Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
San Antonio, TX
Friday, February 23, 2024 1:00 PM – 3:00 PM CST

Co-Chair:	**Margaret MacMillan, MD, MSc; University of Minnesota, Minneapolis, MN; Phone: 612-626-2961, E-mail: macmi002@umn.edu**
Co-Chair:	**Carrie Kitko, MD; Vanderbilt University Medical Center, Nashville, TN; Phone: 615-936-2088, E-mail: carrie.l.kitko@vumc.org**
Co-Chair:	**Zachariah DeFilipp, MD; Massachusetts General Hospital, Boston, MA; Phone: 617-726-5765, E-mail: zdefilipp@mgh.harvard.edu**
Scientific Director:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center, Seattle, WA; Phone: 206-667-6190; E-mail: sjlee@fredhutch.org**
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Statistician:	**Jakob DeVos, MS, CIBMTR Statistical Center, Milwaukee, WI; E-mail : jdevos@mcw.edu**

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1. **Introduction**
   a. Minutes from April 2023 meeting (Attachment 1)

2. **Accrual Summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   a. **GV18-01b** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Badawy SM, Bhatt N, Bhatt VR, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Hashmi S, Hematti P, Hossain NM, Inamoto Y, Lekakis LJ, Sharma A, Solomon S, Lee SJ, Couriel DR. Severity of chronic graft-versus-host disease and late effects following allogeneic hematopoietic cell transplantation for adults with hematologic malignancy. ***Transplantation and Cellular Therapy. 2024 Jan 1; 30(1):97.e1-97.e14. doi:10.1016/j.jtct.2023.10.010. Epub 2023 Oct 14.***
   b. **GV18-02** Wallis W, Gulbis AM, Wang T, Lee CJ, Sharma A, Williams KM, Nishihori T, Prestidge T, Gowda L, Byrne M, Krem M, MacMillan ML, Kitko C, Pidala J, Spellman SR, Lee SJ, Alousi AM. Incidence of Bacterial Blood Stream Infections in Patients with Acute GVHD. ***Submitted.***
   c. **GV19-01** Gillis N, Padron E, Wang T, Chen K, DeVos JD, Spellman SR, Lee SJ, Kitko CL, MacMillan ML, West J, Tang YH, Teng M, McNulty S, Druley TE, Pidala JA, Lazaryan A. Pilot study of donor-engrafted clonal hematopoiesis evolution and clinical outcomes in allogeneic hematopoietic cell transplantation recipients using a national registry. ***Transplantation and Cellular Therapy. 2023 Oct 1; 29(10):640.e1-640.e8. doi:10.1016/j.jtct.2023.07.021. Epub 2023 Jul 28. PMC10592088.***

d. **GV20-02** Sandhu KS, Altin J, Wang T, DeVos JD, Askar M, Phillip Z, Gendzekhadze K, Kitko CL, Lee SJ, MacMillan ML, Spellman SR, Nakamura R. Prediction of Graft-versus-Host Disease (GVHD) in Recipients of Hematopoietic Cell Transplant (alloHCT) from a Single Mismatched Unrelated Donor Using a Highly Multiplexed Proteomics Assay: MHC-PepSeq. ***Poster Presentation, ASH 2023.***

e. **GV22-01/22-03** Farhadfar N, Rashid N, DeVos JD, Wang T, Ballen K, Beitinjaneh A, Bhatt VR, Hamilton B, Hematti P, Gadalla S, Solomon SR, Jurdi NE, Lee CJ, MacMillan ML, Rangarajan H, Schoemans H, Sharma A, Spellman SR, Wingard JR, Lee SJ. Racial, Ethnic, and Socioeconomic Diversity and Outcomes of Patients with Graft-versus-Host Disease: A CIBMTR Analysis. ***Submitted.***

4. Studies in progress (Attachment 3)

a. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (T Kindwall-Keller/ B Lobo) **Analysis.**

b. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/ J Altin/ M Askar/ R Nakamura) **Manuscript Preparation.**

c. **GV21-02** Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (J Pidala/ B Logan/ M Martens) **Analysis.**

d. **GV22-01** Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (M Nishitani/ C Duncan/ R Graham/ M Qayed) **Manuscript Preparation.**

e. **GV22-02** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (A Im/ S Pavletic) **Datafile Preparation .**

f. **GV23-01** The effect of calcineurin inhibitor vs post-transplant cyclophosphamide (with or without mycophenolate mofetil) based graft-vs-host disease prophylaxis on HLA matched hematopoietic cell transplantation (R Mehta/ R Nath) **Protocol Development.**

g. **GV23-02** Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts. (K Maurer) **Protocol Development.**

5. Future/proposed studies

a. **PROP 2310-175** Independent validation of a data-driven grading system for acute GVHD in HCT patients receiving post-transplant cyclophosphamide (PTCy). (AT Turki) (Attachment 4)

b. **PROP 2310-172** Effect of acute graft-versus-host disease (GVHD) on the outcome of hematopoietic cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy): a CIBMTR analysis (AD Hadjis/ SR McCurdy) (Attachment 5)

c. **PROP 2310-155** Post-Transplantation Cyclophosphamide (PTCy)/Sirolimus versus PTCy/Calcineurin-inhibitor (CNI) -based Graft-Versus-Host Disease Prophylaxis (R Mehta/ N Bejanyan) (Attachment 6)

d. **PROP 2310-58** Differences in the characteristics of Acute and Chronic Graft-Versus-Host Disease (GVHD) After Post-Transplantation Cyclophosphamide Versus Conventional Calcineurin Inhibitor-based GVHD Prophylaxis (R Mehta/ RM Saliba) (Attachment 7)

e. **PROP 2310-178** Quantification of Severe and Highly Morbid Chronic Graft-Versus-Host Disease Forms in Pediatric Hematopoietic Cell Transplantation Patients Since Implementation of the 2014 NIH Consensus Criteria (J Boiko) (Attachment 8)

Dropped proposed studies

f. **PROP 2308-02** A comparison of post transplant cyclophosphamide with MTX and CNI for GVHD prophylaxis in myeloablative conditioning regimens with PBSC graft source with HLA matched donors related and unrelated. *Overlap with CIBMTR study GV23-01.*
g. **PROP 2309-13** Abatacept in Combination with a Calcineurin Inhibitor and Methotrexate Following Allogeneic Hematopoietic Stem Cell Transplantation using FluBu2: Analysis of the Center for International Blood and Marrow Transplant Research Database. *Insufficient sample size.*
h. **PROP 2309-17** Incidence of Genital cGVHD in recipients of Allogeneic Stem Cell Transplantation. *Insufficient data collection.*
i. **PROP 2310-07** Mismatched (7/8) unrelated donor transplantation versus haploidentical transplantation using PTCy: Analysis of the Center for International Blood and Marrow Transplant Research Database. *Overlap with IB23-02.*
j. **PROP 2310-08** Post-transplant cyclophosphamide for Graft versus Host Disease Prophylaxis in patients undergoing allogeneic transplantation using Myeloablative conditioning: Analysis of the Center for International Blood and Marrow Transplant Research Database. *Overlap with GV23-01.*
k. **PROP 2310-101** Post-transplant cyclophosphamide versus abatacept for GVHD prevention in recipients of unrelated donor Allo-HCT. *Insufficient sample size.*
l. **PROP 2310-107** Comparing outcomes between HLA-haploidentical and mismatched unrelated donor transplantation among patients receiving reduced intensity conditioning with posttransplant cyclophosphamide-based graft versus host disease prophylaxis. *Overlap with IB23-02.*
m. **PROP 2310-138** The Impact of Organ Function on GVHD Prophylaxis Outcomes. *Insufficient data collection.*
n. **PROP 2310-171** Outcomes of Non-First Degree Relative Haploidentical Blood or Marrow Transplantation Using Post-Transplant Cyclophosphamide. *Insufficient sample size.*
o. **PROP 2310-179** Haploidentical vs HLA-matched Donor Allogenic Stem Cell Transplantation with Post-Transplant Cyclophosphamide in Acute Myeloid Leukemia with Measurable Residual Disease. Alloreactivity vs. disease kinetics. *Overlap with LK21-01.*
p. **PROP 2310-228** Post-transplant Cyclophosphamide vs Abatacept for GVHD prophylaxis in Mismatched Unrelated Donor Transplant. *Insufficient sample size.*
q. **PROP 2310-239** Dose optimization for post-transplantation cyclophosphamide as GVHD prophylaxis after allogeneic hematopoietic stem cell transplantation. *Insufficient data collection.*
r. **PROP 2310-243** Outcome of renal impairment on outcomes after post-transplantation cyclophosphamide as GVHD prophylaxis. *Insufficient data collection.*
s. **PROP 2310-260** Outcomes for Haploidentical Transplantation with First and Second Degree Relatives. *Insufficient sample size.*
t. **PROP 2310-32** Impact of graft-versus-host disease on salvage treatment selection and outcomes of patients with myeloid neoplasms relapsing following allogeneic HCT. *Insufficient data collection.*
u. **PROP 2310-63** Risk of Relapse for Pediatric Patients with Hematologic Malignancies Undergoing Allogeneic Hematopoietic Cell Transplantation with Post-Transplant Cyclophosphamide as GvHD Prophylaxis vs Other GvHD Prophylaxis Regimens. *Dropped by PI.*
v. **PROP 2310-96** Outcomes in Pediatric Patients with Hematologic Malignancies Undergoing Allogeneic Hematopoietic Cell Transplantation with Post-Transplant Cyclophosphamide Based GVHD Prophylaxis vs Other GVHD Prophylaxis Regimens. *Insufficient sample size.*

6. Other Business/Questions

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Thursday, February 16, 2023, 12:45 - 2:15 PM

Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute; Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
Co-Chair:	**Margaret MacMillan, MD, MSc; University of Minnesota, Minneapolis, MN; Telephone: 612-626-2961, E-mail: macmi002@umn.edu**
Co-Chair:	**Carrie Kitko, MD; Vanderbilt University Medical Center; Telephone: 615-936-2088, E-mail: carrie.l.kitko@vumc.org**
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8334; E-mail: sspellma@nmdp.org**
Scientific Director:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Center Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org**
Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4339; E-mail: taowang@mcw.edu**
Statistician:	**TBD**

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1. Introduction

The CIBMTR Working Committee for Graft-Versus-Host Disease met on Thursday, February 16th, 2023 at 12:45 PM. Dr. MacMillan welcomed the attendees and introduced the working committee leadership. Dr. Pidala was thanked for his contributions to the working committee during his acting time as a chair, and Dr. Zachariah DeFilipp was welcomed as the incoming chair. Dr. MacMillan discussed the committee's goals, expectations, and limitations, the proposal scoring process, and rules of authorship. Two exciting new opportunities were shared: (1) for early career investigators to work with CIBMTR, (2) CIBMTR's new Patient-Reported Outcomes (PRO) Protocol and data collection. Attendees were also encouraged to attend the Collaborative Session, especially as there was one proposal from the committee being presented.

2. Accrual Summary

The accrual tables were included in the meeting materials but were not reviewed in the interest of time.

3. Presentations, published or submitted papers

Updates on the committee's presentations, published or submitted papers were included in the meeting materials but were not discussed at the meeting.

a. **GV17-03** Saliba RM, Alousi AM, Pidala J, Arora M, Spellman SR, Hemmer MT, Wang T, Abboud C, Ahmed S, Antin JH, Beitinjaneh A, Buchbinder D, Byrne M, Cahn J, Choe H, Hanna R, Hematti P, Kamble RT, Kitko CL, Laughlin M, Lekakis L, MacMillan ML, Martino R, Mehta PA, Nishihori T, Patel SS, Perales M, Rangarajan HG, Ringdén O, Rosenthal J, Savani BN, Schultz KR, Seo S, Teshmia T, Van der Poel M, Verdonck LF, Weisdorf D, Wirk B, Yared JA, Schriber J, Champlin R, Ciurea S. Characteristics of Graft-versus-Host Disease (GvHD) after Post-transplant Cyclophosphamide

versus Conventional GvHD Prophylaxis. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):681-693. doi: 10.1016/j.jtct.2022.07.013.***

b. **GV18-01a** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Auletta JJ, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Gale RP, Hashem H, Hashmi S, Hematti P, Hong S, Hossain NM, Inamoto Y, Lekakis LJ, Modi D, Patel S, Sharma A, Solomon S, Couriel DR. Association of Chronic Graft-versus-Host Disease with Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Children with Hematologic Malignancy. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):712.e1-712.e8. doi: 10.1016/j.jtct.2022.07.014.***

c. **GV18-01b** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Hashmi S, Hematti P, Hossain NM, Inamoto Y, Lekakis LJ, Sharma A, Solomon S, Lee S, Couriel DR. Severity of Chronic Graft-versus-Host Disease and Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancy. ***Submitted.***

d. **GV21-01** Farhadfar N, Al-Mansour Z, Wang T, Chen K, Pidala J, MacMillan ML, Kitko CL, Spellman SR, Wingard JR, Lee SJ. Racial, Ethnic and Socioeconomic Disparity in Outcomes of Patients with Chronic Graft-Versus-Host Disease: A CIBMTR Analysis. ***Poster presentation, ASH 2022.***

4. Studies in progress

The committee did not share updates on in-progress studies, though they were referenced in the meeting materials.

a. **GV18-02** Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease (Wallis W/ Alousi AM/ Gulbis A) **Manuscript Preparation.**

b. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A) **Manuscript Preparation.**

c. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B) **Analysis.**

d. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R) **Data File Preparation.**

e. **GV21-01/GV22-03** Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z/Rashid N) **Analysis.**

f. **GV21-02** Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M) **Analysis.**

g. **GV22-01** Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (Nishitani M/ Duncan C/ Graham R/ Qayed M) **Protocol Development.**

h. **GV22-02** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (Im A/ Pavletic S) **Protocol Development.**

5. Future/proposed studies

a. **PROP 2210-62/2210-75** The Effect of Graft-Versus-Host Disease Prophylaxis on Survival after HLA-Matched Hematopoietic cell transplantation (HCT): a CIBMTR analysis (McCurdy S/ Pashna M/ Mehta R)

The proposal was presented by Dr. Rohtesh Mehta. The study hypothesizes that PTCy use will be associated with improved GRFS and less NRM compared to other GVHD prophylaxis strategies in recipients receiving reduced intensity or myeloablative conditioning regimens. Proposal feasibility analysis of CIBMTR data found N=169 patients receiving PTCy, and N=2,091 CNI+MTX, N=153 CNI+MTX+ATG in the comparator groups. The population was restricted to patients age 18 or older undergoing first alloHCT for AML, ALL or MDS, from matched related or unrelated donors from 2010-2020. The following questions and comments were addressed during the Q&A:

i. Will the study involve a sub-analysis of PM vs BM grafts? There may not be enough numbers in some of the comparator groups to detect any significance but it would be worth either adjusting for in a multivariate model or performing a sub-analysis, pending statistical input.
ii. Is the aim to assess GRFS at 1 or 2-years post-HCT? Ideally 2 as in the RIC setting GRFS at 1-year is already known.
iii. Should the study focus on MAC conditioning and PB? That may be more practice changing than results from the current proposed cohort. A recent clinical trial performing a similar investigation in RIC did not include ATG so this remains unexplored, and it is common practice to use MUD + ATG but the results are still not well-known.
iv. How will the study adjust for diverse disease risk and comorbidity index due to bias in patient selection deemed fit for PTCy use? There is no statistical analysis that can adequately account for that.

b. **PROP 2210-76** PTCy/CNI with or without MMF in HLA-matched donor HCT (Mehta R)

The proposal was presented by Dr. Rohtesh Mehta. The study hypothesizes that MMF when added to PTCy/CNI is associated with a higher risk of aGVHD than PTCy/CNI alone in HCTs using HLA-matched donors, based on single center data from MD Anderson. Proposal feasibility analysis of CIBMTR data showed N=627 receiving PTCY+MMF, N=243 PTCy w/o MMF, N=671 CNI+MMF, N=5,390 CNI w/o MMF. The following questions and comments were addressed during the Q&A:

i. In the single center study, what factors determine the use of MMF? Around 2014-15 PTCy+TAC use became standard due to a single institutional clinical trial. Then, emerging data from CTN study showed PTCY+TAC+MMF is standard.
ii. How can one differentiate GI toxicity vs GVHD due to MMF use? It is possible to differentiate MMF toxicity histologically, though the criteria were not discussed in detail.
iii. A comment was made that the timing of MMF discontinuation varies with the donor, so the later onset of GVHD could be impossible to disentangle.
iv. The timing of administration of the PTCy (+TAC) group will differ, which could cause some issues. This is why there are two other comparator groups for CNI+MMF and CNI alone (w/o PTCy).
v. How will patients that receive PTCy+TAC+sirolimus fit into these groups? Also, how will the analysis account for patients who are intended to receive a drug to day +35 but due to toxicities or cytopenias, adjustments are made? We will not have the start or stop dates of administration.
vi. In pediatrics, MMF dosing is performed (adjustment based on pharmacokinetics). This is not standard in adults, and not even in all pediatric centers. This cannot be adjusted for since the data is not captured, and would be a limitation.

c. **PROP 2210-108** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplant (Gallogly M/ Metheny L)

Dr. Molly Gallogly presented the proposal. The study aims to determine the optimal ATG dose based on conditioning intensity, donor, and graft source, as dosage and timing varies widely by

center. Study feasibility assessment of CIBMTR data found N=2,499 patients undergoing first alloHCT for AML, ALL or MDS between 2008-2019 registered to the CRF track and receiving ATG. The following questions and comments were addressed during the Q&A:

i. A concern was expressed that the timing and pharmacokinetics of ATG will be significant confounders. If the forms capture absolute lymphocyte count on the starting day of ATG this may be helpful to adjust for.
ii. The forms only capture total dose and not fractioned dosage and timing.
iii. The type of ATG is captured. Since the source differs geographically, this would be a US-based analysis.
iv. Other published research has shown AUC-based dosing patterns impact outcomes, and CIBMTR's data may not be able to provide such granularity.
v. Patient characteristics would also impact dosing and outcomes, would the study account for this by subgroup analysis or other? The goal would be to determine optimal dosing within each subgroup, but at this time it is unknown if the sample size and data will have enough power.

d. **PROP 2210-155** ATG versus PTCy for peripheral blood matched-sibling donor hematopoietic cell transplantation (Arcuri L/ Hamerschlak N)

Dr. Leonardo Arcuri presented the proposal. The study hypothesizes that GVHD outcomes will be the same between PTCy and ATG in the HLA-matched donor setting with peripheral blood and myeloablative conditioning. Study feasibility of CIBMTR data found N=5,257 patients age 18-60 undergoing first alloHCT for AML or MDS receiving ATG + CNI (N=4,131) or PTCy + CNI (N=1,126) in the HLA-matched + PB + MAC setting. The following questions and comments were addressed during the Q&A:

i. The differences in ATG dosing may have an impact on outcomes, how will this be accounted for? This is not the aim of the study; the aim is to show that any ATG use is comparable to PTCy and various doses have been effective.
ii. Regardless of the results, this may not change practice or people's minds, a randomized study may be the best or only way to change practice.
iii. Is there overlap with the first study that was presented? Why do the numbers differ? The years, diseases, donors, conditioning regimen, and other factors differ.

e. **PROP 2210-23** Post-Transplant Cyclophosphamide (PTCy) vs. Anti-Thymocyte Globulin (ATG) in Patients with Acute Leukemia (AL) and Myelodysplastic Syndrome (MDS) receiving HLA-Mismatched Unrelated Donor (MMUD) Hematopoietic Cell Transplant (HCT). A CIBMTR Analysis (Jimenez A / Shaffer B)

Dr. Antonio Jimenez Jimenez presented the proposal. The main objective of the study is to assess if the use of PTCy in MMUD transplants would improve outcomes compared to the current standard with ATG. Study feasibility of CIBMTR data found N=620 ATG and N=164 PTCy among recipients age 18+ of first alloHCT for AML, ALL or MDS with a MMUD from 2010-2020. The following questions and comments were addressed during the Q&A:

i. Will the study look at the impact of individual allele mismatch? This is a great question, though the numbers in the PTCy arm are likely too small.
ii. The PTCy arm is the same as the population of the ACCESS trial, which is a prospective trial and is still accruing. Although this study would include a comparison of PTCy vs ATG, will the study be a duplicate? There is some overlap with other studies, but if patients up to 2020 are included this would provide an advantage. This question also remains a high priority in racial and ethnic minorities.
iii. The feasibility tables show ATG is more common before 2015 and PTCy more common after. Even after adjusting for the year of transplant, is this a fair comparison? In Dr.

Jimenez's single-center experience, this analysis has been done and the advantages of PTCy persisted after these and other factors, such as for toxicity management.

iv. How will the study adjust for the graft source imbalance between the two groups? The statisticians will help inform this adjustment.

f. **PROP 2210-203** Allogeneic stem cell transplant (Allo- SCT) in patients older than 70 years using posttransplant cyclophosphamide (PTCy) based Graft versus Host disease (GVHD) prophylaxis: An analysis from the CIBMTR database (Nath R/ Zhou Z)

Dr. Rajneesh Nath presented the proposal. The study aims to determine how frequently alloHCTs occur in patients over age 70 using PTCy-based GVHD prophylaxis, describe the baseline characteristics, and investigate outcomes. Study feasibility of CIBMTR data showed N=439 patients meeting the selection criteria between 2008-2020 and registered to the CRF track. The study also proposes a potential comparison to an aged 60-70 cohort. The following questions and comments were addressed during the Q&A:

i. A suggestion to investigate what regimens are defined as myeloablative in this age group.

ii. Is it worth waiting to complete this study in 1-2 years because of a recent BMT CTN presentation on PTCy use? There would be more patients at that time, but it is an urgent question due to the intensity of Cytoxan. The population also differs as it allows MAC and includes broader donor types.

iii. A suggestion that a comparison aspect of the study would be helpful to know the organ toxicity prevalence.

iv. Should relapse be analyzed as separate endpoint instead of the proposed composite GRFS, because there is concern PTCy is associated with long term relapse. Relapse could be included as a secondary outcome.

v. Is PTCy dose collected? It was added to the F2100 within the last couple of years.

vi. A suggestion to consult with the protocol team of BMT CTN 1703.

vii. The oldest patient in the feasibility tables was 88. Would it be worth comparing 70-79 vs 80+? The sample size is likely too small.

6. Dropped proposed studies

g. **PROP 2209-17** GvHD prediction using machine learning. *Overlap with CIBMTR study GV20-01; insufficient detail about methods.*

h. **PROP 2210-07** Does early phase grade 1-2 mild or moderate skin GVHD have a benefit on OS and DFS after ASCT? *Unclear comparator group; lower scientific impact relative to other proposals.*

i. **PROP 2210-54** Impact of the additional immunosuppressant option on graft versus host disease and outcomes in patients who receive post-transplant cyclophosphamide for graft versus host disease prophylaxis. *Heterogeneous population; lower scientific impact relative to other proposals.*

j. **PROP 2210-127** Outcomes of Patients with Acute Myeloid Leukemia (AML) and Measurable Residual Disease (MRD) Undergoing Allogeneic Transplantation using Post-Transplant Cyclophosphamide versus Conventional Graft-versus-Host Disease (GvHD) Prophylaxis. *Limited MRD data availability; heterogeneous population.*

k. **PROP 2210-158** Effect of chronic graft-versus-host disease treatment on primary disease relapse. *Heterogeneous population; chronic GVHD severity correlated with type and number of treatments used.*

l. **PROP 2210-294** Optimal duration of ruxolitinib after acute and chronic GVHD: real world practices after 2020. *Duration of ruxolitinib influenced by many factors; lower scientific impact relative to other proposals.*

7. Concluding Notes

a. The meeting adjourned at about 2:15 PM.

b. *After the new proposals were presented, each participant in the meeting had an opportunity to score each proposal electronically using the Tandem app or website. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following proposal was accepted to move forward to be added to the committee's active studies:*

PROP 2210-62/75/76/203 The effect of calcineurin inhibitor vs post transplant cyclophosphamide (with or without mycophenolate mofetil) based graft-vs-host disease prophylaxis on HLA matched hematopoietic cell transplantation. *After the meeting the working committee leadership combined these proposals, and they were accepted as one study.*

PROP 2209-15 Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts. *This study was presented at the Collaborative Working Committee Session but accepted as a study within the Graft-versus-Host Disease Working Committee.*

Working Committee Overview Plan for 2023-2024		
Study Number and Title	**Current Status**	**Priority**
GV18-02 Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease	Manuscript Preparation	**1**
GV19-01 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Manuscript Preparation	**1**
GV20-01 Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants	Analysis	**2**
GV20-02 Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq	Data File Preparation	**2**
GV21-01/GV22-03 Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease	Analysis	**2**
GV21-02 Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study	Analysis	**1**
GV22-01 Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation	Protocol Development	**3**
GV22-02 Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation	Protocol Development	**3**
GV23-01 The effect of calcineurin inhibitor vs post transplant cyclophosphamide (with or without mycophenolate mofetil) based graft-vs-host disease prophylaxis on HLA matched hematopoietic cell transplantation	Protocol Pending	**3**
GV23-02 Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts	Protocol Pending	**3**

Table 1. Characteristics of leukemia patients receiving alloHCT between 2008-2023

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
No. of patients	37509	15432	3674	62920	8276
No. of centers	427	329	349	395	287
Age at transplant, years, median (range) - median (min-max)	50.5 (0.3-99.7)	51.4 (0.2-87.8)	47.9 (0.4-78.6)	56.1 (0.4-83.5)	31.6 (0.3-84.8)
Disease - no. (%)					
AML	18371 (49.0)	7646 (49.5)	1805 (49.1)	30987 (49.2)	4128 (49.9)
ALL	8961 (23.9)	3855 (25.0)	950 (25.9)	11259 (17.9)	2624 (31.7)
Other leukemia	2037 (5.4)	651 (4.2)	164 (4.5)	3235 (5.1)	380 (4.6)
MDS	6248 (16.7)	2646 (17.1)	604 (16.4)	13668 (21.7)	1055 (12.7)
MPN	1892 (5.0)	634 (4.1)	151 (4.1)	3771 (6.0)	89 (1.1)
Sex - no. (%)					
Male	21419 (57.1)	9264 (60.0)	2133 (58.1)	36181 (57.5)	4514 (54.5)
Female	16090 (42.9)	6168 (40.0)	1541 (41.9)	26739 (42.5)	3762 (45.5)
Graft source - no. (%)					
BM	6423 (17.1)	3693 (23.9)	817 (22.2)	9998 (15.9)	0 (0.0)
PBSC	30951 (82.5)	11652 (75.5)	2817 (76.7)	52839 (84.0)	0 (0.0)
Missing	135 (0.4)	87 (0.6)	40 (1.1)	83 (0.1)	8276 (100)
GVHD prophylaxis - no. (%)					
Ex-vivo T-cell depletion	284 (0.8)	699 (4.5)	88 (2.4)	543 (0.9)	54 (0.7)
CD34 selection	353 (0.9)	316 (2.0)	68 (1.9)	699 (1.1)	525 (6.3)
Post-tx Cyclophosphamide +/- others	2620 (7.0)	12699 (82.3)	1313 (35.7)	8535 (13.6)	36 (0.4)
Tac + MTX	12233 (32.6)	172 (1.1)	599 (16.3)	22556 (35.8)	199 (2.4)
Tac + MTX + others	1036 (2.8)	13 (0.1)	89 (2.4)	3640 (5.8)	48 (0.6)
Tac + MMF	2169 (5.8)	641 (4.2)	177 (4.8)	4154 (6.6)	1960 (23.7)
Tac + MMF + others	126 (0.3)	111 (0.7)	17 (0.5)	615 (1.0)	169 (2.0)
Tac	853 (2.3)	79 (0.5)	63 (1.7)	1338 (2.1)	154 (1.9)
Tac + others	2001 (5.3)	16 (0.1)	64 (1.7)	3167 (5.0)	177 (2.1)
CsA + MTX	9951 (26.5)	306 (2.0)	561 (15.3)	9199 (14.6)	126 (1.5)
CsA + MTX + others	230 (0.6)	21 (0.1)	31 (0.8)	358 (0.6)	21 (0.3)
CsA + MMF	2668 (7.1)	85 (0.6)	186 (5.1)	3518 (5.6)	3329 (40.2)
CsA + MMF + others	76 (0.2)	6 (0.0)	16 (0.4)	820 (1.3)	473 (5.7)
CsA	1891 (5.0)	40 (0.3)	120 (3.3)	2211 (3.5)	666 (8.0)
CsA + others	52 (0.1)	1 (0.0)	2 (0.1)	59 (0.1)	98 (1.2)

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
Others	651 (1.7)	80 (0.5)	92 (2.5)	1065 (1.7)	201 (2.4)
Missing	315 (0.8)	147 (1.0)	188 (5.1)	443 (0.7)	40 (0.5)
Conditioning regimen intensity - no. (%)					
Myeloablative	24653 (65.7)	7745 (50.2)	2229 (60.7)	34428 (54.7)	6014 (72.7)
Reduced intensity	10226 (27.3)	3388 (22.0)	882 (24.0)	23426 (37.2)	1102 (13.3)
Non-myeloablative	2226 (5.9)	4183 (27.1)	521 (14.2)	4459 (7.1)	1136 (13.7)
Missing	404 (1.1)	116 (0.8)	42 (1.1)	607 (1.0)	24 (0.3)
Acute GVHD grade - no. (%)					
None	17275 (46.1)	6505 (42.2)	1638 (44.6)	23044 (36.6)	3130 (37.8)
Grade I	1880 (5.0)	1873 (12.1)	268 (7.3)	5048 (8.0)	748 (9.0)
Grade II	2416 (6.4)	2296 (14.9)	292 (7.9)	7082 (11.3)	1382 (16.7)
Grade III	1221 (3.3)	737 (4.8)	129 (3.5)	2525 (4.0)	670 (8.1)
Grade IV	507 (1.4)	285 (1.8)	62 (1.7)	1429 (2.3)	301 (3.6)
Not reported	14210 (37.9)	3736 (24.2)	1285 (35.0)	23792 (37.8)	2045 (24.7)
aGVHD organ involvement - no.					
Skin +/- others - no.	1098	684	175	3473	989
Liver +/- others - no.	546	183	77	1104	326
UGI +/- others - no.	834	404	101	2209	624
LGI +/- others - no.	1055	535	157	2694	875
Incidence of cGVHD - no. (%)					
No	18457 (49.2)	10095 (65.4)	2067 (56.3)	32572 (51.8)	5703 (68.9)
Yes	14236 (38.0)	3728 (24.2)	1008 (27.4)	22315 (35.5)	1954 (23.6)
Missing	4816 (12.8)	1609 (10.4)	599 (16.3)	8033 (12.8)	619 (7.5)
cGVHD organ involvement - no.					
Skin +/- others - no.	748	185	76	1544	133
Liver +/- others - no.	1309	259	136	2036	1623
Eyes +/- others - no.	1377	356	151	2846	228
GI tract +/- others – no.	772	224	91	1842	452
Joints and fascia +/- others - no.	84	26	10	179	18
Lungs +/- others - no.	345	107	39	647	61
Genital tract +/- others - no.	238	46	18	396	27
Mouth +/- others - no.	1711	419	186	3223	304
N/A, TED track patient - no.	11410	2696	358	16463	810

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
Missing	22	11	3	39	11
Maximum grade of cGVHD - no. (%)					
Limited	2652 (18.6)	999 (26.8)	252 (25.0)	3927 (17.6)	719 (36.8)
Extensive	11564 (81.2)	2721 (73.0)	755 (74.9)	18355 (82.3)	1219 (62.4)
Missing	20 (0.1)	8 (0.2)	1 (0.1)	33 (0.1)	16 (0.8)
Overall severity of cGVHD – no. (%)					
Mild	3457 (24.3)	1584 (42.5)	304 (30.2)	6477 (29.0)	929 (47.5)
Moderate	3433 (24.1)	1101 (29.5)	247 (24.5)	5821 (26.1)	408 (20.9)
Severe	2777 (19.5)	600 (16.1)	185 (18.4)	4304 (19.3)	218 (11.2)
Missing	4569 (32.1)	443 (11.9)	272 (27.0)	5713 (25.6)	399 (20.4)
Year of transplant – no. (%)					
2008-2009	5295 (14.1)	361 (2.3)	406 (11.1)	5912 (9.4)	1343 (16.2)
2010-2011	5415 (14.4)	512 (3.3)	358 (9.7)	7026 (11.2)	1481 (17.9)
2012-2013	5269 (14.0)	728 (4.7)	430 (11.7)	7912 (12.6)	1384 (16.7)
2014-2015	5058 (13.5)	1178 (7.6)	490 (13.3)	7909 (12.6)	1206 (14.6)
2016-2017	4909 (13.1)	2149 (13.9)	760 (20.7)	8146 (12.9)	995 (12.0)
2018-2019	4403 (11.7)	2982 (19.3)	694 (18.9)	8668 (13.8)	816 (9.9)
2020-2022	5752 (15.3)	5899 (38.2)	417 (11.4)	13191 (21.0)	875 (10.6)
2022-2023	1408 (3.8)	1623 (10.5)	119 (3.2)	4156 (6.6)	176 (2.1)
Follow-up of survivors, months, median (range) – median (range)	49.4 (0.0-10861.4)	25.4 (0.0-171.0)	48.1 (0.0-178.9)	46.7 (0.0-2199.5)	63.3 (0.0-176.2)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, MDS=Myelodysplastic diseases, MPN=Myeloproliferative diseases, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Table 2. Characteristics of non-leukemia patients receiving alloHCT between 2008-2022

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
No. of patients	17612	5782	2690	16867	3714
No. of centers	415	305	326	368	235
Age at transplant, years, median (range) – median (min-max)	25.6 (0.0-78.6)	25.7 (0.0-79.7)	18.9 (0.0-78.8)	37.4 (0.1-84.1)	5.2 (0.1-99.9)
Disease – no. (%)					
NHL	4868 (27.6)	1785 (30.9)	565 (21.0)	6430 (38.1)	689 (18.6)
HD	1031 (5.9)	670 (11.6)	165 (6.1)	1246 (7.4)	156 (4.2)
SAA	3565 (20.2)	941 (16.3)	378 (14.1)	2808 (16.6)	190 (5.1)
MM-PCD	1466 (8.3)	263 (4.5)	349 (13.0)	1559 (9.2)	83 (2.2)
Inherited abnormalities of erythrocyte diff-or function	6 (0.0)	0 (0.0)	3 (0.1)	3 (0.0)	0 (0.0)
SCID & other immune system disorders	1033 (5.9)	619 (10.7)	371 (13.8)	1689 (10.0)	779 (21.0)
Inherited abnormality of platelets	58 (0.3)	9 (0.2)	2 (0.1)	65 (0.4)	44 (1.2)
Histiocytic disorders	317 (1.8)	172 (3.0)	75 (2.8)	634 (3.8)	244 (6.6)
Inherited disorders of metabolism	205 (1.2)	107 (1.9)	41 (1.5)	358 (2.1)	797 (21.5)
Others	5063 (28.7)	1216 (21.0)	741 (27.5)	2075 (12.3)	732 (19.7)
Sex – no. (%)					
Male	10580 (60.1)	3573 (61.8)	1573 (58.5)	10433 (61.9)	2260 (60.9)
Female	7032 (39.9)	2209 (38.2)	1117 (41.5)	6434 (38.1)	1454 (39.1)
GVHD prophylaxis – no. (%)					
Ex-vivo T-cell depletion	68 (0.4)	344 (5.9)	56 (2.1)	338 (2.0)	14 (0.4)
CD34 selection	181 (1.0)	227 (3.9)	63 (2.3)	428 (2.5)	112 (3.0)
Post-tx Cyclophosphamide +/- others	1008 (5.7)	4425 (76.5)	522 (19.4)	1489 (8.8)	19 (0.5)
Tac + MTX	3293 (18.7)	16 (0.3)	194 (7.2)	4305 (25.5)	103 (2.8)
Tac + MTX + others	542 (3.1)	5 (0.1)	52 (1.9)	937 (5.6)	20 (0.5)
Tac + MMF	1225 (7.0)	260 (4.5)	97 (3.6)	1320 (7.8)	726 (19.5)
Tac + MMF + others	76 (0.4)	73 (1.3)	15 (0.6)	175 (1.0)	76 (2.0)
Tac	355 (2.0)	31 (0.5)	39 (1.4)	508 (3.0)	128 (3.4)
Tac + others	493 (2.8)	14 (0.2)	22 (0.8)	626 (3.7)	72 (1.9)
CsA + MTX	5573 (31.6)	60 (1.0)	604 (22.5)	2801 (16.6)	167 (4.5)

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
CsA + MTX + others	336 (1.9)	3 (0.1)	35 (1.3)	181 (1.1)	17 (0.5)
CsA + MMF	1632 (9.3)	83 (1.4)	176 (6.5)	1824 (10.8)	1272 (34.2)
CsA + MMF + others	56 (0.3)	12 (0.2)	12 (0.4)	199 (1.2)	172 (4.6)
CsA	1443 (8.2)	34 (0.6)	162 (6.0)	1024 (6.1)	618 (16.6)
CsA + others	145 (0.8)	4 (0.1)	17 (0.6)	78 (0.5)	69 (1.9)
Others	877 (5.0)	108 (1.9)	208 (7.7)	484 (2.9)	104 (2.8)
Missing	309 (1.8)	83 (1.4)	416 (15.5)	150 (0.9)	25 (0.7)
Graft source – no. (%)					
BM	8052 (45.7)	2648 (45.8)	1188 (44.2)	6104 (36.2)	0 (0.0)
PBSC	9533 (54.1)	3118 (53.9)	1490 (55.4)	10751 (63.7)	0 (0.0)
Missing	27 (0.2)	16 (0.3)	12 (0.4)	12 (0.1)	3714 (100)
Conditioning regimen intensity – no. (%)					
Myeloablative	7615 (43.2)	1820 (31.5)	1282 (47.7)	5726 (33.9)	2331 (62.8)
Reduced intensity	4794 (27.2)	1370 (23.7)	616 (22.9)	5918 (35.1)	553 (14.9)
Non-myeloablative	3821 (21.7)	2375 (41.1)	556 (20.7)	4128 (24.5)	634 (17.1)
Missing	1382 (7.8)	217 (3.8)	236 (8.8)	1095 (6.5)	196 (5.3)
Acute GVHD grade – no. (%)					
None	10657 (60.5)	2981 (51.6)	1565 (58.2)	7556 (44.8)	1871 (50.4)
Grade I	607 (3.4)	485 (8.4)	140 (5.2)	987 (5.9)	342 (9.2)
Grade II	645 (3.7)	596 (10.3)	163 (6.1)	1248 (7.4)	418 (11.3)
Grade III	319 (1.8)	237 (4.1)	95 (3.5)	494 (2.9)	197 (5.3)
Grade IV	176 (1.0)	130 (2.2)	45 (1.7)	278 (1.6)	110 (3.0)
Not reported	5208 (29.6)	1353 (23.4)	682 (25.4)	6304 (37.4)	776 (20.9)
aGVHD organ involvement - no.					
Skin +/- others – no.	348	256	151	770	385
Liver +/- others - no.	175	84	74	216	83
UGI +/- others - no.	226	120	71	387	149
LGI +/- others - no.	404	216	143	602	311
Incidence of cGVHD - no. (%)					
No	11181 (63.5)	4112 (71.1)	1872 (69.6)	9767 (57.9)	2716 (73.1)
Yes	4295 (24.4)	1107 (19.1)	471 (17.5)	5121 (30.4)	759 (20.4)
Missing	2136 (12.1)	563 (9.7)	347 (12.9)	1979 (11.7)	239 (6.4)

Characteristic	HLA-identical sibling	Haploidentical	Other related	Unrelated donor	Cord blood
cGVHD organ involvement - no.					
Skin +/- others - no.	748	185	76	1544	133
Liver +/- others - no.	1309	259	136	2036	1623
Eyes +/- others - no.	1377	356	151	2846	228
GI tract +/- others – no.	772	224	91	1842	452
Joints and fascia +/- others - no.	84	26	10	179	18
Lungs +/- others - no.	345	107	39	647	61
Genital tract +/- others - no.	238	46	18	396	27
Mouth +/- others - no.	1711	419	186	3223	304
N/A, TED track patient	3449	729	257	3797	298
Missing	17	1	2	15	6
Maximum grade of cGVHD - no. (%)					
Limited	1075 (25.0)	348 (31.4)	151 (32.1)	1227 (24.0)	361 (47.6)
Extensive	3206 (74.6)	752 (67.9)	316 (67.1)	3873 (75.6)	393 (51.8)
Missing	14 (0.3)	7 (0.6)	4 (0.8)	21 (0.4)	5 (0.7)
Overall severity of cGVHD - no. (%)					
Mild	1046 (24.4)	478 (43.2)	158 (33.5)	1432 (28.0)	359 (47.3)
Moderate	824 (19.2)	296 (26.7)	103 (21.9)	1074 (21.0)	150 (19.8)
Severe	605 (14.1)	167 (15.1)	85 (18.0)	841 (16.4)	88 (11.6)
Missing	1820 (42.4)	166 (15.0)	125 (26.5)	1774 (34.6)	162 (21.3)
Year of transplant - no. (%)					
2008-2009	2601 (14.8)	189 (3.3)	414 (15.4)	2011 (11.9)	649 (17.5)
2010-2011	2636 (15.0)	230 (4.0)	340 (12.6)	2304 (13.7)	683 (18.4)
2012-2013	2398 (13.6)	344 (5.9)	302 (11.2)	2550 (15.1)	675 (18.2)
2014-2015	2183 (12.4)	518 (9.0)	390 (14.5)	2367 (14.0)	524 (14.1)
2016-2017	2117 (12.0)	827 (14.3)	390 (14.5)	2154 (12.8)	441 (11.9)
2018-2019	2047 (11.6)	1082 (18.7)	402 (14.9)	1952 (11.6)	297 (8.0)
2020-2022	2771 (15.7)	2045 (35.4)	333 (12.4)	2723 (16.1)	368 (9.9)
2022-2023	859 (4.9)	547 (9.5)	119 (4.4)	806 (4.8)	77 (2.1)

Abbreviations: NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, SAA=Severe aplastic anemia, MM=Multiple myeloma, SCID=Severe combined immunodeficiency, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

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TO: Graft-Versus-Host Disease Working Committee Members

FROM: Stephanie Lee, MD, MPH and Stephen Spellman, MBS; Scientific Directors for GVWC

RE: Studies in Progress Summary

GV20-01: Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B)
This study aims to develop a machine learning model to predict the risk of developing acute and chronic GVHD in adult AML patients based on patient, disease and transplant-specific factors. The end goal is to create a tool that will provide information to both physician and patient to support clinical decision-making regarding transplant. The initial statistician conducting analysis dropped from the study. A new statistician was found in November 2023 and analysis is ongoing.

GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R)
This study aims to evaluate the performance of a risk score derived from the MHC-PepSeq assay in predicting the development of acute and chronic GVHD in recipients of allogeneic HCT from either an 8/8 matched donor with mismatch in HLA-DP or a 7/8 mismatched donor. This study was presented as ASH 2023, manuscript preparation will continue afterwards.

GV21-02: Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M)
This study aims to develop and validate prediction models for immune suppression discontinuation and immune suppression discontinuation failure in patients who received allogeneic HCT for hematologic malignancies. The protocol was reviewed at the CIBMTR Statistical Meeting in January 2022. Additional work was completed over summer/fall 2023 to check for BMT CTN study population overlap and add new GVHD outcome variables. A data request was sent to centers regarding immunosuppression data relating to GVHD prophylaxis for patients that did not develop GVHD. Analysis is on hold until this data is received.

GV22-01: Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (Nishitani M/ Duncan C/ Graham R/ Qayed M)
This study aims to compare the incidence and severity of acute and chronic GVHD in children and young adults following HCT between 2002-2011 and 2012-2021 and to evaluate the impact of transplant related factors on GVHD risk. An abstract was submitted to Tandem for presentation. Manuscript preparation is ongoing.

GV22-02: Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (Im A/ Pavletic S)
This study aims to develop and validate a risk score based on weighted clinical factors to predict the likelihood of developing moderate-severe chronic GVHD. Datafile preparation began in fall 2023 and is ongoing.

GV23-01: The effect of CNI- vs. PTCy- (with or without MMF) based GVHD prophylaxis on HLA-matched HCT (Mehta R/ Munshi P/ Nath R/ Zhou Z/ Mccurdy S)
This study aims to determine whether post-transplant cyclophosphamide is superior to CNI/methotrexate as GVHD prophylaxis for HLA-matched related and unrelated donor transplantation. Important subset analyses will also evaluate the potential importance of conditioning intensity, donor type and recipient age, and whether MMF is included in the prophylaxis regimen. Several proposals were combined in this study. Protocol development ongoing, awaiting statistician assignment.

GV23-02: Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts (Maurer K)
This study aims to determine whether cryopreservation of unrelated donor grafts is associated with a lower incidence of chronic GVHD compared to fresh products. Protocol development ongoing, awaiting statistician assignment.

Field	Response
Proposal Number	2310-175-TURKI
Proposal Title	Independent validation of a data-driven grading system for acute GVHD in HCT patients receiving post-transplant cyclophosphamide (PTCy).
Key Words	Hematopoietic cell transplantation, GVHD classification, aGVHD, non-relapse mortality, Artificial Intelligence, AI, Principal Component analysis, unsupervised learning, Hierarchical clustering, Partitional clustering, dimensionality reduction, UMAP, t-SNE.
Principal Investigator #1: - First and last name, degree(s)	Amin T. Turki, MD PhD
Principal Investigator #1: - Email address	amin.turki@uk-essen.de
Principal Investigator #1: - Institution name	University Hospital Bochum, Germany
Principal Investigator #1: - Academic rank	Faculty member, Junior group leader
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Member of working committee. Feedback provided on past proposals (e.g. IN19-01)
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Graft vs Host Disease
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Acute graft-versus-host disease (aGVHD) remains the leading complication after HCT, yet with heterogeneous outcomes, even within the same severity grades. The heterogeneity of phenotypes faces limitations in conventional grading and data-driven approaches have only recently been explored.
RESEARCH HYPOTHESIS:	We hypothesize that data-driven grading systems for acute GVHD developed using unsupervised learning approaches may refine grading beyond 4 grades to complement conventional grading in clinical practice and support our understanding of aGVHD with respect to organ involvement, clinical outcome and risk cohorts in the PTCy setting.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	The objective of this study is to test, whether data-driven grading systems for acute GVHD developed using unsupervised learning approaches (Bayraktar et al. Nature Communications, accepted) can be validly applied in the post-transplant cyclophosphamide (PTCy) setting. Conventional and data-driven grading systems will be extensively compated using performance metrics, such as the Akaike information criterion and concordance index as well as for their association with clinical outcomes, e.g. non-relapse mortality (NRM). i. Primary objective • Non Relapse Mortality (NRM) at 12 Months from HCT, stratified according to the data-driven aGVHD grading system and compared to conventional grading systems (e.g. MAGIC) ii. Secondary objective (s) • Overall survival (OS) at 12 months from HCT • Non Relapse Mortality (NRM) at 24 Months from HCT • Incidence of chronic GVHD in this population depending on aGVHD phenotypes
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Standardized, correct and validated aGVHD grading is crucial for clinical practice, for the design of prospective trials evaluating the efficacy of aGVHD treatments with respect to NRM, as well as for retrospective cohort studies. However, heterogeneity in outcomes and in the distribution of aGVHD phenotypes remain within the conventional aGVHD grading systems. Data-driven grading covering 12 distinct aGVHD severity grades responds to some of these issues (Bayraktar et al. Nature Communications, accepted October 3rd 2023). The validation of this data-driven grading approach would allow to leverage this technique in the PTCy setting. Given the rapidly increasing use of PTCy platform, we think that testing the validity of the different existing aGVHD classification approaches within this prophylaxis is important to the HCT community.

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.	Acute graft-versus-host disease (aGVHD) remains the major cause of substantial morbidity and non-relapse mortality (NRM) after allogeneic hematopoietic stem cell transplantation (HCT).2 Its grading, based on staging categories for 3 primarily affected organs (skin, liver, intestine) has been first introduced by Glucksberg et al. in 1974 3 and revised during the Keystone consensus conference (also named modified Glucksberg criteria) in 1994.4 The consensus grading- (Grades I-IV)4 and the International Blood and Marrow Transplant Registry (IBMTR) grading system (Grades A-D)5 have been prospectively validated in a multicenter study and were considered to be equally performing.6 The Mount Sinai aGVHD international consortium (MAGIC) has undertaken a major effort to reframe aGVHD grading10 and revised in particular the criteria for grade IV aGVHD. Despite these efforts of standardization in HCT, insufficiencies and inconsistencies of current aGVHD diagnosis and grading practices have been previously discussed by several groups. 7-10 Today, multiorgan involvement and resistance to treatment remain the major issues in the care for patients with aGVHD. Most recently we were able to develop and validate a data-driven grading system for aGVHD (Bayraktar et al. Nature Communications, accepted, October 3rd 2023) in a multicenter cohort of German patients receiving HCT with ciclosporin-based GVHD prophylaxis and ATG. Using this data-driven classification approach, the model interpreted clinical aGVHD organ involvements differently from conventional gradings and revealed its potential to complement current grading practice, in particular for multiorgan involvement. The basis for this approach is the clinical assessment of the organ involvement of the three aGVHD target organs, skin, GI and liver. These organ involvements covering 125 possible aGVHD phenotypes were plotted in a multidimensional space and dimensionality reduction was applied using principal component analysis. A derivate of the first principal component (PC1) was transformed into a linear severity score with 12 grades. In particular for multiorgan involvement, data driven grading may refine grading beyond 4 grades, which opens possibilities for differential treatment trials depending on the phenotypes. In principle, the data-driven grading should be equally valid in the PTCy setting, as this is the case for conventional grading systems. However, this has yet to be proven by this study. The same is true for the previously observed association of impaired clinical outcome with increasing severity grades, which might be different in patients receiving PTCy. Given the increasing use of the PTCy-based GVHD prophylaxis, the advantages of the

Field	Response
	data-driven grading platform could benefit this growing patient population as it provides an expandable platform for transplant risk assessment.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_1Nn9vl3XPgFVFjY
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	CIBMTR2.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	173145
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria • HCT between 2015 and 2022 • Adult patients (above 18 years) • GVHD prophylaxis using PTCy with Tac/MMF • Haplo and MUD HCT (additional subgroup analysis of each, haplo and MUD PTCy) • Diagnosis of aGVHD • Documented organ staging of at least skin, liver and GI Exclusion criteria -Missing data on GVHD organ staging (skin, liver, intestine) - Other immunosuppressive regimens than PTCy based immunosuppression (e.g. ATG, ex-vivo T cell depletion, ciclosporin)
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Excluding pediatric patients can increase the homogeneity of the PTCy cohort but is not mandatory for this study.
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient: age, sex, comorbidities, Karnofsky, CMV, ABO blood type Donor: age, sex, graft source, relationship to recipient, degree of HLA mismatch, CMV, ABO blood type Disease: Diagnosis, if available information for computation of the Disease Risk Index (disease, disease status at transplantation, cytogenetics when indication), time from diagnosis to transplantations, previous transplantation Transplantation: conditioning intensity, GVHD prophylaxis, center experience Outcomes: OS, NRM, EFS, RI, acute GVHD organ stages for each organ (at least skin, liver, intestine. If available also upper GI and lower GI) and reported overall acute and chronic GVHD grades
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 desc	Not applicable.
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	Yes, but the resulting grading system can be easily applied for validation purpose.

Field	Response
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 o	Not applicable.
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.	Not applicable.

Field	Response
REFERENCES:	2. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic cell transplantation. The New England journal of medicine. 2010;363(22):2091-2101. 3. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18(4):295-304. 4. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828. 5. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol. 1997;97(4):855-864. 6. Cahn J-Y, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Société Française de Greffe de Moëlle et Thérapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. Blood. 2005;106(4):1495-1500. 7. Atkinson K, Horowitz MM, Biggs JC, Gale RP, Rimm AA, Bortin MM. The clinical diagnosis of acute graft-versus-host disease: a diversity of views amongst marrow transplant centers. Bone Marrow Transplant. 1988;3(1):5-10. 8.Martin P, Nash R, Sanders J, et al. Reproducibility in retrospective grading of acute graft-versus-host disease after allogeneic marrow transplantation. Bone Marrow Transplant. 1998;21(3):273-279. 9. Wolff D, Ayuk F, Elmaagacli A, et al. Current Practice in Diagnosis and Treatment of Acute Graft-versus-Host Disease: Results from a Survey among German-Austrian-Swiss Hematopoietic Stem Cell Transplant Centers. Biology of Blood and Marrow Transplantation. 2013;19(5):767-776. 10. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016;22(1):4-10. 11. MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(4):761-767. Unpublished, but accepted for publication: Bayraktar E et al., Data-driven grading of acute graft-versus-host disease, Nature Communications, accepted as Research Article on October 3rd 2023

Field	Response
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	Yes, I have conflicts of interest pertinent to this proposal
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.	Employment: University Hospital Bochum, University Hospital Essen. Consultancy: Maat Pharma, CSL Behring, Biomarin and Onkowissen.

Table 1. Characteristics of patients undergoing a 1st allo HCT for any hematological malignancy with PTCy/TAC-based or PTCy/MMF-based GVHD prophylaxis, 2015-2022

Characteristic	Grade I	Grade II	Grade III	Grade IV	Total
No. of patients	1921	2222	645	245	5033
No. of centers	182	181	150	95	215
Age group - no. (%)					
Median (min-max)	58.1 (18.0-80.8)	56.7 (18.0-82.2)	58.2 (18.1-77.4)	56.5 (18.5-77.0)	57.5 (18.0-82.2)
10-20	26 (1.4)	40 (1.8)	12 (1.9)	6 (2.4)	84 (1.7)
20-30	201 (10.5)	253 (11.4)	66 (10.2)	31 (12.7)	551 (10.9)
30-40	192 (10.0)	234 (10.5)	71 (11.0)	32 (13.1)	529 (10.5)
40-50	243 (12.6)	306 (13.8)	63 (9.8)	24 (9.8)	636 (12.6)
50-60	395 (20.6)	453 (20.4)	142 (22.0)	57 (23.3)	1047 (20.8)
60-70	639 (33.3)	684 (30.8)	218 (33.8)	72 (29.4)	1613 (32.0)
70-80	224 (11.7)	251 (11.3)	73 (11.3)	23 (9.4)	571 (11.3)
80-90	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
TED or RES track - no. (%)					
Ted (registration) patient	1376 (71.6)	1546 (69.6)	412 (63.9)	148 (60.4)	3482 (69.2)
Research patient	545 (28.4)	676 (30.4)	233 (36.1)	97 (39.6)	1551 (30.8)
CCN region at transplant - no. (%)					
US	1694 (88.2)	1933 (87.0)	535 (82.9)	194 (79.2)	4356 (86.5)
Canada	33 (1.7)	61 (2.7)	5 (0.8)	4 (1.6)	103 (2.0)
Europe	34 (1.8)	22 (1.0)	16 (2.5)	6 (2.4)	78 (1.5)
Asia	17 (0.9)	28 (1.3)	16 (2.5)	12 (4.9)	73 (1.5)
Australia/New Zealand	54 (2.8)	46 (2.1)	19 (2.9)	7 (2.9)	126 (2.5)
Mideast/Africa	8 (0.4)	10 (0.5)	7 (1.1)	6 (2.4)	31 (0.6)
Central/South America	81 (4.2)	122 (5.5)	47 (7.3)	16 (6.5)	266 (5.3)
Sex - no. (%)					
Male	1206 (62.8)	1273 (57.3)	396 (61.4)	145 (59.2)	3020 (60.0)
Female	715 (37.2)	949 (42.7)	249 (38.6)	100 (40.8)	2013 (40.0)
Race - no. (%)					
White	1459 (76.0)	1635 (73.6)	469 (72.7)	163 (66.5)	3726 (74.0)
Black or African American	181 (9.4)	237 (10.7)	77 (11.9)	37 (15.1)	532 (10.6)
Asian	98 (5.1)	102 (4.6)	19 (2.9)	7 (2.9)	226 (4.5)
Native Hawaiian or other Pacific Islander	3 (0.2)	11 (0.5)	3 (0.5)	0 (0.0)	17 (0.3)
American Indian or Alaska Native	6 (0.3)	17 (0.8)	3 (0.5)	4 (1.6)	30 (0.6)
More than one race	16 (0.8)	20 (0.9)	9 (1.4)	4 (1.6)	49 (1.0)
Not reported	158 (8.2)	200 (9.0)	65 (10.1)	30 (12.2)	453 (9.0)
Karnofsky score - no. (%)					

Characteristic	Grade I	Grade II	Grade III	Grade IV	Total
< 90	756 (39.4)	989 (44.5)	288 (44.7)	87 (35.5)	2120 (42.1)
90 - 100	1115 (58.0)	1184 (53.3)	345 (53.5)	149 (60.8)	2793 (55.5)
Not reported	50 (2.6)	49 (2.2)	12 (1.9)	9 (3.7)	120 (2.4)
HCT-CI - no. (%)					
0	490 (25.5)	508 (22.9)	164 (25.4)	68 (27.8)	1230 (24.4)
1	310 (16.1)	331 (14.9)	100 (15.5)	36 (14.7)	777 (15.4)
2	307 (16.0)	335 (15.1)	84 (13.0)	31 (12.7)	757 (15.0)
3	308 (16.0)	387 (17.4)	101 (15.7)	38 (15.5)	834 (16.6)
4	222 (11.6)	254 (11.4)	71 (11.0)	29 (11.8)	576 (11.4)
5	123 (6.4)	162 (7.3)	53 (8.2)	17 (6.9)	355 (7.1)
6	78 (4.1)	102 (4.6)	31 (4.8)	9 (3.7)	220 (4.4)
7+	71 (3.7)	120 (5.4)	37 (5.7)	14 (5.7)	242 (4.8)
Missing/TBD	12 (0.6)	23 (1.0)	4 (0.6)	3 (1.2)	42 (0.8)
Primary disease - no. (%)					
Acute myelogenous leukemia or ANLL	839 (43.7)	1018 (45.8)	269 (41.7)	96 (39.2)	2222 (44.1)
Acute lymphoblastic leukemia	342 (17.8)	376 (16.9)	87 (13.5)	29 (11.8)	834 (16.6)
Other leukemia	27 (1.4)	38 (1.7)	13 (2.0)	5 (2.0)	83 (1.6)
Chronic myelogenous leukemia	56 (2.9)	69 (3.1)	20 (3.1)	6 (2.4)	151 (3.0)
Myelodysplastic/myeloprolifterative disorders	414 (21.6)	407 (18.3)	147 (22.8)	60 (24.5)	1028 (20.4)
Other acute leukemia	22 (1.1)	33 (1.5)	16 (2.5)	7 (2.9)	78 (1.5)
Non-Hodgkin lymphoma	134 (7.0)	198 (8.9)	60 (9.3)	24 (9.8)	416 (8.3)
Hodgkin lymphoma	62 (3.2)	60 (2.7)	28 (4.3)	16 (6.5)	166 (3.3)
Plasma cell disorder/Multiple Myeloma	24 (1.2)	22 (1.0)	5 (0.8)	2 (0.8)	53 (1.1)
Other Malignancies	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Graft type - no. (%)					
Bone marrow	238 (12.4)	324 (14.6)	90 (14.0)	38 (15.5)	690 (13.7)
Peripheral blood	1677 (87.3)	1890 (85.1)	553 (85.7)	206 (84.1)	4326 (86.0)
BM + PB	6 (0.3)	7 (0.3)	1 (0.2)	1 (0.4)	15 (0.3)
Other, specify	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)
PB + OTH	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Donor type - no. (%)					
Haploidentical	1375 (71.6)	1661 (74.8)	502 (77.8)	195 (79.6)	3733 (74.2)
Well-matched unrelated (8/8)	546 (28.4)	561 (25.2)	143 (22.2)	50 (20.4)	1300 (25.8)
Conditioning regimen intensity - no. (%)					
No drugs reported	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
MAC	742 (38.6)	937 (42.2)	266 (41.2)	91 (37.1)	2036 (40.5)
RIC	569 (29.6)	636 (28.6)	183 (28.4)	86 (35.1)	1474 (29.3)
NMA	587 (30.6)	621 (27.9)	188 (29.1)	65 (26.5)	1461 (29.0)

Characteristic	Grade I	Grade II	Grade III	Grade IV	Total
TBD	20 (1.0)	25 (1.1)	6 (0.9)	3 (1.2)	54 (1.1)
Not reported	2 (0.1)	1 (0.0)	2 (0.3)	0 (0.0)	5 (0.1)
GVHD prophylaxis - no. (%)					
PTCy/TAC-based	1688 (87.9)	1941 (87.4)	530 (82.2)	198 (80.8)	4357 (86.6)
PTCy/MMF-based	233 (12.1)	281 (12.6)	115 (17.8)	47 (19.2)	676 (13.4)
Year of current transplant - no. (%)					
2015	55 (2.9)	84 (3.8)	31 (4.8)	18 (7.3)	188 (3.7)
2016	71 (3.7)	91 (4.1)	27 (4.2)	6 (2.4)	195 (3.9)
2017	81 (4.2)	99 (4.5)	33 (5.1)	19 (7.8)	232 (4.6)
2018	122 (6.4)	155 (7.0)	44 (6.8)	19 (7.8)	340 (6.8)
2019	272 (14.2)	277 (12.5)	85 (13.2)	26 (10.6)	660 (13.1)
2020	430 (22.4)	491 (22.1)	128 (19.8)	53 (21.6)	1102 (21.9)
2021	454 (23.6)	531 (23.9)	135 (20.9)	65 (26.5)	1185 (23.5)
2022	436 (22.7)	494 (22.2)	162 (25.1)	39 (15.9)	1131 (22.5)
Median follow-up of survivors (range), months - median (range)	24.4 (2.8-96.5)	24.3 (2.9-99.9)	24.5 (3.1-95.3)	24.6 (3.1-73.0)	

Field	Response
Proposal Number	2310-172-HADJIS
Proposal Title	Effect of acute graft-versus-host disease (GVHD) on the outcome of hematopoietic cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy): a CIBMTR analysis
Key Words	Acute graft-versus-host disease, post-transplantation cyclophosphamide
Principal Investigator #1: - First and last name, degree(s)	Ashley D. Hadjis
Principal Investigator #1: - Email address	ashley.hadjis@pennmedicine.upenn.edu
Principal Investigator #1: - Institution name	University of Pennsylvania
Principal Investigator #1: - Academic rank	resident
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Shannon R. McCurdy
Principal Investigator #2 (If applicable): - Email address:)	shannon.mccurdy@pennmedicine.upenn.edu
Principal Investigator #2 (If applicable): - Institution name:	University of Pennsylvania
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Shannon McCurdy
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Dr. McCurdy is a PI on CIBMTR IB19-02.
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Graft vs Host Disease
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Does the development of grade II acute GVHD (aGVHD) improve overall survival and decrease relapse after hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide (PTCy)? How do grade III-IV acute and chronic GVHD (cGVHD) impact survival after HCT with PTCy?

Field	Response
RESEARCH HYPOTHESIS:	Recipients that develop grade II acute GVHD (aGVHD) after HCT with PTCy will have improved relapse-free survival and overall survival when compared to recipients that do not develop aGVHD or develop grades III-IV aGVHD.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1) To determine the impact of grades II, III, or IV aGVHD on non-relapse mortality (NRM), relapse, relapse-free survival, and overall survival after haploidentical (haplo), matched sibling donor (MSD), and matched unrelated donor (MUD) HCT utilizing PTCy. 2) To determine the impact of cGVHD on NRM, relapse, relapse-free survival, and overall survival after haplo, MSD, and MUD HCT utilizing PTCy. 3) While not the primary outcome, we plan to evaluate potential risk factors for the degree of aGVHD severity after HCT with PTCy (i.e. recipient and donor age, female donors for male recipients, cytomegalovirus (CMV) serology, donor type, graft source). We will also determine the impact of graft cell dose on development of GVHD and survival as well as the incidence of graft failure and graft dysfunction.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	In a landmark paper in 1990, Horowitz et al. provided some of the earliest evidence of graft-versus-leukemia (GVL), demonstrating reduced relapse in patients with mild aGVHD or chronic GVHD (cGVHD), but worsened survival in patients with severe GVHD (1). PTCy reduces severe aGVHD and cGVHD, but rates of grade II aGVHD are similar to other platforms (2,3). Utilization of PTCy as GVHD prophylaxis is quickly extending across many transplant platforms. Including haplo, mismatched unrelated, matched sibling, and matched unrelated donor platforms and was, in fact, used in 91% of haplo and 64% of mismatched unrelated (MMUD) HCT in 2021 (4). Our prior work showed that, after HCT with PTCy, grade II aGVHD is associated with improved survival after HLA- haplo (3) and matched (5) bone marrow transplant (BMT). However, subsequent studies did not find a benefit of GVHD on survival (6-8). Given these discrepant findings we aim to explore this in a large registry study, controlling for different conditioning intensities and different graft sources (bone marrow vs. peripheral blood stem cell grafts).

Field	Response
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.	GVHD has been shown to be protective against relapse in HCT without PTCy as a result of GVL effect (1). We have shown that the development of grade II aGVHD in HCT with PTCy improves overall survival (OS) and progression free survival (PFS) in both haplo (3) and matched (5) bone marrow transplant platforms. Improved OS was due to a lower incidence of relapse in those patients that developed grade II aGVHD, compared to those that had not developed grades II to IV aGVHD by day 100 post-HCT (p<0.001) with no difference in NRM (Figure 1) (3). This was also true in an analysis of a PTCy HCT platform with MSD and MUD (p=0.001) (Figure 2) (5). In addition, we demonstrated that higher total nucleated cell graft doses improved OS (3,9). Since our analyses, several groups have also examined the association of GVHD with relapse and OS after HCT with PTCy, all with haploidentical donors. One study demonstrated that in patients that developed grade II aGVHD 2-year OS after haplo PBSCT with PTCy was significantly improved compared to those that developed grades 0-1 or III-IV aGVHD (p=0.0007) (10). In contrast, several recent studies have shown that development of grade II aGVHD in PTCy-based platforms was not associated with improved OS (6-8), with one study showing an association of grade II aGVHD with increased NRM (HR 2.09, p=0.005) (8). Given these differing findings, a larger database study is warranted to determine if development of GVHD with PTCy-based prophylaxis is truly associated with improvement of OS via a reduction in relapse. In addition, we aim to uncover reasons for the differing findings. For instance, different graft cell dose, graft source, different disease type or stage (i.e. presence of absence of minimal residual disease), and conditioning intensity may all influence the impact of GVHD on survival. Moreover, the GVHD treatment employed, which may differ by transplant center, may also influence survival.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_phNwE2WPzakTuz7
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Figure CIBMTR Proposal.png
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	225418
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/png
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion: All patients receiving HLA- haplo, MSD, or MUD donor transplantation with PTCy for acute leukemia, myelodysplastic syndrome, or lymphoma up through one year prior to the analysis. Exclusions Criteria: Patients with ex-vivo T cell depletion

Field	Response
Does this study include pediatric patients?	No
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	2000: Recipient baseline data 2006: Hematopoietic Stem Cell Transplant Infusion 2100: Post-HSCT data 2450: Post-transplant essential data (for engraftment, chimerism, GVHD, relapse, non-relapse mortality, survival)
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 desc	n/a
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	n/a
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 o	n/a
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.	We would be open to potential for collaboration with the EBMT if it is determined that additional patient numbers are needed for statistical power.

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Field	Response
	post-transplantation cyclophosphamide for relapsed/refractory acute leukemia. Bone Marrow Transplantation. 2023/08/01 2023;58(8):947-949. doi:10.1038/s41409-023-01986-6 10. Chevallier P, Berceanu A, Peterlin P, et al. Grade 2 acute GVHD is a factor of good prognosis in patients receiving peripheral blood stem cells haplo-transplant with post-transplant cyclophosphamide. Acta Oncologica. 2021/04/03 2021;60(4):466-474. doi:10.1080/0284186X.2020.1837947
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Table 1. Characteristics of patients undergoing a 1st allo HCT for acute leukemia, MDS, or lymphoma with PTCy-based GVHD prophylaxis, 2008-2022

Characteristic	No aGVHD	Grade I	Grade II	Grade III/IV	Not reported
No. of patients	7728	2333	2668	1150	2950
No. of centers	281	214	214	195	238
Age group - no. (%)					
Median (min-max)	55.0 (0.3-87.8)	56.0 (0.5-80.8)	54.2 (0.5-82.2)	55.1 (0.6-77.4)	51.5 (0.6-81.1)
0-10	274 (3.5)	86 (3.7)	89 (3.3)	59 (5.1)	103 (3.5)
10-20	431 (5.6)	128 (5.5)	142 (5.3)	87 (7.6)	146 (4.9)
20-30	883 (11.4)	240 (10.3)	289 (10.8)	119 (10.3)	328 (11.1)
30-40	765 (9.9)	220 (9.4)	270 (10.1)	122 (10.6)	355 (12.0)
40-50	913 (11.8)	279 (12.0)	349 (13.1)	97 (8.4)	464 (15.7)
50-60	1502 (19.4)	433 (18.6)	513 (19.2)	230 (20.0)	678 (23.0)
60-70	2214 (28.6)	711 (30.5)	758 (28.4)	336 (29.2)	701 (23.8)
70-80	740 (9.6)	235 (10.1)	256 (9.6)	100 (8.7)	173 (5.9)
80-90	6 (0.1)	1 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
TED or RES track - no. (%)					
Ted (registration) patient	5953 (77.0)	1645 (70.5)	1801 (67.5)	709 (61.7)	2850 (96.6)
Research patient	1775 (23.0)	688 (29.5)	867 (32.5)	441 (38.3)	100 (3.4)
CCN region at transplant - no. (%)					
US	6127 (79.3)	1962 (84.1)	2211 (82.9)	889 (77.3)	2362 (80.1)
Canada	311 (4.0)	88 (3.8)	126 (4.7)	32 (2.8)	74 (2.5)
Europe	166 (2.1)	38 (1.6)	24 (0.9)	25 (2.2)	157 (5.3)
Asia	214 (2.8)	26 (1.1)	43 (1.6)	47 (4.1)	66 (2.2)
Australia/New Zealand	239 (3.1)	73 (3.1)	58 (2.2)	35 (3.0)	71 (2.4)
Mideast/Africa	99 (1.3)	17 (0.7)	28 (1.0)	20 (1.7)	25 (0.8)
Central/South America	572 (7.4)	129 (5.5)	178 (6.7)	102 (8.9)	195 (6.6)
Sex - no. (%)					
Male	4566 (59.1)	1477 (63.3)	1484 (55.6)	707 (61.5)	1759 (59.6)
Female	3162 (40.9)	856 (36.7)	1184 (44.4)	443 (38.5)	1191 (40.4)
Race - no. (%)					
White	5209 (67.4)	1696 (72.7)	1914 (71.7)	784 (68.2)	2201 (74.6)
Black or African American	894 (11.6)	209 (9.0)	265 (9.9)	131 (11.4)	253 (8.6)
Asian	473 (6.1)	119 (5.1)	120 (4.5)	39 (3.4)	153 (5.2)
Native Hawaiian or other Pacific Islander	38 (0.5)	3 (0.1)	12 (0.4)	4 (0.3)	8 (0.3)
American Indian or Alaska Native	28 (0.4)	8 (0.3)	19 (0.7)	10 (0.9)	14 (0.5)
More than one race	83 (1.1)	28 (1.2)	29 (1.1)	24 (2.1)	17 (0.6)

Characteristic	No aGVHD	Grade I	Grade II	Grade III/IV	Not reported
Not reported	1003 (13.0)	270 (11.6)	309 (11.6)	158 (13.7)	304 (10.3)
Karnofsky score - no. (%)					
< 90	2892 (37.4)	839 (36.0)	1088 (40.8)	441 (38.3)	1000 (33.9)
90 - 100	4608 (59.6)	1431 (61.3)	1520 (57.0)	684 (59.5)	1846 (62.6)
Not reported	228 (3.0)	63 (2.7)	60 (2.2)	25 (2.2)	104 (3.5)
HCT-CI - no. (%)					
0	2162 (28.0)	658 (28.2)	709 (26.6)	340 (29.6)	908 (30.8)
1	1175 (15.2)	386 (16.5)	396 (14.8)	183 (15.9)	449 (15.2)
2	1075 (13.9)	355 (15.2)	405 (15.2)	134 (11.7)	444 (15.1)
3	1251 (16.2)	374 (16.0)	438 (16.4)	181 (15.7)	470 (15.9)
4	850 (11.0)	245 (10.5)	282 (10.6)	112 (9.7)	309 (10.5)
5	508 (6.6)	142 (6.1)	177 (6.6)	82 (7.1)	154 (5.2)
6	310 (4.0)	79 (3.4)	116 (4.3)	48 (4.2)	97 (3.3)
7+	329 (4.3)	78 (3.3)	122 (4.6)	61 (5.3)	96 (3.3)
Missing/TBD	68 (0.9)	16 (0.7)	23 (0.9)	9 (0.8)	23 (0.8)
Primary disease - no. (%)					
Acute myelogenous leukemia or ANLL	3545 (45.9)	1097 (47.0)	1303 (48.8)	491 (42.7)	1470 (49.8)
Acute lymphoblastic leukemia	1477 (19.1)	504 (21.6)	541 (20.3)	230 (20.0)	598 (20.3)
Myelodysplastic/myeloprolifterative disorders	1439 (18.6)	461 (19.8)	453 (17.0)	232 (20.2)	363 (12.3)
Other acute leukemia	129 (1.7)	34 (1.5)	54 (2.0)	31 (2.7)	52 (1.8)
Non-Hodgkin lymphoma	805 (10.4)	156 (6.7)	239 (9.0)	110 (9.6)	358 (12.1)
Hodgkin lymphoma	333 (4.3)	81 (3.5)	78 (2.9)	56 (4.9)	109 (3.7)
Graft type - no. (%)					
Bone marrow	1943 (25.1)	436 (18.7)	508 (19.0)	241 (21.0)	962 (32.6)
Peripheral blood	5747 (74.4)	1889 (81.0)	2149 (80.5)	903 (78.5)	1965 (66.6)
BM + PB	22 (0.3)	8 (0.3)	8 (0.3)	3 (0.3)	5 (0.2)
Other, specify	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
BM + OTH	2 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)	0 (0.0)
PB + OTH	14 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)	18 (0.6)
Donor type - no. (%)					
HLA-identical sibling	1086 (14.1)	223 (9.6)	199 (7.5)	112 (9.7)	434 (14.7)
Haploidentical	4827 (62.5)	1509 (64.7)	1821 (68.3)	804 (69.9)	1889 (64.0)
Well-matched unrelated (8/8)	1815 (23.5)	601 (25.8)	648 (24.3)	234 (20.3)	627 (21.3)
Conditioning regimen intensity - no. (%)					
No drugs reported	10 (0.1)	2 (0.1)	2 (0.1)	0 (0.0)	28 (0.9)
MAC	3393 (43.9)	1023 (43.8)	1257 (47.1)	531 (46.2)	1463 (49.6)
RIC	2134 (27.6)	661 (28.3)	705 (26.4)	325 (28.3)	500 (16.9)
NMA	2060 (26.7)	618 (26.5)	665 (24.9)	272 (23.7)	918 (31.1)

Characteristic	No aGVHD	Grade I	Grade II	Grade III/IV	Not reported
TBD	112 (1.4)	26 (1.1)	38 (1.4)	19 (1.7)	37 (1.3)
Not reported	19 (0.2)	3 (0.1)	1 (0.0)	3 (0.3)	4 (0.1)
GVHD prophylaxis - no. (%)					
PtCy + other(s)	7528 (97.4)	2290 (98.2)	2635 (98.8)	1125 (97.8)	2731 (92.6)
PtCy alone	200 (2.6)	43 (1.8)	33 (1.2)	25 (2.2)	219 (7.4)
Year of current transplant - no. (%)					
2008	42 (0.5)	3 (0.1)	14 (0.5)	5 (0.4)	24 (0.8)
2009	39 (0.5)	7 (0.3)	9 (0.3)	5 (0.4)	53 (1.8)
2010	54 (0.7)	3 (0.1)	4 (0.1)	0 (0.0)	81 (2.7)
2011	85 (1.1)	0 (0.0)	3 (0.1)	3 (0.3)	95 (3.2)
2012	116 (1.5)	5 (0.2)	5 (0.2)	2 (0.2)	113 (3.8)
2013	151 (2.0)	24 (1.0)	36 (1.3)	13 (1.1)	80 (2.7)
2014	204 (2.6)	34 (1.5)	55 (2.1)	28 (2.4)	145 (4.9)
2015	312 (4.0)	70 (3.0)	95 (3.6)	53 (4.6)	243 (8.2)
2016	461 (6.0)	82 (3.5)	100 (3.7)	51 (4.4)	328 (11.1)
2017	652 (8.4)	97 (4.2)	115 (4.3)	64 (5.6)	515 (17.5)
2018	784 (10.1)	153 (6.6)	180 (6.7)	76 (6.6)	608 (20.6)
2019	993 (12.8)	319 (13.7)	318 (11.9)	133 (11.6)	349 (11.8)
2020	1132 (14.6)	489 (21.0)	561 (21.0)	218 (19.0)	100 (3.4)
2021	1277 (16.5)	525 (22.5)	601 (22.5)	238 (20.7)	96 (3.3)
2022	1426 (18.5)	522 (22.4)	572 (21.4)	261 (22.7)	120 (4.1)
Median follow-up of survivors (range), months - median (range)	26.0 (0.0-171.2)	24.3 (2.8-155.7)	24.4 (1.8-154.7)	24.5 (1.1-171.4)	55.1 (0.0-173.9)

Field	Response
Proposal Number	2310-155-MEHTA
Proposal Title	Post-Transplantation Cyclophosphamide (PTCy)/Sirolimus versus PTCy/Calcineurin-inhibitor (CNI) -based Graft-Versus-Host Disease Prophylaxis
Key Words	GVHD, Post-transplant Cyclophosphamide, Calcineurin inhibitor, Sirolimus, allogeneic hematopoietic cell transplant
Principal Investigator #1: - First and last name, degree(s)	Rohtesh Mehta, MD MPH MS
Principal Investigator #1: - Email address	rmehta@fredhutch.org
Principal Investigator #1: - Institution name	Fred Hutchinson Cancer Center, Seattle, WA
Principal Investigator #1: - Academic rank	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Nelli Bejanyan, MD
Principal Investigator #2 (If applicable): - Email address:)	nelli.bejanyan@moffitt.org
Principal Investigator #2 (If applicable): - Institution name:	H Lee Moffitt Cancer Center, FL
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Rohtesh Mehta
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	PI of IB23-02 co-PI of GV23-01
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Graft vs Host Disease
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Steve Spellman

Field	Response
RESEARCH QUESTION:	1. Is PTCy/Sirolimus at least as effective GVHD prophylaxis as PTCy/CNI in patients undergoing allogeneic hematopoietic cell transplantation (HCT)? 2. Is PTCy/Sirolimus GVHD prophylaxis associated with improved toxicity profile as compared to PTCy/CNI prophylaxis?
RESEARCH HYPOTHESIS:	We hypothesize that: 1. PTCy/Sirolimus GVHD prophylaxis will be at least as effective as PTCy/CNI prophylaxis in patients undergoing allogeneic HCT. 2. PTCy/Sirolimus GVHD prophylaxis will be associated with improved toxicity profile as compared to PTCy/CNI prophylaxis.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1) As efficacy measures, we will determine the rates of the following in patients receiving PTCy/Sirolimus vs PTCy/CNI GVHD prophylaxis: a. acute GVHD: i. grade II-IV ii. grade III-IV b. chronic GVHD: i. mild, moderate, severe chronic GVHD ii. Systemic immunosuppressive therapy-requiring chronic GVHD 2) As toxicity measures, we will determine the rates of the following in patients receiving PTCy/Sirolimus vs PTCy/CNI GVHD prophylaxis: a. Viral infections (especially CMV reactivation and BK-cystitis) b. bacterial infections c. fungal infections d. Secondary neoplasms e. thrombotic microangiopathy (TMA) f. Sinosuidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) 3) Other outcomes: a. renal insufficiency (likely be limited to the CRF population -~20% CIBMTR database) and need for hemodialysis (if data available) b. Graft failure, neutrophil and platelet engraftment and chimerism c. Non-relapse mortality d. Relapse e. Overall survival
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If PTCy/sirolimus is at least as effective GVHD prophylaxis regimen as PTCy/CNI, while possessing a better toxicity profile, it could call for a practice change and become a new standard of care. Moreover, with limited toxicity data, even if the study fails to determine robust safety outcomes, an efficacy comparative study would still be quite helpful and provide treating physicians with options for prophylaxis. On the other hand, if the study shows inferior efficacy in preventing GVHD, it would suggest continued use of PTCy/CNI as standard and avoiding the use of PTCy/sirolimus.

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.	Sirolimus may have better safety profile than CNIs: Calcineurin inhibitors (CNI), such as cyclosporine and tacrolimus, are associated with risk of renal insufficiency, hypomagnesemia, hypertension, thrombotic microangiopathy, to name a few. Therefore, CNI-free approaches are being explored, as was done in the Blood and Marrow Transplant Clinical Trial Network (BMT CTN) 1301 trial.1 Another attractive CNI-free regimen is the use of PTCy and Sirolimus with or without additional drugs. As compared to CNI, sirolimus may have a more favorable toxicity profile due to a lower incidence of renal insufficiency2, and a lower risk of infections such as cytomegalovirus (CMV)3,45 and BK virus6,7. Moreover, sirolimus may also be associated with a lower risk of secondary malignancies than CNI. A few systematic review and meta-analyses found sirolimus to be associated with a significantly lower risk of secondary malignancies as compared to CNI in renal transplant patients.8,9 In fact, prospective multicenter trials showed that switching from CNI to sirolimus had an antitumoral effect among renal transplant patients with previous squamous-cell carcinoma.10 Similar findings were noted in patients with heart transplant where a conversion from CNI to sirolimus was associated with a decreased risk of de novo malignancies, post-transplant lymphoproliferative disorders, and subsequent primary occurrences of non-melanoma skin cancers.11 Most of these safety data are derived from studies involving patients with solid organ transplant and from independent studies in HCT patients, without a clear head-to-head comparative analysis of the two prophylacit approaches. Sirolimus may be as effective as CNI when used with PTCy for GVHD prophylaxis: A prospective phase 2 clinical trial assessed the safety and efficacy of PTCy/Sirolimus/mycophenolate mofetil (MMF) prophylaxis in patients undergoing haploidentical HCT with peripheral blood (PB) graft and myeloablative conditioning (MAC).12 The cumulative incidence of grade II-IV acute GVHD at day 100 was 18.8% (95% confidence interval [CI], 7.5%-34.0%), and moderate/severe chronic GVHD was 18.8% (95% CI, 7.4%-34.0%) at 1 year. There were 2 cases of SOS/VOD and no case of TMA or graft failure was noted. These results were quite encouraging and compared favorably to those reported with PTCy/CNI-based prophylaxis in other studies.13,14 Another retrospective study showed encouraging outcomes with PTCy/sirolimus-based GVHD prophylaxis after treosulfan-melphalan MAC and haploidentical donor HCT.15 In this study, the cumulative incidence of grade II-IV acute GVHD was 15%, grade III-IV acute GVHD was

Field	Response
	7.5%, and chronic GVHD at 1 year was 20%. Another retrospective study including two Spanish transplant centers reported the outcomes of PTCy/Sirolimus/MMF prophylaxis after either HLA-matched related (MRD), HLA-matched unrelated (MUD) or haploidentical donor HCT.16 The cumulative incidences of acute GHVD grade II-IV, III-IV and moderate to severe cGVHD were 27%, 9% and 27%, respectively. PTCy/sirolimus-based GVHD prophylaxis is also being assessed in other prospective trials in the haploidentical donor HCT setting with favorable results noted in early trial outcomes.17 The use of PTCy/Sirolimus/MMF was also found to be safe and effective in a few prospective clinical trials in the setting of HLA-mismatched unrelated donor (MMUD) HCT.18,19 With an increasing use of PTCy prophylaxis and mismatched donor HCTs, it is crucial to identify an optimal combination of GVHD prophylaxis drugs used with PTCy. As the numbers of HCT with PTCy and sirolimus are expected to be generally low as compared to PTCy/CNI, such an analysis can only be performed via large registry studies such as the CIBMTR. Definition of renal insufficiency: The Kidney Disease Improving Global Outcomes (KDIGO)20 classifies patients into 5 grades based on the glomerular filteration rate (GFR): 1. G1 − GFR >90 mL/min per 1.73 m2 2. G2 − GFR 60 to 89 mL/min per 1.73 m2 3. G3a − GFR 45 to 59 mL/min per 1.73 m2 4. G3b − GFR 30 to 44 mL/min per 1.73 m2 5. G4 − GFR 15 to 29 mL/min per 1.73 m 6. G5 − GFR <15 mL/min per 1.73 m2 or treatment by dialysis For the purposes of our study, these can be broadly categorized into 3 groups: group 1 (G1+G2), group 2 (G3a) and group 3 (G3b-G5). This is based on a previous CIBMTR study21 that showed no OS differences between G1 and G2, and an increased hazard of overall mortality from G1 to G3a (HR 1.17 in the validation cohort and 1.46 in the discovery cohort) and the worst survival in patients with GFR <45 (HR 1.63 in the validation and 1.74 in the discovery cohort). A decline in the GFR from one group to another will be meet the criteria for “renal insufficiency” for our proposal.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	• Patients who received HCT with any donor (except cord blood) will be included: HLA-matched related/matched sibling (MSD), HLA-matched unrelated (MUD), HLA-mismatched unrelated (MMUD), haploidentical. • HCT between 2014-2022 • Conditioning: MAC or RIC/NMA. • Disease type: any hematologic malignancy • Graft: PB or BM • GVHD prophylaxis: PTCy/Siro-based vs PTCy/CNI-based. Exclude patients with in vivo or ex-vivo T cell depletion/CD34+selected grafts
Does this study include pediatric patients?	Yes

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	i) Patient-related: • Age at HCT, years • Sex: male vs female • Karnofsky performance score: ≥90% vs. <90% • HCT comorbidity index at transplant 0, 1, 2, 3, 4, 5+ • Race/ethnicity: Non-Hispanic White vs. NH-Black vs. Hispanic vs. Asian/pacific islander vs. others • CMV status: seropositive vs. seronegative. • ABO typing ii) Disease-related: • Disease diagnosis • Disease stage • Disease-Risk Index • Time from diagnosis to HCT iii) Transplant-related: • BM vs. PB graft • Conditioning: MAC vs RIC vs. NMA (using standard CIBMTR definitions). • Year of HCT • Donor/Recipient gender (F-to-M vs. other) • Donor/Recipient CMV status (CMV- D/CMV+ R vs. other) • Donor parity (if female) • Donor relationship (for haploidentical): parent, child, sibling, other • Dnor ABO • HLA locus mismatch (for unrelated donors): -A, -B, -C, -DR • -DQb1 match status (for unrelated donors): matched vs mismatched • -DPb1 match status (for unrelated donors): matched, vs permissive mismatch, vs non-permissive mismatch • HLA B-leader matching, -DR, -DQ and -DP mismatch for haploidentical donors if available) • Donor age – continuous • Donor relationship • Additional GVHD prophylaxis drugs used • Viable CD34+ cells/kg of recipient infused (if available) • TNC/kg of recipient (if available) • CD3+/kg of recipient before thawing (if available) iv) Outcome related • Primary efficacy endpoints: o Incidence of grade II-IV acute GVHD o Incidence of grade III-IV acute GVHD o Incidence of mild, moderate and severe chronic GVHD o Incidence of systemic immunosuppression-requiring chronic GVHD • Primary safety endpoints: o Viral infections (especially CMV reactivation/infection and BK-cystitis) o bacterial infections o fungal infections o renal insufficiency [see definition below] o need for hemodialysis post-HCT o thrombotic microangiopathy

Field	Response
	(TMA) o Sinosuidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) o Graft failure o Time to neutrophil and platelet engraftment o Incidence of neutrophil and platelet engraftment o Grades of Cytokine release syndrome (CRS) o Incidence of secondary malignancies • Secondary endpoints: o Donor chimerism (unsorted, sorted: myeloid and T cell) o Relapse o Non-relapse mortality: in all patients (day 0 as starting point) and a landmark analysis in a subset who develop grade III-IV acute GVHD (date of development of grade III-IV aGVHD as starting point) o Overall Survival: in all patients (day 0 as starting point) and a landmark analysis in a subset who develop grade III-IV acute GVHD (date of development of grade III-IV aGVHD as starting point) o Causes of Death
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 desc	N.A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N.A
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 o	N.A
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.	N.A

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Field	Response
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Table 1. Characteristics of patients undergoing a 1st allo HCT with PTCy/Siro or PTCy/CNI based GVHD prophylaxis, 2014-2022

Characteristic	PTCy + Siro	PTCy + CNI (TAC or CSA)	Total
No. of patients	1616	16320	17936
No. of centers	82	295	296
Age group - no. (%)			
Median (min-max)	60.1 (1.4-87.8)	54.6 (0.3-81.8)	55.2 (0.3-87.8)
Age 0-10	11 (0.7)	582 (3.6)	593 (3.3)
Age 10-20	23 (1.4)	877 (5.4)	900 (5.0)
Age 20-30	134 (8.3)	1706 (10.5)	1840 (10.3)
Age 30-40	147 (9.1)	1660 (10.2)	1807 (10.1)
Age 40-50	167 (10.3)	2053 (12.6)	2220 (12.4)
Age 50-60	319 (19.7)	3349 (20.5)	3668 (20.5)
Age 60-70	560 (34.7)	4652 (28.5)	5212 (29.1)
Age 70-80	251 (15.5)	1435 (8.8)	1686 (9.4)
Age 80-90	4 (0.2)	6 (0.0)	10 (0.1)
TED or RES track - no. (%)			
Ted (registration) patient	1196 (74.0)	12594 (77.2)	13790 (76.9)
Research patient	420 (26.0)	3726 (22.8)	4146 (23.1)
CCN region at transplant - no. (%)			
US	1573 (97.3)	13120 (80.4)	14693 (81.9)
Canada	0 (0.0)	674 (4.1)	674 (3.8)
Europe	33 (2.0)	408 (2.5)	441 (2.5)
Asia	3 (0.2)	322 (2.0)	325 (1.8)
Australia/New Zealand	2 (0.1)	503 (3.1)	505 (2.8)
Mideast/Africa	3 (0.2)	172 (1.1)	175 (1.0)
Central/South America	2 (0.1)	1121 (6.9)	1123 (6.3)
Sex - no. (%)			
Male	938 (58.0)	9621 (59.0)	10559 (58.9)
Female	678 (42.0)	6699 (41.0)	7377 (41.1)
Race - no. (%)			
White	1263 (78.2)	11331 (69.4)	12594 (70.2)
Black or African American	187 (11.6)	1787 (10.9)	1974 (11.0)
Asian	50 (3.1)	824 (5.0)	874 (4.9)
Native Hawaiian or other Pacific Islander	3 (0.2)	68 (0.4)	71 (0.4)
American Indian or Alaska Native	13 (0.8)	77 (0.5)	90 (0.5)
More than one race	7 (0.4)	189 (1.2)	196 (1.1)
Not reported	93 (5.8)	2044 (12.5)	2137 (11.9)
Karnofsky score - no. (%)			

Characteristic	PTCy + Siro	PTCy + CNI (TAC or CSA)	Total
< 90	606 (37.5)	6394 (39.2)	7000 (39.0)
90 - 100	988 (61.1)	9526 (58.4)	10514 (58.6)
Not reported	22 (1.4)	400 (2.5)	422 (2.4)
HCT-CI - no. (%)			
0	321 (19.9)	4332 (26.5)	4653 (25.9)
1	212 (13.1)	2533 (15.5)	2745 (15.3)
2	239 (14.8)	2402 (14.7)	2641 (14.7)
3	308 (19.1)	2656 (16.3)	2964 (16.5)
4	224 (13.9)	1838 (11.3)	2062 (11.5)
5	138 (8.5)	1069 (6.6)	1207 (6.7)
6	78 (4.8)	663 (4.1)	741 (4.1)
7+	79 (4.9)	708 (4.3)	787 (4.4)
Missing/TBD	17 (1.1)	119 (0.7)	136 (0.8)
Primary disease - no. (%)			
Acute myelogenous leukemia or ANLL	657 (40.7)	7082 (43.4)	7739 (43.1)
Acute lymphoblastic leukemia	216 (13.4)	3048 (18.7)	3264 (18.2)
Other leukemia	31 (1.9)	239 (1.5)	270 (1.5)
Chronic myelogenous leukemia	56 (3.5)	549 (3.4)	605 (3.4)
Myelodysplastic/myeloprolifterative disorders	336 (20.8)	3016 (18.5)	3352 (18.7)
Other acute leukemia	25 (1.5)	269 (1.6)	294 (1.6)
Non-Hodgkin lymphoma	190 (11.8)	1330 (8.1)	1520 (8.5)
Hodgkin lymphoma	40 (2.5)	535 (3.3)	575 (3.2)
Plasma cell disorder/Multiple Myeloma	43 (2.7)	230 (1.4)	273 (1.5)
Other Malignancies	22 (1.4)	22 (0.1)	44 (0.2)
Graft type - no. (%)			
Bone marrow	267 (16.5)	3218 (19.7)	3485 (19.4)
Peripheral blood	1349 (83.5)	13102 (80.3)	14451 (80.6)
Donor type - no. (%)			
HLA-identical sibling	141 (8.7)	1612 (9.9)	1753 (9.8)
Haploidentical	688 (42.6)	10046 (61.6)	10734 (59.8)
Well-matched unrelated (8/8)	469 (29.0)	3316 (20.3)	3785 (21.1)
Partially-matched unrelated (7/8)	249 (15.4)	1254 (7.7)	1503 (8.4)
Mis-matched unrelated (<= 6/8)	69 (4.3)	92 (0.6)	161 (0.9)
Conditioning regimen intensity - no. (%)			
MAC	611 (37.8)	7413 (45.4)	8024 (44.7)
RIC	572 (35.4)	4661 (28.6)	5233 (29.2)
NMA	433 (26.8)	4246 (26.0)	4679 (26.1)
Year of current transplant - no. (%)			
2014	35 (2.2)	460 (2.8)	495 (2.8)

Characteristic	PTCy + Siro	PTCy + CNI (TAC or CSA)	Total
2015	68 (4.2)	771 (4.7)	839 (4.7)
2016	77 (4.8)	1033 (6.3)	1110 (6.2)
2017	218 (13.5)	1441 (8.8)	1659 (9.2)
2018	249 (15.4)	1834 (11.2)	2083 (11.6)
2019	238 (14.7)	2164 (13.3)	2402 (13.4)
2020	220 (13.6)	2632 (16.1)	2852 (15.9)
2021	239 (14.8)	2884 (17.7)	3123 (17.4)
2022	272 (16.8)	3101 (19.0)	3373 (18.8)
Median follow-up of survivors (range), months - median (range)	36.2 (0.0-101.1)	25.3 (0.0-106.5)	

Field	Response
Proposal Number	2310-58-MEHTA
Proposal Title	Differences in the characteristics of Acute and Chronic Graft-Versus-Host Disease (GVHD) After Post-Transplantation Cyclophosphamide Versus Conventional Calcineurin Inhibitor-based GVHD Prophylaxis
Key Words	GVHD, Post-transplant Cyclophosphamide, Calcineurin inhibitor, Matched-unrelated donor, Matched-related donor, haploidentical; allogeneic stem cell transplant
Principal Investigator #1: - First and last name, degree(s)	Rohtesh S. Mehta, MD MPH MS
Principal Investigator #1: - Email address	rmehta@fredhutch.org
Principal Investigator #1: - Institution name	Fred Hutchinson Cancer Center
Principal Investigator #1: - Academic rank	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Rima Saliba, PhD
Principal Investigator #2 (If applicable): - Email address:)	rsaliba@mdanderson.org
Principal Investigator #2 (If applicable): - Institution name:	The University of Texas MD Anderson Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Rohtesh S. Mehta
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	PI of IB23-02 co-PI of GV23-01
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Graft vs Host Disease
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Briefly discussed with Dr Lee

Field	Response
RESEARCH QUESTION:	1. Aim 1: Characteristics of GVHD: Do the patterns of organ involvement in acute and chronic graft-versus-host disease (GVHD) differ among patients who undergo hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide (PTCy)-based versus conventional calcineurin inhibitor (CNI)-based GVHD prophylaxis? 2. Aim 2: Incidence of type of chronic GVHD: Is the incidence of de novo chronic GVHD and progressive/relapsing chronic GVHD different among patients who undergo HCT with PTCy-based versus conventional CNI-based GVHD prophylaxis? 3. Aim 3: Response and immunosuppression burden after GVHD development: Is GVHD response to treatment (survival after GVHD as a surrogate marker) and immunosuppression burden different among patients who undergo HCT with PTCy-based versus conventional CNI-based GVHD prophylaxis?

Field	Response
RESEARCH HYPOTHESIS:	1. Aim 1: We hypothesize that the distribution of: a. acute GVHD organ involvement will not be different between the PTCy and the conventional prophylaxis groups. I.e. among patients with acute GVHD, the proportion of patients with skin, liver, upper and/or lower gastrointestinal (GI) GVHD will be similar in both the groups [Based on the BMTCTN 1703 trial in the RIC setting as elaborated below; no robust data in the MAC setting]. However, the proportion of patients developing severe (grade III-IV) acute GVHD, especially lower gastrointestinal tract (LGI), will be lower with PTCy [Based on previous CIBMTR study (Saliba et al) comparing MUD (conventional) vs Haploidentical (PTCy) as elaborated below]. b.chronic GVHD organ involvement will differ between the PTCy and the conventional prophylaxis groups depending on the use of in-vivo T cell depletion (TCD) in the latter [Based on previous CIBMTR study (Saliba et al) comparing MUD (conventional) vs Haploidentical (PTCy) as elaborated below] 2. Aim 2: Patients who receive PTCy will have a lower risk of de novo chronic and lower risk of progressive/relapsing chronic GVHD as compared to patients who receive conventional prophylaxis depending on the use of in vivo TCD in the latter [Based on a recent MDACC analysis as elaborated below] 3. Aim 3: Acute and/or chronic GVHD developing after PTCy will be more responsive to treatment (survival post-GVHD as a surrogate marker) as compared to that after conventional prophylaxis [Based on MDACC data for acute GVHD as elaborated below; no data in the chronic GVHD setting] And among survivors, the PTCy group will have a higher likelihood of being free of immunosuppression and without disease relapse by 3-years and 5-years post HCT.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1) Aim 1: To determine the rates of organ involvement with acute and chronic GVHD with PTCy-based versus conventional CNI-based GVHD prophylaxis. 2) Aim 2: To evaluate the rates of de novo and progressive/relapsing chronic GVHD in patients receiving PTCy-based versus conventional CNI-based GVHD prophylaxis. 3) Aim 3: To assess whether acute and/or chronic GVHD developing after PTCy-based prophylaxis is more or less responsive to treatment as compared to that developing after conventional CNI-based GVHD prophylaxis, and to determine the probability of being in remission and free of immunosuppression at 3 years and 5 years post HCT.

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	P.S. There is a 3rd CO-PI on the study: PI Name (Last, First, Middle): McCurdy, Shannon R Degree(s): MD Academic Rank: Assistant Professor of Medicine, Division of Hematology/Oncology Email Address: shannon.mccurdy@pennmedicine.upenn .edu Institution Name: The Univ. of Pennsylvania, Perelman School of Medicine, Philadelphia, PA SCIENTIFIC IMPACT: The epidemiology of acute and chronic GVHD developing after PTCy- vs conventional GVHD prophylaxis in the HLA matched donor setting is not completely defined. Similarly, it is unknown if GVHD developing after PTCy-based prophylaxis is more, less or equally responsive to treatment as compared to the GVHD developing after conventional GVHD prophylaxis, and whether the long-term probability of being immunosuppression-free differ between the groups. Understanding the patterns of acute and chronic GVHD organ involvement, type of chronic GVHD (de novo and progressive/relapsing) and response to treatment, and long-term immunosuppression-free survival after these two GVHD prophylaxis modalities is crucial. This may subsequently inform if/how to modulate prophylaxis regimens, treatment and immunosuppression taper strategies.

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.	Aim 1: Acute and chronic GVHD organ distribution In the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1703 trial, the cumulative incidence of grade II to IV acute GVHD at day 100 was similar in the PTCy and the tacrolimis (Tac)/methotrexate (MTX) groups, and the acute GVHD organ distribution grossly appeared similar across both groups in this population (Table S8)1. The study population was patients who received peripheral-blood (PB) grafts from either HLA-matched unrelated (MUD) or matched sibling donors (MSD) after reduced-intensity conditioning (RIC). It is unclear whether the GVHD organ distribution would differ in patients who receive bone marrow (BM) grafts, MAC, and in comparison to patients who receive in vivo T cell depletion with Tac/MTX. A prior CIBMTR study2 that compared haploidentical-PTCy and MUD-conventional [with antithymocyte globulin (ATG)] showed that stage 3-4 LGI acute GVHD was significantly higher in the MUD-conventional group as compared to the haploidentical-PTCy group. Skin and/or liver acute GVD stages did not differ significantly between the groups. The distribution of organ involvement with chronic GVHD was not reported in the published results of BMT CTN 1703 trial1. However, some indirect data are available to guide our hypothesis. A prior CIBMTR study2 that compared haploidentical-PTCy and MUD-conventional (with ATG) showed that the spectrum of chronic GVHD organ involvement did not differ significantly between the 2 groups, except for less common GI tract involvement in the haploidentical-PTCy group (21%) than MUD-conventional (32%); P = .001). However, as compared to MUD-conventional (without ATG), haploidentical-PTCy cohort was significantly less likely to have chronic GVHD involving gastrointestinal tract (32% vs 21%; P = .001), mouth (66% vs 39%; P < .001), eyes (60% vs 41%; P < .001), liver (42% vs 29%; P < .001), lungs (27% vs 18%; P = .01), musculoskeletal (11% vs 1%; P < .001), and “other” organs (21% vs 12%; P = .01). No such study exists in the HLA-matched donor setting. In a single-center study conducted at the MD Anderson Cancer Center (MDACC) comparing PTCy to conventional GVHD prophylaxis in the HLA-matched donor setting3, we noted that in the MUD cohort, among those who required systemic therapy, the distribution of the NIH defined chronic GVHD severity in the Tac/MTX/ATG and the PTCy groups was mild (9% versus 25%, respectively), moderate (50% versus 35%, respectively), and severe (35% in both groups). In the MSD cohort, among those who required systemic therapy, the distribution of the NIH defined cGVHD severity in the Tac/MTX (without ATG) and the PTCy groups was mild (10% versus 15%, respectively),

	moderate (55% versus 31%, respectively), and severe (33% versus 38%, respectively). However, the chronic GVHD organ distribution was not reported. Incidence of De novo and progressive/relapsing chronic GVHD, and the impact of adding MMF to PTCy: In another recent analysis of patients treated at the MDACC (abstract submitted to ASH 2023), of the 1040 patients who underwent HLA-matched donor HCT and received either PTCy/Tac (with or without MMF) or Tac/MTX (with or without ATG) for GVHD prophylaxis, we assessed the incidence of de novo and progressive / relapsing chronic GVHD. Among the de novo cGvHD risk cohort (N=442) who had not been diagnosed with acute GVHD within 3 months post-HCT, 124 cases of chronic GVHD were diagnosed 3 -36 months post-HCT with a cumulative incidence of 32% (27-37). In multivariate analysis, as compared to Tac/MTX, the use of PTCy/Tac without MMF (Hazard ratio (HR)=0.3, 95% confidence interval (CI) 0.2-0.6, p<0.001) was associated with a significant reduction in the incidence of chronic GVHD. Such a reduction was not observed with PTCy/Tac with MMF (HR vs Tac/MTX=1.0, 95% CI 0.6-1.5, p=0.9). [Figure below] Among the progressive / relapsing chronic GVHD risk cohort (n=450) who had been diagnosed with grade 1 (27%), 2 (59%) or 3-4 (14%) acute GVHD within 3 months post-HCT, 109 cases of chronic GVHD were diagnosed 3 -36 months post-HCT with a cumulative incidence of 28% (24-33). In multivariate analysis, PTCy/Tac ± MMF was associated with a significantly lower rate of progressive / relapsing chronic GVHD in MSD (vs Tac/MTX, no ATG: HR=0.2, 95% CI 0.1-0.4, p<0.001) but not in MUD (vs Tac/MTX with ATG HR=0.6, 95% CI 0.4-1.1, p=0.09). Acute and chronic GVHD response to treatment: In a single-center study conducted at the MDACC comparing PTCy to conventional GVHD prophylaxis in the HLA-matched donor setting3, we noted that in the MUD cohort, the incidence of steroid-refractory (SR) or steroid-dependent (SD) acute GVHD was 16% in the Tac/MTX (with ATG) versus 11% in the PTCy group, P= 0.6. In the MSD cohort, the incidence of SR/SD acute GVHD was 10% in the Tac/MTX (without ATG) versus 13% in the PTCy group, P= 0.6. The response to chronic GVHD treatment in the PTCy vs conventional prophylaxis groups was not described in the study. As the data regarding response to treatment are not collected by the CIBMTR per-se, we will primarily use surrogate outcomes such as the non-relapse mortality and overall survival after the development of GVHD. In addition, we propose to describe the rates of initiation of new immunosuppressants post HCT (i.e. drugs that were not part of prophylaxis), and the rate of discontinuation of all immunosuppresants by 6-and 12-

Field	Response
	months from the time of diagnosis of grade 3-4 acute GVHD, and 2-years and 3-years after the development of mod-severe chronic GVHD (for chronic GVHD cohort). Successful long-term discontinuation of immunosuppression: A previous study of the patients enrolled on the BMTCTN 0201 (bone marrow vs peripheral blood grafts) and BMTCTN 0402 (tacrolimus/methotrexate vs tacrolimus/sirolimus) trials showed that only about 20% of the patients were alive and immunosuppression-free by 5 years post HCT.4 All patients on these trials received CNI-based prophylaxis. Similar probability of being alive, disease relapse-free and free of immunosuppression with PTCy-based prophylaxis has not described. An extensive evaluation assessing the predictors of immunosuppression discontinuation may not be feasible with the available data, and is not the goal of the proposal. Yet, a comparative snapshot of this outcome with CNI-based vs PTCy-based will provide a broad picture and background data for future studies.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_241ua7P7OCxSmrg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Picture1.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	40887
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	All patients who underwent HLA-matched allogeneic HCT - either matched sibling (MSD) or 8/8 unrelated (MUD) or haploidentical HCT, and had data reported in CIBMTR between *2008-2021 Conditioning: MAC or RIC/NMA. Disease type: Any hematologic malignancy Graft: PB or BM GVHD prophylaxis: PTCy-based versus conventional (CNI-based) Exclude patients with ex-vivo T cell depletion/CD34+selected grafts, and exclude patients undergoing second allogeneic HCT
Does this study include pediatric patients?	Yes

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	i) Patient-related: • Age at HCT, years • Sex: male vs female • Karnofsky performance score: ≥90% vs. <90% • HCT comorbidity index at transplant 0, 1, 2, 3, 4, 5+ • Race/ethnicity: Non-Hispanic White vs. NH-Black vs. Hispanic vs. Asian/pacific islander vs. others • CMV: seropositive vs. seronegative. ii) Disease-related: • Disease diagnosis • Disease stage • Disease-Risk Index • Time from diagnosis to HCT iii) Donor/Transplant-related: • BM vs. PB graft • Conditioning: MAC vs RIC vs. NMA. • Year of HCT • Donor sex: male vs female • Donor CMV: seropositive vs. seronegative • Donor age, years (continuous variable) • Donor relationship • DQB1 match status (for MUD): matched vs mismatched • DPB1 match status (for MUD): matched, vs permissive mismatch, vs non-permissive mismatch • In vivo T cell depletion (ATG/Campath vs not) • MMF use in the prophylaxis regimen • New immunosuppresants used within 6 months post HCT (yes vs no, and date of start/end of treatment if yes) • Date of discontinuation of all immunosuppresants iv) Outcome related • Primary outcomes: a. Aim 1: a. Organs involved with acute and chronic GVHD b. Individual organ stage and overall grade of acute GVHD b. Aim 2: incidence of de novo and relapsing/progressing chronic GVHD c. Aim 3: incidence of mortality after development of grade III-IV acute GVHD or moderate-severe chronic GVHD (as a surrogate for response) • Secondary endpoints: o Incidence of acute GVHD o Incidence of mild, moderate and severe chronic GVHD o Relapse o Non-relapse mortality o Overall Survival o Causes of Death o Relapse-free and immunosuppression-free survival We are proposing that Rima Saliba (co-PI on the proposal) perform the analysis. She has prior experience with working with the CIBMTR datasets2. If acceptable to the CIBMTR working committee, we will only need the dataset and no other statistical support from the CIBMTR team. Study design: The study will be retrospective analysis aimed at comparing the incidence

	and characteristics of GVHD according to donor type and GVHD prophylaxis regimen. The study population includes recipients of HLA-matched donor HCT (with PTCy-based or conventional CNI-based GVHD prophylaxis) and haploidentical donor HCT (with PTCy-based prophylaxis). Statistical analysis: Aim 1: Compare the distribution of acute and chronic GVHD organ involvement by GVHD prophylaxis groups and by donor type. The analyses for this aim will be performed on 2 subsets of the study population: 1) patients diagnosed with any acute GVHD within 6 months post-HCT, and 2) patients diagnosed with any chronic GVHD within 5 years after transplant. The distribution of each organ involved will be described as a proportion of the total number of patients diagnosed with acute or chronic GVHD. The distribution of organs involved will be compared across donor and GVHD prophylaxis types using the chi square or Fisher's exact tests. Aim 2: Incidence of de novo chronic GVHD, progressive/relapsing chronic GVHD and overall chronic GVHD. This will be performed on the overall study population for the estimation of the incidence of de novo chronic GVHD, and on the subset of patients diagnosed with acute GVHD for the estimation of the incidence of relapsing/progressive chronic GVHD. Patients who are diagnosed with "overlap" GVHD will be excluded from the estimation of the incidence of relapsing/progressive chronic GVHD. a. de novo chronic GVHD: The incidence of de novo chronic GVHD is defined as the time from HCT to the first diagnosis of chronic GVHD in the absence of antecedent acute GVHD. The cumulative incidence of de novo chronic GVHD will be estimated considering death, relapse of malignancy, or a history of acute GVHD as competing event. The rate of de novo chronic GVHD according to donor and GVHD prophylaxis types will be compared in univariate and multivariate analyses using the Fine-Gray subdistribution hazard regression model. The main effect (type of donor/ GVHD prophylaxis) will be forced in the multivariate model irrespective of statistical significance in univariate analysis. In addition to the main effect, clinically or statistically significant predictors will be considered in multivariate analysis. The backward elimination rule will be used to determine the final multivariate regression model. First degree interaction effects will be evaluated and reported as indicated. Variations in NRM rate over time will be evaluated and adjusted for as indicated. Statistical significance will be determined at the 0.05 level. b. Relapsing/ progressive chronic GVHD: The incidence of relapsing/progressive chronic GVHD is defined as the time from diagnosis of acute GVHD to the time of diagnosis of chronic GVHD. The cumulative incidence

	will be estimated considering death or progression of malignancy as competing risks. The rate of relapsing/progressive chronic GVHD according to donor and GVHD prophylaxis types will be compared in univariate and multivariate analyses using the Fine-Gray subdistribution hazard regression model. The main effect (type of donor/ GVHD prophylaxis) will be forced in the multivariate model irrespective of statistical significance in univariate analysis. In addition to the main effect, clinically or statistically significant predictors will be considered in multivariate analysis. The backward elimination rule will be used to determine the final multivariate regression model. First degree interaction effects will be evaluated and reported as indicated. Variations in NRM rate over time will be evaluated and adjusted for as indicated. Statistical significance will be determined at the 0.05 level. Aim 3: Assess acute and chronic GVHD response and immunosuppression burden: will be performed on the following subsets of the study population: 1) patients diagnosed with grade III-IV acute GVHD within 6 months post-HCT, 2) patients diagnosed with moderate-severe chronic GVHD within 5 years after transplant, and 3) entire cohort to assess the proportion of relapse-free and immunosuppression-free survivors by 3 years and 5 years post HCT in the two GVHD groups. As the data regarding response to treatment are not collected per-se, we will primarily use surrogate outcomes such as the non-relapse mortality and overall survival by 6-months after the development of grade III-IV acute GVHD (for acute GVHD cohort), and 2-years and 3-years after the development of mod-severe chronic GVHD (for chronic GVHD cohort). In addition, for acute GVHD cohort only, we will describe the rates of initiation of new immunosuppressants within 6 months post HCT (i.e. drugs that were not part of prophylaxis), and the rate of discontinuation of all immunosuppressants by 6-and 12- months from the time of diagnosis of grade III-IV acute GVHD. Non-relapse mortality. The incidence of non-relapse mortality (NRM) is defined as the time from diagnosis of GVHD to the time of death in the absence of or progression of the underlying malignancy. The cumulative incidence of NRM will be estimated considering progression of malignancy or death with persistent malignancy as competing risks. The rate of NRM according to donor and GVHD prophylaxis types will be compared in univariate and multivariate analyses using the Fine-Gray subdistribution hazard regression model. The main effect (type of donor/ GVHD prophylaxis) will be forced in the multivariate model irrespective of statistical significance in univariate analysis. In addition to the main effect, clinically or statistically significant

Field	Response
	predictors will be considered in multivariate analysis. The backward elimination rule will be used to determine the final multivariate regression model. First degree interaction effects will be evaluated and reported as indicated. Variations in NRM rate over time will be evaluated graphically and statistically and adjusted for as indicated. Statistical significance will be determined at the 0.05 level. Overall survival. Overall survival (OS) is defined as the time from diagnosis of GVHD to the time of death from any cause. Actuarial OS will be estimated using the Kaplan-Meier method. The rate of mortality according to donor and GVHD prophylaxis types will be compared in univariate and multivariate analyses using Cox's proportional hazards regression analysis. The main effect (type of donor/ GVHD prophylaxis) will be forced in the multivariate model irrespective of statistical significance in univariate analysis. In addition to the main effect, clinically or statistically significant predictors will be considered in multivariate analysis. The backward elimination rule will be used to determine the final multivariate regression model. First degree interaction effects will be evaluated and reported as indicated. The proportionality of the hazards assumption will be evaluated graphically and statistically and adjusted for if violated. Statistical significance will be determined at the 0.05 level. Relapse-free and immunosuppression-free survival: will be assessed as the proportion of survivors who never relapse post HCT and are off immunosuppression by 3 years and 5 years post HCT in the two GVHD groups.
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 desc	N.A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N.A.
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 o	N.A
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.	N.A

Field	Response
REFERENCES:	References: 1. Bolanos-Meade J, Hamadani M, Wu J, et al: Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis. N Engl J Med 388:2338-2348, 2023 2. Saliba RM, Alousi AM, Pidala J, et al: Characteristics of Graft-Versus-Host Disease (GvHD) After Post-Transplantation Cyclophosphamide Versus Conventional GvHD Prophylaxis. Transplant Cell Ther 28:681-693, 2022 3. Mehta RS, Saliba RM, Rondon G, et al: Post-Transplantation Cyclophosphamide Versus Tacrolimus and Methotrexate Graft-Versus-Host Disease Prophylaxis for HLA-Matched Donor Transplantation. Transplant Cell Ther 28:695 e1-695 e10, 2022 4. Pidala J, Martens M, Anasetti C, et al: Factors Associated With Successful Discontinuation of Immune Suppression After Allogeneic Hematopoietic Cell Transplantation. JAMA Oncol 6:e192974, 2020
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal
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.

Table 1. Characteristics of patients undergoing a 1st allo HCT for any hematological malignancy with PTCy-based or CNI-based GVHD prophylaxis, 2008-2021

Characteristic	PTCy-based	CNI-based	Total
No. of patients	3883	14381	18264
No. of centers	201	267	287
Age group - no. (%)			
Median (min-max)	56.6 (0.6-87.8)	56.2 (0.4-83.4)	56.3 (0.4-87.8)
0-10	121 (3.1)	432 (3.0)	553 (3.0)
10-20	190 (4.9)	658 (4.6)	848 (4.6)
20-30	432 (11.1)	1063 (7.4)	1495 (8.2)
30-40	357 (9.2)	1190 (8.3)	1547 (8.5)
40-50	429 (11.0)	1930 (13.4)	2359 (12.9)
50-60	725 (18.7)	3435 (23.9)	4160 (22.8)
60-70	1241 (32.0)	4513 (31.4)	5754 (31.5)
70-80	384 (9.9)	1157 (8.0)	1541 (8.4)
80-90	4 (0.1)	3 (0.0)	7 (0.0)
TED or RES track - no. (%)			
Research patient	3883 (100)	14381 (100)	18264 (100)
CCN region at transplant - no. (%)			
US	3300 (85.0)	12610 (87.7)	15910 (87.1)
Canada	40 (1.0)	112 (0.8)	152 (0.8)
Europe	111 (2.9)	361 (2.5)	472 (2.6)
Asia	118 (3.0)	502 (3.5)	620 (3.4)
Australia/New Zealand	92 (2.4)	356 (2.5)	448 (2.5)
Mideast/Africa	37 (1.0)	163 (1.1)	200 (1.1)
Central/South America	185 (4.8)	277 (1.9)	462 (2.5)
Sex - no. (%)			
Male	2368 (61.0)	8716 (60.6)	11084 (60.7)
Female	1515 (39.0)	5665 (39.4)	7180 (39.3)
Race - no. (%)			
White	2727 (70.2)	11940 (83.0)	14667 (80.3)
Black or African American	551 (14.2)	690 (4.8)	1241 (6.8)
Asian	243 (6.3)	954 (6.6)	1197 (6.6)
Native Hawaiian or other Pacific Islander	27 (0.7)	65 (0.5)	92 (0.5)
American Indian or Alaska Native	27 (0.7)	88 (0.6)	115 (0.6)
More than one race	40 (1.0)	113 (0.8)	153 (0.8)
Not reported	268 (6.9)	531 (3.7)	799 (4.4)
Karnofsky score - no. (%)			
< 90	1677 (43.2)	5666 (39.4)	7343 (40.2)
90 - 100	2137 (55.0)	8474 (58.9)	10611 (58.1)

Characteristic	PTCy-based	CNI-based	Total
Not reported	69 (1.8)	241 (1.7)	310 (1.7)
HCT-CI - no. (%)			
0	1049 (27.0)	4114 (28.6)	5163 (28.3)
1	597 (15.4)	1988 (13.8)	2585 (14.2)
2	533 (13.7)	1918 (13.3)	2451 (13.4)
3	622 (16.0)	2374 (16.5)	2996 (16.4)
4	422 (10.9)	1520 (10.6)	1942 (10.6)
5	274 (7.1)	910 (6.3)	1184 (6.5)
6	161 (4.1)	607 (4.2)	768 (4.2)
7+	192 (4.9)	626 (4.4)	818 (4.5)
Missing/TBD	33 (0.8)	324 (2.3)	357 (2.0)
Primary disease - no. (%)			
Acute myelogenous leukemia or ANLL	1622 (41.8)	5352 (37.2)	6974 (38.2)
Acute lymphoblastic leukemia	575 (14.8)	1793 (12.5)	2368 (13.0)
Other leukemia	80 (2.1)	543 (3.8)	623 (3.4)
Chronic myelogenous leukemia	92 (2.4)	500 (3.5)	592 (3.2)
Myelodysplastic/myeloprolifterative disorders	870 (22.4)	4272 (29.7)	5142 (28.2)
Other acute leukemia	46 (1.2)	142 (1.0)	188 (1.0)
Non-Hodgkin lymphoma	271 (7.0)	1179 (8.2)	1450 (7.9)
Hodgkin lymphoma	262 (6.7)	326 (2.3)	588 (3.2)
Plasma cell disorder/Multiple Myeloma	57 (1.5)	269 (1.9)	326 (1.8)
Other Malignancies	8 (0.2)	5 (0.0)	13 (0.1)
Graft type - no. (%)			
Bone marrow	1134 (29.2)	2293 (15.9)	3427 (18.8)
Peripheral blood	2749 (70.8)	12088 (84.1)	14837 (81.2)
Donor type - no. (%)			
HLA-identical sibling	313 (8.1)	5627 (39.1)	5940 (32.5)
Haploidentical	2932 (75.5)	374 (2.6)	3306 (18.1)
Well-matched unrelated (8/8)	638 (16.4)	8380 (58.3)	9018 (49.4)
Conditioning regimen intensity - no. (%)			
MAC	1594 (41.1)	7179 (49.9)	8773 (48.0)
RIC	919 (23.7)	5925 (41.2)	6844 (37.5)
NMA	1370 (35.3)	1277 (8.9)	2647 (14.5)
Year of current transplant - no. (%)			
2008	59 (1.5)	1501 (10.4)	1560 (8.5)
2009	29 (0.7)	1111 (7.7)	1140 (6.2)
2010	15 (0.4)	892 (6.2)	907 (5.0)
2011	11 (0.3)	626 (4.4)	637 (3.5)
2012	23 (0.6)	661 (4.6)	684 (3.7)
2013	144 (3.7)	1374 (9.6)	1518 (8.3)

Characteristic	PTCy-based	CNI-based	Total
2014	212 (5.5)	1754 (12.2)	1966 (10.8)
2015	362 (9.3)	1510 (10.5)	1872 (10.2)
2016	468 (12.1)	1309 (9.1)	1777 (9.7)
2017	560 (14.4)	1049 (7.3)	1609 (8.8)
2018	646 (16.6)	924 (6.4)	1570 (8.6)
2019	673 (17.3)	734 (5.1)	1407 (7.7)
2020	375 (9.7)	452 (3.1)	827 (4.5)
2021	306 (7.9)	484 (3.4)	790 (4.3)
Median follow-up of survivors (range), months - median (range)	48.6 (0.0-171.4)	73.2 (0.0-181.5)	

Field	Response
Proposal Number	2310-178-BOIKO
Proposal Title	Quantification of Severe and Highly Morbid Chronic Graft-Versus-Host Disease Forms in Pediatric Hematopoietic Cell Transplantation Patients Since Implementation of the 2014 NIH Consensus Criteria
Key Words	Chronic GVHD, pediatrics, scleroderma, bronchiolitis obliterans
Principal Investigator #1: - First and last name, degree(s)	Julie Boiko, MD, MS
Principal Investigator #1: - Email address	jboiko@fredhutch.org
Principal Investigator #1: - Institution name	Fred Hutchinson Cancer Center
Principal Investigator #1: - Academic rank	Acting Instructor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	No current work
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Graft vs Host Disease
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	- In pediatric HCT patients, what is the incidence of severe cGVHD (including highly morbid forms) on an organ-by-organ basis since the 2014 NIH cGVHD Consensus Criteria-based organ score reporting to CIBMTR began? - Which organs/systems are most prone to highly morbid cGVHD in children and young adults? Is there a difference in these organs' incidences of cGVHD which develops within <1 vs >1 year (and what are the associations)?
RESEARCH HYPOTHESIS:	More severe, morbid form, and later-occurring cGVHD in children and adolescents is associated with older patient age, peripheral blood stem cell graft source, prior aGVHD, and preceding organ morbidity or significant post-HCT infection/injury.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary objective: Quantify the incidence of specific cGVHD organ incidences and scores/severities, including highly morbid cGVHD forms (sclerosis, bronchiolitis obliterans, ocular) using the 2014 NIH cGVHD Consensus Criteria for children and adolescents within at least 2 years of undergoing HCT (and up to 5 years per length of reported CIBMTR followup). Secondary objectives: - Describe the impact of patient age, donor age/sex/type, GVHD prophylaxis, prior acute GVHD, infections, and prior organ insults on the incidence, timing, and severity of cGVHD in an organ-based manner. - Describe which organ systems' cGVHD—and specifically morbid forms of cGVHD—is most associated with non-relapse mortality in pediatric HCT patients.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	This will be the first comprehensive analysis of pediatric cGVHD incidence and severity using current consensus criteria to quantify organ-specific severe forms of cGVHD. This will discern risk factors for specific organs' most severe cGVHD. This will potentially shape approaches to GVHD prophylaxis and cGVHD treatment intensity by accounting for such risk factors.

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.	Chronic graft-versus-host disease (cGVHD) is the leading cause of nonrelapse morbidity and mortality among long-term survivors of hematopoietic cell transplantation (HCT) (Kitko et al., 2021; Williams et al., 2021). 6 to 33% of pediatric and young adult survivors develop cGVHD in the current HCT era pending variable patient, donor, and graft/transplant characteristics (Rocha et al., 2000; Eapen et al., 2004; Qayed et al., 2018; Cuvelier et al., 2019). cGVHD incidence in the pediatric HCT population is lower than in the adult population which may range from 30 to 70% (Kitko et al. 2021; Williams et al. 2021). This is attributable to predominate bone marrow and cord blood graft use, younger recipient age, and generally lower hematopoietic cell transplant comorbidity index compared to adults (Zecca et al., 2002; Smith et al., 2011; Qayed et al., 2018). However, cGVHD development during childhood or adolescence has disproportionately negative effects on pediatric patients as a function of their potentially many years of life post-HCT, due both to intrinsic morbidities from cGVHD organ pathology and to potentially years-long immunosuppression exposure with associated infections and growth and metabolic deleterious effects (Inagaki et al., 2015; Lee et al., 2022). In particular, highly morbid forms of cGVHD (principally scleroderma, bronchiolitis obliterans, and ocular cGVHD) can be devastating to patients' ensuing decades' quality of life and functional status; these can be difficult or impossible to reverse once disease is established due to their fibrotic and anatomically destructive nature (Wolff et al., 2021). Although pediatric rates of organ system involvement (dominated by oral, skin, and ocular cGVHD) and global severity (47% severe (Inagaki et al., 2015)) have been reported, the pediatric incidence of these prototypical highly morbid disease forms as well as severity due to any given organ system has not been quantified in detail using the criteria of (or classifications readily compatible with) the most recent NIH Chronic GVHD Consensus Criteria (Jagasia et al., 2015). These contrast with adults' 28% rate of severe disease (most commonly skin, mouth, and liver) (Arora et al., 2016); this prospectively suggests that, when pediatric cGVHD occurs, it has the same if not more potential to be worse than adult patients' rates. It is likewise not clearly known which of these cGVHD sub-diagnoses is most contributory to and/or associated with NRM in pediatric patients. Separately from organ-based severity, mismatched HLA, peripheral blood graft, low performance score, and platelets <100k at cGVHD were associated with worsened pediatric cGVHD mortality; age >10yo further imparted worse OS (Jacobsohn et al.,

	2011). Given often permanent ensuing organ damage and associated detriment to life-years in these young patients, it is imperative to quantify the risk factors for development of highly morbid and/or globally severe cGVHD to both prevent it and treat it when it is still nascent. Beyond known risk factors for cGVHD in the overall HCT population (e.g., graft source, prior aGVHD (Zecca et al., 2002; Arora et al., 2013)), it is entirely possible that preceding organ morbidities and insults predispose to cGVHD in these respective organs. For example, this has been implicated in lung transplantation associations of post-transplant pulmonary Aspergillus infection with subsequent BOS development at a 3.02 hazard ratio, with infection preceding BOS development by median 261 days (Weigt et al., 2009); similarly, CMV infection within the first 100 days of HCT correlate with a 2.88 hazard ratio increase of BOS development (Zhou et al., 2019). Establishing analogous phenomena in additional organs/cGVHD forms may shape approaches to GVHD prophylaxis and decision-making about management of signs/symptoms which may not yet be definitive for cGVHD. This is especially pertinent in clinical approaches to very young patients whose symptom reporting ability and/or cooperation with clinical evaluations (e.g., pulmonary function tests) may limit cGVHD diagnostic sensitivity (Tamburro et al., 2021). The recent NIH Consensus Development Project report on highly morbid cGVHD forms identified prevention, associations with, triggers, and treatment of such fibrotic cGVHD changes as key research priorities, centering children's experience of these effects as a prominent need (Wolff et al., 2021). The publication of the 2014 NIH Consensus Criteria and these criteria's incorporation into CIBMTR's data reporting forms since 2017 provide a timely opportunity to granularly quantify in children and adolescents the incidence of these cGVHD forms, identify associations with NRM, and determine cGVHD correlates with preceding infection and organ toxicity events in patients' HCT courses. As these data have now been reported for >6 years as of this proposal submission, this timeframe can capture occurrence of and predispositions to later-onset (>1 year post-HCT) cGVHD, which may comprise up to 10% of cGVHD diagnoses in adults (Arai et al., 2015). This CIBMTR data timeframe also lends itself to distinguishing the evolution of highly morbid cGVHD phenomena such as scleroderma which are rarely present at cGVHD onset but (in adults) may develop in up to 20% of patients treated for cGVHD after 3 years (Inamoto et al., 2013). These data's timeframe furthermore can potentially capture the leading edge of any pediatric parallels to a sobering phenomenon in adult HCT survivors whereby

Field	Response
	cGVHD-associated NRM does not plateau but increases over time; in an analysis of two prospective, longitudinal observational Chronic GVHD Consortium studies, NRM (of which NIH skin score 2-3 and lung score 1-3 were significant multivariate predictors) was 22% at 5 years and increased to a projected 40% at 12 years post-HCT (DeFilipp et al., 2021). With the availability of granular organ-based reporting across rigorously standardized clinical cGVHD consensus criteria, this study aims to quantify highly morbid as well as globally severe cGVHD forms in the pediatric HCT population as well as relate individual organs' disease to NRM risk. This study will furthermore clarify the risk factors for development of these morbid and severe disease forms in children and adolescents. Establishing these data will enable clinicians to act more rapidly on events preceding and at the start of cGVHD to reduce its morbidity and mortality in children.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion - 21 years old or younger at time of HCT - First allogeneic HCT for a malignant or nonmalignant condition, with the 6 month and subsequent CIBMTR reporting timepoints completed Revision 4 or later of CIBMTR Form 2100 (Post-Infusion Follow-Up) which incorporated the 2014 NIH cGVHD Consensus Criteria - Patients must have survived through at least 100 days post-HCT - Data available through 2 years post-HCT or patient death, whichever event is earlier Exclusion - Patients with missing data on development of cGVHD will be excluded
Does this study include pediatric patients?	Yes

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Referenced question numbers are from the current CIBMTR data form 2100 Revision 8 (Post-Infusion Follow-Up). https://cibmtr.org/Data-Collection-Files/Forms/2100--R8.pdf No data collection beyond existing CIBMTR data forms is proposed. Outcomes: - Chronic GVHD (at 6 months, 1, 2, and 3 years) as a categorical variable (yes/no) for all patients (#134-135) - Categorical variables of chronic GVHD persistence, overlap with acute GVHD, performance scores, and continuous variables of bilirubin and platelet count at time of cGVHD diagnosis (#136-143) - Organs involved at time of cGVHD diagnosis (categorical variables) with respective organ scores (0 to 3) and presence of cGVHD-associated features (categorical variables) and associated non-cGVHD organ abnormalities post-HCT (freetext categorical variables) (#152-184, #188-189) - Maximal cGVHD grade, date, and limited vs. extensive disease (categorical variables) (#185-187) - Current GVHD activity (yes/no) (#204) - Overall survival (with or without relapse of underlying disease) - Non-relapse mortality, defined as time-to variable (in absence of disease progression, relapse, or persistence) - Cause of death for patients who died post-HCT (categorical variables of GVHD, infection, organ failure, other, or not reported) Correlates - Occurrence of engraftment syndrome (yes/no), organ sites (categorical variable), and resolution (yes/no) (#73-74, #78, #83) - Acute GVHD occurrence by day +180 (yes/no), maximum grade and organ scores (ordinal variables), systemic treatment steroids (yes/no) and other treatments (categorical variables) (#94-96, #105-119, #120-121) - Major organ dysfunction - Pulmonary, including idiopathic pulmonary syndrome (yes/no), non-infectious pathologies (categorical variable), intubation/extubation history (yes/no) (#249-250, 253-254, #259-262) - Liver – presence of non-infectious liver toxicity (yes/no), type of toxicity and associated prophylaxis (categorical variables) (#263-268) - Thrombotic microangiopathy – Presence (yes/no), signs/symptoms and treatment (categorical variables), and resolution status (yes/no) (#269-270, #277-280) - Other organ impairment (#281) – categorical variable - Significant infections (#227-239) – occurrence (yes/no), organisms and site (categorical variables), SIRS and septic shock occurrence (yes/no) - Use of growth factors or cytokines (yes/no and categorical variables) (#21-23) Patient-related: - Patient age (both as continuous variables and

Field	Response
	categorical age group cut points) - Sex (female/male) - Race/ethnicity (categorical variable) - Performance score (dichotomized) - Transplant indication (both as categorical variable and dichotomous malignant vs non-malignant variable) Donor-related: - Graft type (bone marrow, cord blood, peripheral blood stem cell) - Donor age (continuous variable) - Donor type (categorical variable) - Donor/recipient sex match (categorical) - ABO mismatch (categorical) - Donor/recipient CMV status (categorical variable) Transplant-related - Conditioning regimen (categorical myeloablative vs. nonmyeloablative/reduced intensity) - TBI (none/low dose/high dose) - Total nucleated cell dose (dichotomous < 2 x 108 /kg or > 2 x 108 /kg); will subset cord blood graft cell doses separately - GVHD prophylaxis (categorical CNI+MTX, CNI+MMF, PTCy, CD34 selection or other ex vivo T depletion) - Steroids as part of GVHD prophylaxis (yes/no) - In vivo T cell depletion as part of conditioning (yes/no)
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 desc	None
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	No
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.	N/A

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Field	Response
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CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Table 1. Characteristics of patients undergoing a 1st allo HCT for malignant or non-malignant disease, 2017-2022

Characteristic	No cGVHD	cGVHD	Total
No. of patients	1933	479	2412
No. of centers	141	108	148
Age group - no. (%)			
Median (min-max)	7.7 (0.0-21.0)	10.3 (0.0-21.0)	8.2 (0.0-21.0)
0-10	1189 (61.5)	231 (48.2)	1420 (58.9)
10-20	686 (35.5)	230 (48.0)	916 (38.0)
20-30	58 (3.0)	18 (3.8)	76 (3.2)
TED or research track - no. (%)			
Research patient	1933 (100)	479 (100)	2412 (100)
CCN region at transplant - no. (%)			
US	1159 (60.0)	342 (71.4)	1501 (62.2)
Canada	33 (1.7)	10 (2.1)	43 (1.8)
Europe	22 (1.1)	3 (0.6)	25 (1.0)
Asia	399 (20.6)	56 (11.7)	455 (18.9)
Australia/New Zealand	76 (3.9)	17 (3.5)	93 (3.9)
Mideast/Africa	144 (7.4)	19 (4.0)	163 (6.8)
Central/South America	100 (5.2)	32 (6.7)	132 (5.5)
Sex - no. (%)			
Male	1164 (60.2)	284 (59.3)	1448 (60.0)
Female	769 (39.8)	195 (40.7)	964 (40.0)
Race - no. (%)			
White	770 (39.8)	215 (44.9)	985 (40.8)
Black or African American	305 (15.8)	111 (23.2)	416 (17.2)
Asian	424 (21.9)	37 (7.7)	461 (19.1)
Native Hawaiian or other Pacific Islander	14 (0.7)	5 (1.0)	19 (0.8)
American Indian or Alaska Native	30 (1.6)	6 (1.3)	36 (1.5)
More than one race	66 (3.4)	16 (3.3)	82 (3.4)
Not reported	324 (16.8)	89 (18.6)	413 (17.1)
Karnofsky score - no. (%)			
< 90	225 (11.6)	64 (13.4)	289 (12.0)
90 - 100	1555 (80.4)	386 (80.6)	1941 (80.5)
Not reported	153 (7.9)	29 (6.1)	182 (7.5)
HCT-CI - no. (%)			
0	1275 (66.0)	260 (54.3)	1535 (63.6)
1	320 (16.6)	78 (16.3)	398 (16.5)
2	86 (4.4)	34 (7.1)	120 (5.0)

Characteristic	No cGVHD	cGVHD	Total
3	134 (6.9)	56 (11.7)	190 (7.9)
4	62 (3.2)	24 (5.0)	86 (3.6)
5	25 (1.3)	7 (1.5)	32 (1.3)
6	17 (0.9)	12 (2.5)	29 (1.2)
7+	10 (0.5)	6 (1.3)	16 (0.7)
Missing/TBD	4 (0.2)	2 (0.4)	6 (0.2)
Primary disease - no. (%)			
Acute myelogenous leukemia or ANLL	179 (9.3)	64 (13.4)	243 (10.1)
Acute lymphoblastic leukemia	178 (9.2)	77 (16.1)	255 (10.6)
Other leukemia	0 (0.0)	2 (0.4)	2 (0.1)
Chronic myelogenous leukemia	14 (0.7)	2 (0.4)	16 (0.7)
Myelodysplastic/myeloprolifterative disorders	44 (2.3)	16 (3.3)	60 (2.5)
Other acute leukemia	10 (0.5)	7 (1.5)	17 (0.7)
Non-Hodgkin lymphoma	25 (1.3)	8 (1.7)	33 (1.4)
Hodgkin lymphoma	21 (1.1)	10 (2.1)	31 (1.3)
Other Malignancies	1 (0.1)	1 (0.2)	2 (0.1)
Severe aplastic anemia	306 (15.8)	69 (14.4)	375 (15.5)
Inherited bone marrow failure syndromes	142 (7.3)	36 (7.5)	178 (7.4)
Hemoglobinopathies	602 (31.1)	97 (20.3)	699 (29.0)
Paroxysmal nocturnal hemoglobinuria	8 (0.4)	1 (0.2)	9 (0.4)
SCID and other immune system disorders	295 (15.3)	58 (12.1)	353 (14.6)
Inherited abnormalities of platelets	4 (0.2)	2 (0.4)	6 (0.2)
Inherited disorders of metabolism	67 (3.5)	16 (3.3)	83 (3.4)
Histiocytic disorders	33 (1.7)	8 (1.7)	41 (1.7)
Autoimmune Diseases	1 (0.1)	1 (0.2)	2 (0.1)
Other, specify	1 (0.1)	1 (0.2)	2 (0.1)
Myeloproliferative Neoplasms	2 (0.1)	3 (0.6)	5 (0.2)
Graft type - no. (%)			
Bone marrow	1269 (65.6)	272 (56.8)	1541 (63.9)
Peripheral blood	360 (18.6)	117 (24.4)	477 (19.8)
Umbilical cord blood	260 (13.5)	75 (15.7)	335 (13.9)
BM + PB	15 (0.8)	5 (1.0)	20 (0.8)
BM + UCB	20 (1.0)	4 (0.8)	24 (1.0)
PB + UCB	3 (0.2)	1 (0.2)	4 (0.2)
PB + OTH	2 (0.1)	3 (0.6)	5 (0.2)
UCB + OTH	4 (0.2)	2 (0.4)	6 (0.2)
Donor type - no. (%)			
HLA-identical sibling	692 (35.8)	96 (20.0)	788 (32.7)
Twin	5 (0.3)	0 (0.0)	5 (0.2)
Haploidentical	341 (17.6)	122 (25.5)	463 (19.2)

Characteristic	No cGVHD	cGVHD	Total
Other related	96 (5.0)	20 (4.2)	116 (4.8)
Mismatched related - not otherwise specified	66 (3.4)	13 (2.7)	79 (3.3)
Well-matched unrelated (8/8)	322 (16.7)	94 (19.6)	416 (17.2)
Partially-matched unrelated (7/8)	78 (4.0)	39 (8.1)	117 (4.9)
Mis-matched unrelated (<= 6/8)	3 (0.2)	3 (0.6)	6 (0.2)
Multi-donor	7 (0.4)	1 (0.2)	8 (0.3)
Unrelated (matching TBD)	25 (1.3)	6 (1.3)	31 (1.3)
Cord blood	287 (14.8)	82 (17.1)	369 (15.3)
Not reported	11 (0.6)	3 (0.6)	14 (0.6)
Conditioning regimen intensity - no. (%)			
No drugs reported	0 (0.0)	1 (0.2)	1 (0.0)
MAC	1222 (63.2)	317 (66.2)	1539 (63.8)
RIC	167 (8.6)	49 (10.2)	216 (9.0)
NMA	342 (17.7)	75 (15.7)	417 (17.3)
TBD	13 (0.7)	3 (0.6)	16 (0.7)
Missing	189 (9.8)	34 (7.1)	223 (9.2)
cGVHD severity - no. (%)			
Limited	0 (0.0)	208 (43.4)	208 (8.6)
Extensive	0 (0.0)	269 (56.2)	269 (11.2)
No cGvHD	1933 (100)	0 (0.0)	1933 (80.1)
Missing	0 (0.0)	2 (0.4)	2 (0.1)
Maximum cGVHD grade - no. (%)			
No GVHD	1933 (100)	0 (0.0)	1933 (80.1)
Mild	0 (0.0)	261 (54.5)	261 (10.8)
Moderate	0 (0.0)	109 (22.8)	109 (4.5)
Severe	0 (0.0)	98 (20.5)	98 (4.1)
Missing	0 (0.0)	11 (2.3)	11 (0.5)
Sclerosis - no. (%)			
No	1933 (100)	435 (90.8)	2368 (98.2)
Yes	0 (0.0)	44 (9.2)	44 (1.8)
Bronchiolitis obliterans - no. (%)			
No	1922 (99.4)	455 (95.0)	2377 (98.5)
Yes	11 (0.6)	24 (5.0)	35 (1.5)
Max NIH eye score - no. (%)			
No	1933 (100)	433 (90.4)	2366 (98.1)
Yes	0 (0.0)	46 (9.6)	46 (1.9)
Max NIH joints/fascia score - no. (%)			
No	1933 (100)	471 (98.3)	2404 (99.7)
Yes	0 (0.0)	8 (1.7)	8 (0.3)
Max NIH lung score - no. (%)			

Characteristic	No cGVHD	cGVHD	Total
No	1933 (100)	460 (96.0)	2393 (99.2)
Yes	0 (0.0)	19 (4.0)	19 (0.8)
GVHD prophylaxis - no. (%)			
None	27 (1.4)	1 (0.2)	28 (1.2)
Ex-vivo T-cell depletion	80 (4.1)	12 (2.5)	92 (3.8)
CD34 selection	89 (4.6)	10 (2.1)	99 (4.1)
PtCy + other(s)	354 (18.3)	127 (26.5)	481 (19.9)
PtCy alone	6 (0.3)	1 (0.2)	7 (0.3)
TAC + MMF +- other(s) (except PtCy)	176 (9.1)	56 (11.7)	232 (9.6)
TAC + MTX +- other(s) (except MMF, PtCy)	236 (12.2)	91 (19.0)	327 (13.6)
TAC + other(s) (except MMF, MTX, PtCy)	18 (0.9)	10 (2.1)	28 (1.2)
TAC alone	23 (1.2)	5 (1.0)	28 (1.2)
CSA + MMF +- other(s) (except PtCy,TAC)	271 (14.0)	67 (14.0)	338 (14.0)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	406 (21.0)	80 (16.7)	486 (20.1)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	40 (2.1)	6 (1.3)	46 (1.9)
CSA alone	80 (4.1)	5 (1.0)	85 (3.5)
Other(s)	104 (5.4)	8 (1.7)	112 (4.6)
Missing	23 (1.2)	0 (0.0)	23 (1.0)
Year of current transplant - no. (%)			
2017	536 (27.7)	140 (29.2)	676 (28.0)
2018	592 (30.6)	133 (27.8)	725 (30.1)
2019	525 (27.2)	127 (26.5)	652 (27.0)
2020	192 (9.9)	51 (10.6)	243 (10.1)
2021	88 (4.6)	28 (5.8)	116 (4.8)
Median follow-up of survivors (range), months - median (range)	47.7 (24.0-83.3)	47.6 (24.0-76.3)	