMTR adult study compared a PBSC allograft and BM allograft among haplo recipients with a reduced intensity conditioning showing similar hematopoietic recovery, overall survival and non-relapse mortality. The risks of grade 2 to 4 acute and chronic graft-versus-host disease were lower with BM allografts compared with PB. This was offset by increased relapse risk after transplantation of BM, compared to PBSC. Further sub-analyses showed that the higher relapse risks after transplantation of BM were limited to patients with leukemias (Bashey et al. 2017). Other studies show mixed results with one showing that only the GVHD rates were higher with PBSC grafts, without offering a benefit in relapse risk (Ruggeri et al. 2018) and another showing BM graft had better survival than PBSC in patients with ALL (Nagler et al. 2020). One study showed that PBSC grafts had a significantly higher risk of bacterial and viral infections, with no advantage in immune reconstitution, relapse, non-relapse mortality, or survival (Mehta et al. 2021). An adult CIBMTR study analyzing the risk factors for GVHD among haplo recipients showed that use of PBSC was a significant risk factor for the development of chronic GVHD only in the reduce intensity conditioning setting. No differences were noted in relapse or overall survival (Im et al. 2020).

Our own experience comparing haplo PBSC allografts with MSD and MUD BM grafts in children with hematological malignancies undergoing a fully myeloablative regiment did not show any differences in outcomes. We did observe a slightly increased risk of cGVHD with MUD BM grafts in comparison to haplo PBSC, though we were not powered to study this outcome (Srinivasan et al. 2022). Hence, a pediatric analysis of the CIBMTR experience will provide guidance for practitioners on what is the optimal stem cell source in the haplo PTCy platform.

What are the factors contributing to the most optimal haploidentical allograft?

Donor age is a known factor for risk of GVHD. Older donors have been shown to be associated more acute GVHD and especially donors >30 years have been reported to be associated with more NRM and worse survival in haplo and other settings (Wang et al. 2014; Ash et al. 1991; Loren et al. 2006; Kollman et al. 2001). A recent study from the CIBMTR showed that none of the donor characteristics including donor age was associated with post-transplant outcomes after adjustment for other patient and disease characteristics (McCurdy et al. 2018). Solomon et al. revealed separately that donor–recipient relationship and recipient age but not donor age were independently associated with survival after TCR HaploSCT with PTCY (Solomon et al. 2018). On the contrary, a different study of Haplo using PTCY in patients with AML and myelodysplastic syndrome (MDS) older than 55 years reported that younger donor age was a predictor for improved survival and the impact of donor age appeared to be more pronounced in patients with good- and intermediate-risk cytogenetics than in patients with poor-risk cytogenetics (S.O. Ciurea et al. 2018). Hence, it is important to study if donor age is a significant factor for children undergoing haplo PT Cy transplantation and what impact, if any it has on the donor source.

Donor gender is another factor that needs to be studies in the PT Cy platform. In the Beijing protocol for haplo, and in a non-myeloablative setting using PTCy, there is a higher incidence of acute GVHD and NRM (Wang et al. 2014; Kasamon et al. 2010). This needs further evaluation in the myeloablative setting to determine if gender matters when selecting PBSC versus bone marrow source.

Family relationship has been shown to have an impact on the haplo Beijing protocol. Inconsistent relationships have been reported by multiple groups (Polchi et al. 1995; Bayraktar and Ciurea 2013; Stefan O. Ciurea and Champlin 2013). Mother donors have been associated with more acute GVHD compared with father donors in some (Wang et al. 2014; Tamaki et al. 2001) but not all studies (van Rood et al. 2002; Stern et al. 2008).

Non-inherited maternal antigens (NIMA) and non-inherited paternal antigens (NIPA) are other important factors to consider when using a haploidentical graft. Children acquire tolerance of NIMAs when they are in utero. There is much debate on whether having a child in utero tolerizes the mother to paternal antigens or primes her lymphocytes against them. There is evidence that there is a long term persistence of microchimerism of the child's cells in the mother's peripheral blood (Evans et al. 1999; Bianchi et al. 1996) and vice versa (Maloney et al. 1999; Ichinohe, Maruya, and Saji 2002). This persistent microchimerism may lead to tolerance of the mother to paternal antigens inherited by the child and the child to NIMAs. Several (Tamaki et al. 2001; van Rood et al. 2002; Stern et al. 2008), but not all (Wang et al. 2014; Ichinohe et al. 2004) studies have shown better survival or reduced GVHD with maternal grafts compared with haplo sibling or paternal grafts. Selection of sibling haplo donors based on NIMA, rather than NIPA, has been

shown in some studies to have reduced GVHD (Polchi et al. 1995; Tamaki et al. 2001; van Rood et al. 2002) and improved survival (Wang et al. 2014), but not all (Stern et al. 2008) studies. It should be noted that not all of these studies were haplo transplants usint he PTCy platform. To date, there is no data available on NIMA and NIPA effect in HaploSCT with PTCY-based GVHD prophylaxis setting (Kongtim and Ciurea 2019). Other factors that have not been studied in the haplo PT Cy platform include the ABO status of donor/recipient, CMV status.
We propose to leverage the CIBMTR data to assess the impact of these factors on outcomes after PT-Cy haplo HSCTs in patients receiving a PBSC graft compared to a BM graft.

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 criteria
o Patient age 0-18 years
Patients who have undergone a first allogeneic transplant between the years of 2010-2021 (inclusive) for a hematological malignancy utilizing an unmanipulated haploidentical allograft with post-transplant cyclophosphamide as GVHD prophylaxis
Exclusion criteria: Patients who do not meet the above criteria

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.

The proposed study will not require the collection of supplemental data, nor will it require combining CIBMTR data with data from another group. As provided on CIBMTR, we propose to utilize the following forms/collected variables contained there-in:

CIBMTR Form 2000 (Recipient Baseline Data)

o To identify transplant recipients and preparative regimens used (Q. 39, 86 and 94) and age under 18 (Q. 104), and to specifically select for pediatric recipients of allogeneic transplants

And/OR CIBMTR 2400 (Pre-Transplant Essential Data)

o To identify allogeneic patients (Q. 44), exclude recipients of second allogeneic transplant (Q.24), donor characteristics including relationship to recipient (if any) (Q. 44-52) and pediatric patients who underwent transplant for a malignant indication (Q. 103)

o To identify donor and recipient characteristics such as ABO, CMV status (Q. 68-70), recipient performance status (Q. 82-83)

o To identify the preparative regimen (Q. 123-130) and GVHD prophylaxis used (Q. 140-143)

CIBMTR Form 2005 (Confirmation of HLA typing)

o To identify HLA typing, NIMA and NIPA data (Q. 3-23)

CIBMTR Form 2006 (Hematopoietic Stem Cell Transplant (HCT) Infusion)

o To identify basic characteristics of allogeneic transplant recipients, including product type, cell dose (Q. 44, 56 and 62)

CIBMTR Form 2100 (Post-HSCT Data)

o To identify the dates of neutrophil and platelet engraftment for the two cohorts (Q.9-Q18), graft failure (Q.11), chimerism data (Q. 55-57), incidence and severity of aGVHD (Q.84-119) and cGVHD (Q. 134-189) and whether cGVHD required systemic treatment (Q. 190-203)

CIBMTR Form 2402 (Pre-Transplant Essential Data: Disease Classification)

o To identify diagnose, and select for malignant indications for allogeneic transplant only (Q.2)

o To identify the CR status and risk stratification of malignancy (Q.3-394)

Outcomes data (disease assessment and best response) for patients with applicable diagnoses who underwent allogeneic HSCT:

o CIBMTR Form 2450 (Post-Transplant Essential Data): Determination of patient survival (Q.2) and graft failure (if any) (Q.3)

o CIBMTR Form 2110 (Acute myeloid leukemia Post-HCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.2) and disease status at time of reporting period (Q.104-144)

o CIBMTR Form 2111 (Acute lymphoblastic leukemia Post-HCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.2) and disease status at time of reporting period (Q.95-129)

o CIBMTR Form 2112 (Chronic myeloid leukemia Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.100) and disease status at time of reporting period (Q.195)

o CIBMTR Form 2114 (Myelodysplastic syndrome Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.88-170) and disease status at time of reporting period (Q.233)

o CIBMTR Form 2114 (Juvenile Myelomonocytic Leukemia Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.4) and disease status at time of reporting period (Q.21)

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

The proposed study does not require biologic samples; 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.

Not applicable

Q26. REFERENCES:

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

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

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

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

N/A

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

Embedded Data:

N/A

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Table 1A. Characteristics of pediatric patients who underwent first Allo HCT for Hematological Malignancies with unmanipulated Haploidentical grafts utilizing PT-CY as GvHD Prophylaxis between 2010 and 2019

Characteristic	N (%)
No. of patients	581
No. of centers	98
Age category - no. (%)	
Median (min-max)	10 (1-18)
< 10	280 (48)
10 - 17	301 (52)
Sex of recipient - no. (%)	
Male	344 (59)
Female	237 (41)
Performance score - no. (%)	
80 - 100	491 (85)
< 80	81 (14)
Not reported	9 (2)
Disease - no. (%)	
AML	219 (38)
ALL	256 (44)
Other Leukemia	13 (2)
CML	14 (2)
MDS	40 (7)
NHL	23 (4)
HD	16 (3)
Graft type - no. (%)	
Bone marrow	398 (69)
Peripheral blood	183 (31)
GVHD prophylaxis - no. (%)	
Post-CY + other(s)	579 (100)
Post-CY alone	2 (0)
Reported planned conditioning intensity - no. (%)	
RIC/NMA	70 (12)
Myeloablative	508 (87)
TBD after review	3 (1)
Transplant year - no. (%)	
2012	3 (1)

Characteristic	N (%)
2013	9 (2)
2014	30 (5)
2015	41 (7)
2016	85 (15)
2017	123 (21)
2018	149 (26)
2019	141 (24)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	317 (55)
Yes	264 (45)