A G E N D A
CIBMTR WORKING COMMITTEE FOR MORBIDITY, RECOVERY, AND SURVIVORSHIP
Orlando, Florida
Thursday, February 16, 2023, 12:15 p.m. – 2:15 p.m. (EST)

Co-Chair:	**Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven; Leuven, Belgium;** **Phone: 321-634-6880; E-mail: helene.schoemans@uzleuven.be**
Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA;** **Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Co-Chair:	**Betty Hamilton, MD, Cleveland Clinic Foundation, Cleveland, OH;** **Telephone: 216-445-7580; E-mail: hamiltb2@ccf.org**
Co-Chair:	**Edward Stadtmauer, MD; University of Pennsylvania Medical Center** **Phone: 215-662-7910; Email: Edward.Stadtmauer@uphs.upenn.edu**
Co-Chair:	**Bipin Savani, MD; Vanderbilt University Medical Center** **Phone: 615-936-8422; Email: bipin.savani@vumc.org**
Co-Chair:	**Mohamed Sorror, MD, MSc; Fred Hutchinson Cancer Research Center** **Phone: 206-667-6298; Email: msorror@fredhutch.org**
Scientific Director:	**Rachel Phelan MD, MPH, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-955-4153; E-mail: rphelan@mcw.edu**
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1. **Introduction**
   a. **Minutes and Overview Plan from April 2022 meeting**
      - Late Effects and Supportive Care (Attachment 1a)
      - Regimen-Related Toxicity and Supportive Care (Attachment 1b)

2. **Accrual Summary** (Attachment 2) and PRO Data Accrual (Attachment 3)

3. **Presentations, Published or Submitted Papers**
   a. **R718-S1:** Broglie L, Friend BD, Chhabra S, Bupp C, Schiller GJ, Logan B, Pasquini MC, Savani B, Stadtmauer EA, Thakar MS, Sorror M. Differential use of the hematopoietic cell transplantation-comorbidity index among adult and pediatric transplant physicians. ***Leukemia & Lymphoma. 2022 Oct 1; 63(10):2507-2510. doi:10.1080/10428194.2022.2076848. Epub 2022 May 18.***
   b. **RT18-02:** Abou-Ismail MY, Fraser R, Allbee-Johnson M, Metheny L 3rd, Ravi G, Ahn KW, Bhatt NS, Lazarus HM, de Lima M, El Jurdy N, Hematti P, Beitinjaneh AM, Nishihori T, Badawy SM, Sharma A, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation? ***British Journal of Haematology. 2022 May 1; 197(3):326-338. doi:10.1111/bjh.18108. Epub 2022 Mar 14. PMC9675037.***

c. **RT18-03:** Patel SS, Ahn KW, Khanal M, Bupp C, Allbee-Johnson M, Majhail NS, Hamilton BK, Rotz SJ, Hashem H, Beitinjaneh A, Lazarus HM, Krem MM, Prestidge T, Bhatt NS, Sharma A, Gadalla SM, Murthy HS, Broglie L, Nishihori T, Freytes CO, Hildebrandt GC, Gergis U, Seo S, Wirk B, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Noninfectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2022 Jun 1; 28(6):310-320. doi:10.1016/j.jtct.2022.03.015. Epub 2022 Mar 18. PMC9197865.***

d. **LE20-02:** Association between patient-reported social determinant of health outcomes and a social genomics profile in allogeneic hematopoietic cell transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) ***Oral presentation, ASH 2022. Poster presentation, Tandem 2023.***

e. **RT18-01a:** Expanded Definitions in the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Better Classifies Comorbidity in Children and Young Adults with Non-Malignant Diseases. (L Broglie/B Friend/G Schiller/M Thakar /M Sorror) ***Accepted.***

f. **RT18-01b:** Adapting the HCT-CI Applicability for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation. (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) ***Accepted.***

4. Studies in Progress (Attachment 4)

a. **LE16-02b** Late effects after AlloHCT for pediatric patients with non-malignant diseases (J Kahn/ P Satwani) **Manuscript Preparation.**

b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Manuscript Preparation.**

c. **LE17-01a** Late effects after hematopoietic stem cell transplantation for sickle cell disease. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) **Manuscript Preparation.**

d. **LE17-01b** Comparison of survival between transplanted and non-transplanted SCD patients. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) **Data File Preparation.**

e. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Manuscript Preparation.**

f. **LE18-03** Incorporating patient reported outcomes into individualized prognostication tools for survival and quality of life in transplant patients. (B Shaw) **Manuscript Preparation.**

g. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) **Analysis.**

h. **LE19-02** Incidence and predictors of long-term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for **hem**atological malignancies. (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) **Analysis.**

i. **LE20-01** Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) **Protocol Development.**

j. **LE20-02** Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) **Manuscript Preparation.**

k. **LE21-01** Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M- Angel Perales/A Kansagra) **Data File Preparation.**

l. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/B Savani/A Nagler) **Data File Preparation.**

m. **RT19-02** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/N Ali/O Frankfurt/L Metheny/J Moreira/M de Lima) **Protocol Development.**

n. **RT20-01** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients (R Jayani/H Murff) **Data File Preparation.**

o. **MRS22-01** Racial/ethnic disparities and role of poverty in long-term health outcomes among survivors of allogeneic hematopoietic cell transplant performed in childhood (N Bhatt/A Sharma/C Duncan/L Jimenez-Kurlander) **Protocol Development.**
p. **MRS22-02** Post-transplant cyclophosphamide related cardiomyopathy; incidence, risk factors and outcome: A retrospective review from CIBMTR database (K Poonsombudlert/C Strouse) **Protocol Development.**

5. Future/Proposed Studies

a. **PROP 2210-30** Impact of melphalan dose reduction on regimen-related toxicity in multiple myeloma patients undergoing autologous transplant. (M Krem/C Wagner) (Attachment 5)
b. **PROP 2210-63/2210-117/2210-219** Modifying the risk and mortality of veno-occlusive disease via development of a contemporary risk assessment model. (M Schoettler/K Williams/W Stock/ G Roloff/C Strouse) (Attachment 6)
c. **PROP 2210-91** Updated analysis of long-term survival and late deaths after allogeneic hematopoietic cell transplantation for hematologic malignancies and severe aplastic anemia. (U Rao/M Battiwalla) (Attachment 7)
d. **PROP 2210-141** Evaluation of total and fractionated total body irradiation doses on late effects and outcomes in pediatric patients with acute leukemia undergoing allogeneic hematopoietic cell transplantation. (L Appell/A Sharma) (Attachment 8)
e. **PROP 2210-199/2210-202** Prediction of non-relapse mortality by EASIX and HCT-CI scores in patients undergoing allogeneic stem cell transplant (H Alkhateeb/A Baranwal) (Attachment 9)

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

f. **PROP 2204-02/2210-103/2210-173/2210-180/2210-227/2210-251/2210-269** Incidence, risk factors, and characteristics of secondary malignancies following CAR-T therapy and its impact on survival. (V Irizarry-Gatell/M Shah/H Alkhateeb/R Faramand/D McQuinn/K Nadiminti/M Veeraputhiran/C Schinke/A Mirza/L Gowda/A Tun/P Johnston) ó!ŭúI·ŎKY˜Ŝyű млó

Dropped Proposed Studies

a. **PROP 2210-49** Allogeneic hematopoietic stem cell transplant outcomes for patients with varying degrees of pre-transplant dysfunction and/or cirrhosis. *Dropped due to unavailability of data.*
b. **PROP 2210-157** Factors at the onset of cytokine release syndrome may predict the development of severe immune effector cell-associated neurotoxicity syndrome post-CAR-T cell therapy for relapsed/refractory lymphoma. *Dropped for overlap with an existing study.*
c. **PROP 2210-165** Impact of obesity on post-transplant cyclophosphamide. *Dropped due to low scientific impact.*
d. **PROP 2210-181** Investigation of augmented hematopoietic cell transplant co-morbidity index as a predictor of outcomes following first allogeneic transplant in children. *Dropped due to low scientific impact.*
e. **PROP 2210-233** Toxicity and outcome differences by conditioning regimen received in severely obese allogeneic stem cell transplant recipients. *Dropped due to low scientific impact.*
f. ***PROP 2210-298*** *Hemophagocytic lympho-histiocytosis in the context of cellular therapies. Dropped due to low sample size.*

6. Closing Remarks

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Salt Lake City, UT
Monday, April 25, 2022, 12:15 – 1:45 pm MDT

Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Co-Chair:	**Betty Hamilton, MD, Cleveland Clinic Foundation, Cleveland, OH; Telephone: 216-445-7580; E-mail: hamiltb2@ccf.org**
Co-Chair:	**Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven Phone: 32 16 34 68 80; E-mail: helene.schoemans@uzleuven.be**
Scientific Director:	**Rachel Phelan, MD, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4153; E-mail: rphelan@mcw.edu**
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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 12:15pm MDT on Monday, April 25, 2022 by Dr. Rachel Phelan. She introduced the current working committee leadership and reviewed the CIBMTR COI policy. Dr. Betty Hamilton continued the introduction by outlining the processes of participating in the working committee, guidelines for voting, and rules of authorship. The two sources of HCT data (TED vs. CRF level) were introduced, mentioning that Late Effects data mostly comes from CRF level data. Dr. Hélène Schoemans gave a reminder that data sets from studies are publicly available for secondary analysis and encouraged attendees to visit the Collaborative Working Committee proposal session, taking place on Monday, April 25, 2022 at 2:00pm MDT.

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

Dr. Hélène Schoemans gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **LE18-02:** Neel S Bhatt, Ruta Brazauskas , Rachel B Salit, Karen Syrjala, Stephanie Bo-Subait, Heather Tecca, Sherif M Badawy, K Scott Baker, Amer Beitinjaneh, Nelli Bejanyan, Michael Byrne, Ajoy Dias, Nosha Farhadfar, César O Freytes, Siddhartha Ganguly, Shahrukh Hashmi, Robert J Hayashi, Sanghee Hong, Yoshihiro Inamoto, Kareem Jamani, Kimberly A Kasow, Raquel Schears, Tal Schechter-Finkelstein, Gary Schiller, Ami J Shah, Akshay Sharma, Trent Wang, Baldeep Wirk, Minoo Battiwalla, Hélène Schoemans, Betty Hamilton, David Buchbinder, Rachel Phelan, Bronwen Shaw. Return to work among young adult survivors of allogeneic hematopoietic cell transplantation in the united states. **Transplantation and Cellular Therapy. 2021 Aug 1; 27(8):679.e1-679.e8. doi:10.1016/j.jtct.2021.04.013.** ***Epub 2021 Apr 22. PMC8425287.***

b. **LE16-02b:** Late Effects after Allogeneic Hematopoietic Cell Transplantation Among Children and Adolescents with Non-Malignant Disorders: A Report from the Center for International Blood and

Marrow Transplant Research. ***Oral presentation, ASH 2021.***

c. **LE18-01:** Prakash S, Larisa B, Phelan R, Stella C, Brazauskas R, Buchbinder DK, Hamilton BK, Hélène S, Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies. ***Presented at 2022 Tandem Meetings in Salt Lake City.***

3. **Studies in progress**

Dr. Hélène Schoemans briefly listed all studies in progress.

a. **LE16-02b:** Late effects after AlloHCT for pediatric patients with non-malignant diseases (J Kahn/ P Satwani) ***Manuscript Preparation.***

b. **LE12-03:** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) ***Manuscript Preparation.***

c. **LE17-01a:** Late effects after hematopoietic stem cell transplantation for sickle cell disease. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) ***Manuscript Preparation.***

d. **LE17-01b:** Comparison of survival between transplanted and non-transplanted SCD patients. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) ***Data File Preparation.***

e. **LE18-01:** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) ***Analysis.***

f. **LE18-03:** Incorporating patient reported outcomes into individualized prognostication tools for survival and quality of life in transplant patients. (B Shaw) ***Manuscript Preparation.***

g. **LE19-01:** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) ***Analysis.***

h. **LE19-02:** Incidence and predictors of long-term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) ***Data File Preparation.***

i. **LE20-01:** Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) ***Data File Preparation.***

j. **LE20-02:** Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) ***Analysis.***

k. **LE21-01:** Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M-Angel Perales/A Kansagra) ***Data File Preparation.***

4. **Future/proposed studies**

a. **PROP 2110-27:** Bladder cancer incidence and mortality after hematopoietic stem cell transplantation (*Herr/Hahn*)

Dr. Megan Herr presented this proposal aiming to assess bladder cancer incidence and mortality rate after HCT and to identify risk factors for bladder cancer after HCT, including investigation of bladder cancer incidence as an effect of pre-HCT cyclophosphamide dosage. It was acknowledged that additional documentation would need to be requested for the study to proceed, since only 25% of 2nd GU cancers currently have path reports, and that study PIs would be willing to review this documentation.

After a comment from the audience, it was explained that bladder cancer was chosen as the event of interest based on clinical observations as PTCy exposures have increased over time. At least one audience member was concerned about accounting for smoking history in the analysis, which was addressed by stating that this information is captured on CRF forms (including pack-years). Some questions were posed about the data sources. One audience member asked how much pre-HCT data was available; this data includes number of cycles as well as start and stop dates. Another question was about the path reports and whether there was a concern about misclassification. Dr. Herr addressed this concern by stating that in previous experience reviewing melanoma path reports, there were few misclassification errors and would expect to see few errors in this project. The final question pertained to the relatively recent surge in PTCy use and whether this limited the scope of the study, although the presenter said that prior to PTCy use, many patients were still exposed above the chosen threshold for the study due to multiple lines of therapy. This proposal was not accepted due to resource constraints and low priority.

b. **PROP 2110-55:** Racial/ Ethnic Disparities in Long-Term Health Outcomes Among Survivors of Allogeneic Hematopoietic Cell Transplant Performed in Childhood. (*Neel S. Bhatt/Akshay Sharma*)

Dr. Neel Bhatt presented this proposal aiming to determine the effect of race/ethnicity on the incidence of non-malignant late effects among survivors of alloHCT performed during childhood and to investigate the differences in the risk of developing subsequent neoplasms by race/ ethnicity among survivors of alloHCT performed during childhood.

There was a suggestion to increase the age range of this study (i.e. include young adults) in order to capture more data, which was received by the presenter as a possible avenue of investigation as long as there is no overlap with other studies. This suggestion was given along with concerns of missingness in the data. Another concern involved the high representation of White/Caucasian patients and the possibility of detection bias due to the fact that the underrepresented patients may not be able to afford or seek care. One audience member suggested looking at HLA data for polymorphisms that may correlate with differences in outcomes, and the presenter acknowledged that this study could be a good first step that may eventually lead to that line of research. It was also acknowledged that disparities results from a wide range of factors, some of which are not mentioned in the initial proposal, such as poverty level. While zip codes and other SES variables were not collected for the entire duration of the study time period, there was a comment about potentially combining this study with the study involving poverty and late effects by Duncan and Jimenez-Kurlander (PROP 2110-240). This proposal was accepted, with a request to combine the study with PROP 2110-240.

c. **PROP 2110-74:** Cumulative Incidence and Risk Factors for Breast Cancer after Allogeneic Hematopoietic Cell Transplant. *(Kareem Jamani/K. Scott Baker)*

Dr. Kareem Jamani presented this proposal aiming to estimate the cumulative incidence of breast cancer after alloHCT; to elucidate risk factors for the occurrence of breast cancer after alloHCT, particularly the association between breast cancer and TBI (at varying dose and fractionation), age at alloHCT, and time post alloHCT; and to estimate the excess risk of breast cancer in alloHCT recipients as compared to the general population. It was mentioned that this study is important

because there already exists an effective screening modality for breast cancer, and the results of this study may lead to increased screening recommendations for low-dose TBI patients or younger patients.

There was a comment about whether the study will differentiate between pre-menopausal and post-menopausal breast cancer incidence, as exposure may have the most impact on pre-menopausal incidence. It is difficult to differentiate these patients except by an estimated age of menopause, although SIR analysis will account for age at diagnosis compared to the general population. There was a concern about the long length of time between HCT and the typical onset of breast cancer as a late effect, and the fact that this might lead to incomplete data as comprehensive reporting tapers off over time. In line with this comment, it was recommended that the time period for cohort selection was chosen with this lead time in mind. There were some questions about whether confounding factors are available in the data set or were considered for this study, such as hormonal status (i.e. ovarian insufficiency may be protective), anthracycline exposure (data available as exposed vs. not exposed without dosage levels), and predisposing factors for breast cancer (data not available). One audience member suggested including males in the study as they also have incidence of breast cancer, although rare. Mary Horowitz was concerned about the interval from diagnosis to breast cancer, doubt adding one-year survivors would help. Dr. Kareem explained that the interval could be long, maybe 5 years, he would look at it. This proposal was not accepted due to resource constraints and low priority.

d. **PROP 2110-240:** The Role of Poverty in Late Effects Following Hematopoietic Cell Transplantation. (*Christine Duncan/Lauren Jimenez-Kurlander*)

Dr. Lauren Jimenez-Kurlander virtually presented this proposal, via pre-recorded presentation, aiming to compare the cumulative incidence of late organ toxicity and mental health diagnoses in survivors of allogeneic HCT from areas of low and high-neighborhood poverty. Secondary aims include the determination of how patients and treatment-related factors influence the development of these effects, a report of the overall survival and transplant-related mortality of survivors of alloHCT coming from areas of low-versus-high neighborhood poverty, and a comparison of late organ toxicity and mental health late effects in alloHCT survivors with private insurance versus those with Medicaid/Medicare insurance coverage.

There was a question about where the data for mental health outcomes is sourced from; clinical diagnoses of depression, anxiety, and PTSD are collected on the forms, which provides some limited insight, although this does not capture sub-clinical levels of mental health distress. This may be a limitation in the study. A related inquiry concerned the existence of baseline mental health data; these diagnoses are not collected on the baseline forms, although HCT-CI data may be able to provide some limited information. One audience member suggested incorporating PROs data, which would be helpful in future studies, but there is not enough data for this yet. There was a concern about the feasibility of differential follow-up by socioeconomic status because the completeness index by zip code was not favorable- related to this concern, there was a suggestion that an analysis of late effects could simply be added on to the study by Kira Bona looking at neighborhood poverty. There was also a concern about the high missingness of insurance status for the study cohort because insurance status is only collected on CRF level forms, although this means insurance status could be analyzed on a subset of the population. Finally, there was a cautionary statement that this study would be descriptive at best and would be unable to uncover causation. This proposal was accepted as a combination with PROP 2110-55.

e. **PROP 2110-299:** Risk of secondary colorectal cancer development after allogeneic hematopoietic stem cell transplantation (HCT) (*Jed Calata/Larisa Broglie*)

Dr. Jed Calata virtually presented this proposal, via pre-recorded presentation, aiming to describe the incidence of colorectal cancer in HCT patients and compare to the general population, to characterize the location and type of colorectal cancer in HCT patients, and to identify risk factors for secondary colorectal cancers including the role of GVHD.

There was a comment that a study like this could be important for colon cancer screening guidelines, especially since a previous study that did not reveal increased risk of colon cancer after TBI exposure had only a small cohort of patients. There was a suggestion to increase the age range and include even younger patients, which was received by the presenter as a likely possibility for the final study, as the age range presented in the proposal was not a strict specification. There was some concern, however, that colon cancer incidence would be underreported in younger patients due to less frequent screening, which may be a limitation. There was also a concern that too few patients within the study population would have path reports submitted for secondary malignancy, and that this could also pose a limitation. This proposal was not accepted due to resource constraints and low priority.

Dropped proposed studies

a. **PROP 2110-05:** Fertility, Pregnancy, Post-Transplant Cyclophosphamide, Allogeneic hematopoietic cell transplant. ***Dropped due to feasibility.***

b. **PROP 2110-06:** Fracture and bony events in adult patients after allogeneic hematopoietic cell transplant with graft versus host disease prophylaxis using post-transplant cyclophosphamide as graft versus host prophylaxis. ***Dropped for overlap with an existing study.***

c. **PROP 2110-66:** Post-transplant Diabetes Mellitus in long term survivors of pediatric allogeneic hematopoietic cell transplantation: An Analysis of Trends and associated risk factors. ***Dropped due to feasibility.***

d. **PROP 2110-179:** Impact of Stem Cell Mobilization Regimen on Risk of Therapy-Related Myeloid Neoplasms (t-MN) and Non-Relapse Mortality. ***Dropped due to feasibility.***

e. **PROP 2110-186:** Impact of therapies for oral cGVHD oral therapies on the development of oral cancers. ***Dropped due to feasibility.***

f. **PROP 2110-196:** Impact of Granulocyte Colony-Stimulating Factor on Gonadal Function and Fertility Following Hematopoietic Cell Transplantation. ***Dropped due to feasibility.***

g. **PROP 2110-227:** Impact of graft-versus-host disease on late effects in pediatric and young adult patients undergoing hematopoietic cell transplantation for non-malignant hematologic conditions. ***Dropped for overlap with an existing study.***

h. **PROP 2110-288:** Depression and Anxiety During the COVID-19 Pandemic Following Pediatric and Young Adult Allogeneic HCT. ***Dropped due to feasibility.***

i. **PROP 2110-321:** Trends in Late Mortality for Middle Aged and Elderly Undergoing Allogeneic Hematopoietic Stem Cell transplant. ***Dropped for overlap with an existing study.***

5. **Other Business**

Dr. David Buchbinder introduced Dr. Rachel Cusatis to present an update on PROs data at CIBMTR and Dr. Seth Rotz to present on HCT Survivorship guidelines.

a. **Update on PROs data at CIBMTR**

Dr. Rachel Cusatis provided an overview of the Patient Reported Outcomes (PROs) program at CIBMTR. She then gave an update on the status of PROs data at CIBMTR, including enrollment trends and demographics. It was noted that future plans for PROs data includes expansion to new sites, with contact information for sites that may be interested in participating. Next steps also include translation of surveys to Spanish, surveys for pediatric patients, and making information available on new website. Questions were deferred to Dr. Cusatis' email in the interest of time.

b. **HCT Survivorship Guidelines**

Dr. Seth Rotz presented an update on recommended screening and preventative practices for long-term survivors of HCT. These survivorship guidelines are being updated 10 years after initially being established by multiple societies in collaboration, including CIBMTR. Objectives, methodology, and a timeline for the update were provided, as well as a list of team members associated with this update.

c. **EBMT/CIBMTR Late Effects Systematic Reviews**

An update on the EBMT/CIMBTR late effects systematic reviews, which now has a formal proposal process, was presented by Dr. Rachel Phelan. The 2019 focus of male-specifics late effects review has resulted in an adult-only publication in TCT and BMT, with a pediatric version close to completion. The second formal call for proposals occurred in late 2021, with 11 submitted proposals and a final selection of female-specific late effects, merging in two other related topics. A reminder was given to look for emails if interested in being involved.

6. **Closing Remarks**

Dr. Rachel Phelan concluded the session at 1:50pm MDT.

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
LE12-03: Solid organ transplantation and hematopoietic cell transplantation	Manuscript preparation	1
LE16-02b: Late effects after AlloHCT for pediatric patients with non-malignant diseases	Manuscript preparation	3
LE17-01a: Late effects after hematopoietic stem cell transplantation for sickle cell disease	Manuscript preparation	3
LE17-01b: Comparison of survival between transplanted and non-transplanted SCD patients	Data file preparation	3
LE18-01: Survival trends in two-year survivors of alloHCT	Analysis	2
LE19-01: Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Analysis	1
LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.	Data file preparation	2
LE20-01: Cardiometabolic Risk after Total Body Irradiation during Childhood	Protocol development	1
LE20-02: Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant	Analysis	2
LE21-01: Risk of subsequent neoplasms (SN) after the use of post-transplant cyclophosphamide (PTCy) for Graft-versus-host disease (GvHD) prophylaxis	Data file preparation	3
EL22-01: The role of racial/ethnic disparities and poverty in long-term outcomes among survivors of allogeneic hematopoietic stem cell transplants	Protocol pending	3

A G E N D A
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
Salt Lake City, UT
Sunday April 24, 2022, 6:45 AM – 8:15 AM MDT

Co-Chair:	**Edward Stadtmauer, MD, University of Pennsylvania Medical Center** **Telephone: 215-662-7910; E-mail: Edward.stadtmauer@uphs.upenn.edu**
Co-Chair:	**Bipin Savani, MD; Vanderbilt University Medical Center;** **Telephone: 615-936-8422; E-mail: bipin.savani@vumc.org**
Co-Chair:	**Mohamed Sorror, MD, MSc; Fred Hutchinson Cancer Research Center;** **Email: msorror@fredhutch.org; Phone: (206) 667-6298**
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1. Introduction

Dr. Bipin Savani opened the meeting at 6:50 am by welcoming the working committee members for attending the Regimen-Related Toxicity and Supportive Care Working Committee (RRTWC) meeting. He introduced the RRTWC leadership and discussed the disclosures of the committee and the CIBMTR. Dr. Stadtmauer then stated the goals and limitations of the RRTWC and introduced Dr. Chhabra to the podium to continue.

2. Accrual Summary (Attachment 2)

The accrual summary was not presented in order to provide more time for the discussion of RT studies that are ongoing, published or presented in the last year, and the proposed studies to be presented at the meeting.

3. Presentations, published or submitted papers

Dr. Chhabra gave an overview of the studies published and submitted in the past year. He also presented new areas of data collection on both the TED and CRF forms, rules of authorship, goals, expectations, and limitations. Dr. Chhabra brought up the importance of contributing at each step of the study.

a. **RT17-01** Farhadfar N, Dias A, Wang T, Fretham C, Chhabra S, Murthy HS, Broglie L, D'Souza A, Gadalla SM, Gale RP, Hashmi S, Al-Homsi AS, Hildebrandt GC, Hematti P, Rizzieri D, Chee L, Lazarus HM, Bredeson C, Jaimes EA, Beitinjaneh A, Bashey A, Prestidge T, Krem MM, Marks DI, Benoit S, Yared JA, Nishihori T, Olsson RF, Freytes CO, Stadtmauer E, Savani BN, Sorror ML, Ganguly S, Wingard JR, Pasquini M. Impact of pretransplantation renal dysfunction on outcomes after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2021 May 1; 27(5):410-422. doi:10.1016/j.jtct.2021.02.030. Epub 2021 Feb 26. PMCID:PMC8168834.***
b. **RT18-02** Abou-Ismail MY, Fraser R, Allbee-Johnson M, Metheny III L, Ravi G, Ahn KW, Bhatt NS, Lazarus HM, de Lima M, El Jurdy N, Hematti P, Beitinjaneh AM, Nishihori T, Badawy SM, Sharma A, Pasquini MC, Savani BN, Sorror ML, Stadtmauer E, Chhabra S. Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation? ***British Journal of Haematology. doi:10.1111/bjh.18108. Epub 2022 Mar 14.***
c. **RT18-03** Patel SS, Ahn KW, Khanal M, Bupp C, Allbee-Johnson M, Majhail NS, Hamilton BK, Rotz SJ, Hashem H, Beitinjaneh A, Lazarus HM, Krem MM, Prestidge T, Bhatt NS, Sharma A, Gadalla SM, Murthy HS, Broglie L, Nishihori T, Freytes CO, Hildebrandt GC, Gergis U, Seo S, Wirk B, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Non-infectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2022.03.015. Epub 2022 Mar 18.***
d. **RT18-01a** Expanded Definitions in the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Better Classifies Comorbidity in Children and Young Adults with Non-Malignant Diseases. (L Broglie/B Friend/G Schiller/M Thakar /M Sorror) ***Submitted.***
e. **RT18-01b** Adapting the HCT-CI Applicability for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation. (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) ***Submitted.***
f. **RT18-S1** Differential use of the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) among adult and pediatric HCT physicians. (L Broglie/B Friend) ***Submitted****.*

4. Studies in progress (Attachment 3)

Dr. Chhabra presented the studies in progress. The older studies will be given priority to finish this year. The rest of the studies are on schedule to meet their current goals.

a. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler) **Analysis**
b. **RT19-02** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima) **Datafile prep**
c. **RT20-01** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff) **Protocol development**

5. Proposals

Future/proposed studies

a. **PROP 2109-09/ PROP 2110-02/ PROP 2110-257** Validating the HCT-CI score and exploring additional prognostic factors in patients undergoing second allogeneic transplants (Attachment 4).

Dr. Stadtmauer introduced Dr. Tomas. The hypothesis of this proposal is that HCT-CI is an

accurate determinant of non-relapse survival and overall survival in pediatric and adult patients received their second allogeneic transplant.

The CIBMTR identified n=4982 cases of second allo transplant in reported between 2008-2019 for all ages and for malignant and non-malignant diseases.

The aims of this proposal are to validate the HCT-CI as a predictor of non-relapse mortality in second transplant. identify determinants of non-relapse mortality in second transplant. The secondary aims of this proposal are to validate the HCT-CI as a predictor of overall survival in second transplant and to identify comorbidities that influence non-relapse mortality in second transplant.

Dr. Rangarajan discussed the potential use of the modified HCT-CI score developed in the RT18-01 study by Drs. Broglie and Friend. Dr. Tomas recommended both the modified and original score be examined. Dr. Stadtmauer asked about other pediatric data that we haven't collected that would be important to assess? Dr. Friend confirmed the examination of BMI, mechanical ventilation, and nutritional status are important to consider in this population as well. Dr. Silver discussed the differences in primary graft failure and relapse on second transplant and recommended the groups be split by indication for transplant. There was discussion around the separation of malignant and non-malignant disease and pediatric and adult patients. Dr. Dvorak discussed that due to the population of this proposal there could potentially be multiple manuscripts produced from this proposal. Dr. Stadtmauer recommended the regimen from the first allogeneic transplant be included in the analysis for the second transplant.

b. **PROP 2109-25** Correlation of melphalan dose with regimen-related toxicity in multiple myeloma patients undergoing autologous transplant (Attachment 5).
Dr. Stadtmauer invited Dr. Krem to the podium to present. The hypothesis of this proposal is Mel 140 will have more reduced toxicity related outcomes than Mel 200 with the same level of disease control. Additionally, due to patient selection, Mel 140 will correlate with frailty and NRM.

The CIBMTR found n=7033 adult patients with auto transplant for multiple myeloma who received melphalan conditioning regimen reported between 2008 and 2019. Of those, there were n=6014 who received standard Mel 200 conditioning.

The primary aim of the study is to examine non-relapse mortality for Mel 140 and Mel 200. Secondary aims include examining differences in regimen-related toxicities, infection, relapse, progression-free survival, overall survival, secondary malignancies, and cause of death will be described between the two regimens.

Dr. Stadtmauer asked about the exclusion criteria and the lack of exclusion for cases with previous auto transplant and lower does used for salvage. Dr. Krem recommended including these cases and including a variable for prior auto as there are a number of second transplants performed. Dr. Wall discussed measures of frailty and recommended partnering with institutions with robust assessments for geriatric patients.

c. **PROP 2110-23** Allogeneic hematopoietic cell transplantation (HCT) in patients 75 years and older-utilization and outcomes (Attachment 6).

Dr. Savani invited Dr. Artz to the podium to present the proposal. The hypothesis of this proposal is that the utilization of HCT in older populations is safe in the modern era with increased transplant rates and rates of non-relapse mortality.

The CIBMTR found n=392 adults over 75 years old transplanted for AML, ALL, and MDS between 2008 and 2019.

The primary aim or the proposal is to compare utilization of HCT for older patients o(75 years and older) over time. The secondary aims are to describe the utilization by driving factors, to examine non-relapse mortality, overall survival, leukemia free survival and GVHD at 1 and 2 years. Additional aim includes exploring risk of 75 years and older on non-relapse mortality compared to a slightly younger group (70-74 years) adjusting for common transplant factors such as HCT-CI, donor match, and performance score.

Dr. Savani asked about what the upper age limit for transplants at institutions is and asked about the collection of cases that were not selected for transplant due to age. The CIBMTR does not collect that information. Dr. Krem discussed the inclusion of older cases a cellular therapy inclusion and commented that secondary studies can answer with direct contact to centers regarding the cases not recommended to transplant due to age. The discussion included identifying an age cut off for transplants in older patients.

d. **PROP 2110-51** Trends of major organ injuries amongst children and young adults following allogeneic hematopoietic cell transplantation for hematologic malignancies (H Rangarajan/P Satwani) (Attachment 7).

Dr. Savani invited Dr. Rangarajan to the podium to present the proposal. The hypothesis of the proposal is that major organ toxicities in the first 100 days after transplant have decreased over time for children and young adults who received allogeneic transplants for hematologic malignancies. These decreases in toxicities have led to lower transplant related mortality.

The CIBMTR found n= 6210 pediatric and young adult patients (<30 years old) for AML and ALL who received allogeneic transplant between 2008 and 2019

The primary aim is to evaluate the trends in organ toxicities after allo transplant and to differentiate into the pulmonary, renal, CNS, liver, cardiac, and genitourinary systems. Secondary aims include comparing outcomes of non-relapse mortality, overall survival, acute GVHD between those with major organ toxicities and those without. Additional aim is to examine risk factors associated with major organ injuries.

Dr. Savani asked about the interactions between conditioning regimen, disease, and infection complications. Dr. Rangarajan, infection could be looked at as bias or confounding factor if the proposal is accepted. Dr. Friend asked about the broad time period in the proposal and asked for clarity on how time periods would be examined in the study. Dr. Rangarajan suggested time would be split to look at trends over every 5 years. Dr. Stadtmauer asked about availability of data related to the testing and confirmation of toxicities. Dr. Phelan commented that data is available for some toxicities but is center

reported, some testing available for review such as echocardiogram and MRIs available for a small subset of the patients. Primarily the data is reliant on the physician reporting. There was a question raised on how the organ function would be examined in the study. Dr. Rangarajan mentioned the analysis could look at any organ injuries compared to none. It was discussed primary analysis focus on the factors related to toxicity and subset analysis of cases where organ toxicity occurs and the impact on the outcomes.

e. **PROP 2110-80/ PROP 2110-244/ PROP 2110-315** Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database (Attachment 8).

Dr. Stadtmauer invited Dr. Poonsombudlert to the podium to present the proposal. The hypothesis of this proposal is use of PT-Cy increased risk of cardiac events and those who develop adverse cardiac events (ACE) have worse short- and long-term outcomes after transplant.

The CIBMTR identified n= 5561 (n=2089 with PT-Cy) adult cases with hematologic malignancies who received their first allogeneic transplant reported between 2017-2019.

The primary aim of the proposal is evaluate incidence of ACE by GVHD prophylaxis and identify pre-transplant risk factors associated with the development of ACE. Secondary aims are to examine overall survival, disease-free survival and non-relapse mortality by ACE development.

Dr. Stadtmauer commented that the PT-Cy and mis-matched donor is a package, will that make the comparison more difficult? Adding more years may increase the matched donors who received PT-Cy. Dr. Krem commented on the heterogeneity of cyclophosphamide use and total *cyclophosphamide dose. Dr. Poonsombudlert recommended cumulative dose should be looked at if the data is available. Limitation is pre-transplant exposure and dosing.*

Dr. Stadtmauer invited Dr. Friend to the podium to present the results of RT18-01 (a and b) which expanded the HCT-CI in the pediatric population for non-malignant and malignant patients.

Dr. Stadtmauer closed the session at 8:10am.

Working committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chair Priority**
RT18-01: A modified HCT risk assessment tool for pediatric and young adult patients undergoing alloHCT.	Submitted	1
RT19-01: Analysis of comorbidity-associated toxicity at a regimen based level.	Analysis	1
RT19-02: Hemorrhagic cystitis as a complication of HCT in the Pt-Cy GVHD prophylaxis era compared to other alloHCTs.	Datafile preparation	2
RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients	Datafile preparation	3
EL22-02: PT-Cy related cardiomyopathy in allo transplants	Protocol development	3

Oversight Assignments for Working Committee Leadership (May 2022)

Edward Stadtmauer	**RT22-01:** PT-Cy related cardiomyopathy in allo transplant
Bipin Savani	**RT19-01: A**nalysis of comorbidity-associated toxicity at a regimen based level.
	RT19-02: Hemorrhagic cystitis as a complication of HCT in the Pt-Cy GVHD prophylaxis era compared to other alloHCTs.
Mohamed Sorror	**RT18-01:** A modified HCT risk assessment tool for pediatric and young adult patients undergoing alloHCT.
	RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients

Accrual Summary for the Late Effects and Quality of Life Working Committee

Follow-up of **adult** patients (age≥18) after **allogeneic** transplant reported to CIBMTR, 1990-2022

Variable	TED	CRF
All patients	207074	66416
3 year survivors	66279	21673
5 year survivors	45760	15240
10 year survivors	18599	6398
15 year survivors	6730	2212
Acute Myelogenous Leukemia	76614	21551
3 year survivors	22511	6744
5 year survivors	14972	4773
10 year survivors	5451	1846
Acute Lymphoblastic Leukemia	28863	7996
3 year survivors	8389	2403
5 year survivors	5500	1674
10 year survivors	1933	670
Chronic Myelogenous Leukemia	25314	9188
3 year survivors	10367	3179
5 year survivors	8029	2507
10 year survivors	4388	1490
Myelodysplastic/Myeloproliferative Diseases	33079	13224
3 year survivors	9412	4226
5 year survivors	5927	2615
10 year survivors	1989	844
Multiple Myeloma/Plasma Cell Disorders	3433	1132
3 year survivors	1148	353
5 year survivors	795	238
10 year survivors	345	86
Lymphoma	18554	5633
3 year survivors	6604	1930
5 year survivors	4969	1458
10 year survivors	2253	703

Variable	TED	CRF
Other Malignant	9590	3132
3 year survivors	3236	1076
5 year survivors	2299	760
10 year survivors	905	299
Severe Aplastic Anemia	7992	3411
3 year survivors	3383	1334
5 year survivors	2495	952
10 year survivors	1077	345
Immune deficiencies	471	130
3 year survivors	175	49
5 year survivors	97	31
10 year survivors	15	6
Other Non-malignant	2842	1082
3 year survivors	1015	379
5 year survivors	651	232
10 year survivors	228	82

Follow-up of **pediatric** patients (age<18) after **allogeneic** transplant reported to CIBMTR, 1990-2022

Variable	TED	CRF
All patients	61315	24302
3 year survivors	26009	10608
5 year survivors	19229	7967
10 year survivors	8709	3877
15 year survivors	3083	1234
Acute Myelogenous Leukemia	11052	3945
3 year survivors	4108	1523
5 year survivors	3048	1178
10 year survivors	1459	573
Acute Lymphoblastic Leukemia	15794	5729
3 year survivors	5949	2198
5 year survivors	4459	1693
10 year survivors	2103	860
Chronic Myelogenous Leukemia	2271	862
3 year survivors	1048	408
5 year survivors	823	331
10 year survivors	420	188
Myelodysplastic/Myeloproliferative Diseases	3349	1332
3 year survivors	1409	585
5 year survivors	1066	474
10 year survivors	525	283
Multiple Myeloma/Plasma Cell Disorders	28	4
3 year survivors	10	2
5 year survivors	6	1
10 year survivors	4	0
Lymphoma	1308	454
3 year survivors	460	153
5 year survivors	344	120
10 year survivors	145	48

Variable	TED	CRF
Other Malignant	1177	426
3 year survivors	445	183
5 year survivors	322	146
10 year survivors	148	70
Severe Aplastic Anemia	5923	2413
3 year survivors	3002	1195
5 year survivors	2252	879
10 year survivors	987	374
Immune deficiencies	5980	2713
3 year survivors	2825	1433
5 year survivors	2039	1082
10 year survivors	929	543
Other Non-malignant	14358	6411
3 year survivors	6742	2928
5 year survivors	4864	2063
10 year survivors	1989	938

Follow-up of **adult** patients (age≥18) after **autologous** transplant reported to CIBMTR, 1990-2022

Variable	TED	CRF
All patients	269298	36869
3 year survivors	124263	18227
5 year survivors	82014	11679
10 year survivors	27785	3699
15 year survivors	8440	837
Acute Myelogenous Leukemia	7261	1348
3 year survivors	2573	443
5 year survivors	1883	303
10 year survivors	1003	127
Acute Lymphoblastic Leukemia	1168	210
3 year survivors	299	41
5 year survivors	201	26
10 year survivors	102	11
Chronic Myelogenous Leukemia	663	209
3 year survivors	285	96
5 year survivors	189	56
10 year survivors	86	22
Myelodysplastic/Myeloproliferative Diseases	256	45
3 year survivors	117	23
5 year survivors	77	12
10 year survivors	33	3
Multiple Myeloma/Plasma Cell Disorders	123711	15344
3 year survivors	61175	9501
5 year survivors	38260	6077
10 year survivors	9599	1716
Lymphoma	101620	11906
3 year survivors	46671	5666
5 year survivors	32643	3841
10 year survivors	12775	1427

Variable	TED	CRF
Other Malignant	32582	7645
3 year survivors	12689	2386
5 year survivors	8453	1308
10 year survivors	4044	361
Severe Aplastic Anemia	15	3
3 year survivors	4	1
5 year survivors	3	1
10 year survivors	0	0
Immune deficiencies	16	3
3 year survivors	11	2
5 year survivors	3	1
10 year survivors	0	0
Other Non-malignant	1792	154
3 year survivors	383	67
5 year survivors	258	53
10 year survivors	114	31

Follow-up of **pediatric** patients (age<18) after **autologous** transplant reported to CIBMTR, 1990-2022

Variable	TED	CRF
All patients	18150	2899
3 year survivors	7349	1204
5 year survivors	5111	810
10 year survivors	2122	367
15 year survivors	738	95
Acute Myelogenous Leukemia	992	251
3 year survivors	396	51
5 year survivors	306	30
10 year survivors	163	15
Acute Lymphoblastic Leukemia	389	123
3 year survivors	127	19
5 year survivors	87	7
10 year survivors	47	0
Chronic Myelogenous Leukemia	23	3
3 year survivors	12	1
5 year survivors	7	0
10 year survivors	4	0
Myelodysplastic/Myeloproliferative Diseases	23	4
3 year survivors	7	0
5 year survivors	5	0
10 year survivors	3	0
Multiple Myeloma/Plasma Cell Disorders	102	3
3 year survivors	18	2
5 year survivors	11	1
10 year survivors	3	0
Lymphoma	3128	385
3 year survivors	1354	191
5 year survivors	950	133
10 year survivors	374	37

Variable	TED	CRF
Other Malignant	13146	2038
3 year survivors	5319	899
5 year survivors	3667	613
10 year survivors	1505	312
Severe Aplastic Anemia	7	3
3 year survivors	4	2
5 year survivors	4	2
10 year survivors	1	0
Immune deficiencies	81	59
3 year survivors	36	29
5 year survivors	20	16
10 year survivors	0	0
Other Non-malignant	223	29
3 year survivors	68	10
5 year survivors	48	8
10 year survivors	19	3

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	47323	19111	12053
Source of data			
CRF	24443 (52)	7079 (37)	5666 (47)
TED	22880 (48)	12032 (63)	6387 (53)
Number of centers	264	241	378
Disease at transplant			
AML	16388 (35)	7160 (37)	3977 (33)
ALL	6871 (15)	2478 (13)	1928 (16)
Other leukemia	1469 (3)	423 (2)	310 (3)
CML	3528 (7)	1111 (6)	1028 (9)
MDS	6936 (15)	3307 (17)	1526 (13)
Other acute leukemia	501 (1)	230 (1)	142 (1)
NHL	4211 (9)	1361 (7)	904 (8)
Hodgkin Lymphoma	947 (2)	258 (1)	212 (2)
Plasma Cell Disorders, MM	940 (2)	292 (2)	206 (2)
Other malignancies	58 (<1)	14 (<1)	22 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1519 (3)	594 (3)	510 (4)
Inherited abnormalities erythrocyte diff fxn	728 (2)	255 (1)	231 (2)
Inherited bone marrow failure syndromes	26 (<1)	32 (<1)	20 (<1)
Hemoglobinopathies	22 (<1)	22 (<1)	15 (<1)
Paroxysmal nocturnal hemoglobinuria	4 (<1)	7 (<1)	2 (<1)
SCIDs	827 (2)	328 (2)	370 (3)
Inherited abnormalities of platelets	40 (<1)	16 (<1)	12 (<1)
Inherited disorders of metabolism	301 (1)	89 (<1)	143 (1)
Histiocytic disorders	387 (1)	125 (1)	129 (1)
Autoimmune disorders	27 (<1)	14 (<1)	11 (<1)
Other	53 (<1)	18 (<1)	25 (<1)
MPN	1507 (3)	947 (5)	297 (2)
Disease missing	26 (<1)	27 (<1)	32 (<1)
AML Disease status at transplant			
CR1	8855 (54)	4408 (62)	1974 (50)
CR2	3149 (19)	1237 (17)	782 (20)
CR3+	337 (2)	108 (2)	92 (2)
Advanced or active disease	3862 (24)	1364 (19)	984 (25)
Missing	185 (1)	43 (1)	145 (4)
ALL Disease status at transplant			
CR1	3403 (50)	1426 (58)	814 (42)
CR2	1956 (28)	631 (25)	557 (29)
CR3+	570 (8)	167 (7)	180 (9)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced or active disease	860 (13)	230 (9)	257 (13)
Missing	82 (1)	24 (1)	120 (6)
MDS Disease status at transplant			
Early	1480 (21)	609 (18)	351 (23)
Advanced	4487 (65)	2464 (75)	836 (55)
Missing	969 (14)	234 (7)	339 (22)
NHL Disease status at transplant			
CR1	598 (14)	262 (19)	125 (14)
CR2	781 (19)	259 (19)	145 (16)
CR3+	365 (9)	114 (8)	80 (9)
PR	448 (11)	112 (8)	95 (11)
Advanced	1928 (46)	588 (43)	424 (47)
Missing	71 (2)	18 (1)	32 (4)
Recipient age at transplant			
0-9 years	3974 (8)	1246 (7)	1582 (13)
10-17 years	3152 (7)	969 (5)	1122 (9)
18-29 years	5720 (12)	1928 (10)	1607 (13)
30-39 years	5327 (11)	1851 (10)	1428 (12)
40-49 years	7110 (15)	2503 (13)	1748 (15)
50-59 years	9750 (21)	3711 (19)	2071 (17)
60-69 years	10023 (21)	5257 (28)	2052 (17)
70+ years	2267 (5)	1646 (9)	443 (4)
Median (Range)	48 (0-84)	53 (0-82)	42 (0-84)
Recipient race/ethnicity			
White	39105 (83)	15871 (83)	8419 (70)
Black or African American	2150 (5)	753 (4)	555 (5)
Asian	1167 (2)	602 (3)	520 (4)
Native Hawaiian or other Pacific Islander	59 (<1)	31 (<1)	32 (<1)
American Indian or Alaska Native	172 (<1)	73 (<1)	49 (<1)
Hispanic	2873 (6)	1076 (6)	718 (6)
Missing	1797 (4)	705 (4)	1760 (15)
Recipient sex			
Male	27519 (58)	11189 (59)	7161 (59)
Female	19804 (42)	7922 (41)	4892 (41)
Karnofsky score			
10-80	16419 (35)	7366 (39)	3802 (32)
90-100	29141 (62)	11142 (58)	7620 (63)
Missing	1763 (4)	603 (3)	631 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	31 (<1)	54 (<1)	5 (<1)
4/6	246 (1)	98 (1)	58 (1)
5/6	6320 (14)	1956 (12)	1680 (15)
6/6	39021 (86)	13671 (87)	9199 (84)
Unknown	1705 (N/A)	3332 (N/A)	1111 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	907 (2)	104 (1)	82 (1)
6/8	1783 (4)	159 (1)	224 (3)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
7/8	8777 (20)	2047 (16)	1797 (23)
8/8	33290 (74)	10596 (82)	5866 (74)
Unknown	2566 (N/A)	6205 (N/A)	4084 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11284 (29)	1543 (23)	914 (26)
Single allele mismatch	20903 (54)	3374 (51)	1832 (52)
Full allele matched	6608 (17)	1716 (26)	787 (22)
Unknown	8528 (N/A)	12478 (N/A)	8520 (N/A)
High resolution release score			
No	11606 (25)	19036 (>99)	11519 (96)
Yes	35717 (75)	75 (<1)	534 (4)
KIR typing available			
No	33478 (71)	19085 (>99)	11980 (99)
Yes	13845 (29)	26 (<1)	73 (1)
Graft type			
Marrow	16451 (35)	5091 (27)	4800 (40)
PBSC	30790 (65)	13824 (72)	7191 (60)
BM+PBSC	10 (<1)	6 (<1)	1 (<1)
PBSC+UCB	38 (<1)	170 (1)	10 (<1)
Others	34 (<1)	20 (<1)	51 (<1)
Conditioning regimen			
Myeloablative	28854 (61)	10141 (53)	7518 (62)
RIC/Nonmyeloablative	18244 (39)	8909 (47)	4372 (36)
TBD	225 (<1)	61 (<1)	163 (1)
Donor age at donation			
To Be Determined/NA	396 (1)	563 (3)	147 (1)
0-9 years	5 (<1)	37 (<1)	4 (<1)
10-17 years	2 (<1)	13 (<1)	1 (<1)
18-29 years	23149 (49)	9900 (52)	5152 (43)
30-39 years	13299 (28)	4964 (26)	3623 (30)
40-49 years	7988 (17)	2533 (13)	2357 (20)
50+ years	2484 (5)	1101 (6)	769 (6)
Median (Range)	30 (0-123)	29 (0-121)	32 (0-123)
Donor/Recipient CMV serostatus			
+/+	11583 (24)	4767 (25)	3042 (25)
+/-	5466 (12)	2181 (11)	1479 (12)
-/+	15215 (32)	5254 (27)	3593 (30)
-/-	13359 (28)	4498 (24)	3132 (26)
CB - recipient +	34 (<1)	136 (1)	9 (<1)
CB - recipient -	4 (<1)	42 (<1)	2 (<1)
CB - recipient CMV unknown	0	1 (<1)	0
Missing	1662 (4)	2232 (12)	796 (7)
GvHD Prophylaxis			
No GVHD prophylaxis	200 (<1)	94 (<1)	67 (1)
Ex vivo T-cell depletion	1160 (2)	319 (2)	408 (3)
CD34 selection	720 (2)	339 (2)	194 (2)
Post-CY + other(s)	3020 (6)	2569 (13)	743 (6)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Post-CY alone	228 (<1)	109 (1)	58 (<1)
Tacrolimus + MMF +- others	5383 (11)	1947 (10)	920 (8)
Tacrolimus + MTX +- others (except MMF)	20389 (43)	8407 (44)	3390 (28)
Tacrolimus + others (except MTX, MMF)	2432 (5)	1220 (6)	469 (4)
Tacrolimus alone	1182 (2)	484 (3)	216 (2)
CSA + MMF +- others (except Tacrolimus)	3083 (7)	909 (5)	1017 (8)
CSA + MTX +- others (except Tacrolimus, MMF)	6993 (15)	1899 (10)	3358 (28)
CSA + others (except Tacrolimus, MTX, MMF)	1089 (2)	335 (2)	452 (4)
CSA alone	482 (1)	136 (1)	402 (3)
Other GVHD prophylaxis	752 (2)	270 (1)	208 (2)
Missing	210 (<1)	74 (<1)	151 (1)
Donor/Recipient sex match			
Male-Male	19283 (41)	7409 (39)	4699 (39)
Male-Female	11786 (25)	4525 (24)	2668 (22)
Female-Male	8013 (17)	3384 (18)	2383 (20)
Female-Female	7842 (17)	3072 (16)	2157 (18)
CB - recipient M	18 (<1)	96 (1)	3 (<1)
CB - recipient F	20 (<1)	83 (<1)	8 (<1)
Missing	361 (1)	542 (3)	135 (1)
Year of transplant			
1986-1990	350 (1)	46 (<1)	106 (1)
1991-1995	1839 (4)	439 (2)	748 (6)
1996-2000	3305 (7)	1185 (6)	1215 (10)
2001-2005	5345 (11)	1074 (6)	1880 (16)
2006-2010	9622 (20)	1923 (10)	1829 (15)
2011-2015	13414 (28)	3587 (19)	2563 (21)
2016-2020	10431 (22)	7184 (38)	2758 (23)
2021-2022	3017 (6)	3673 (19)	954 (8)
Follow-up among survivors, Months			
N Eval	20064	9350	5352
Median (Range)	60 (0-385)	24 (0-362)	40 (0-372)

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	6214	1700	2170
Source of data			
CRF	4494 (72)	1137 (67)	1068 (49)
TED	1720 (28)	563 (33)	1102 (51)
Number of centers	154	142	223
Disease at transplant			
AML	2354 (38)	580 (34)	706 (33)
ALL	1279 (21)	373 (22)	468 (22)
Other leukemia	98 (2)	30 (2)	37 (2)
CML	132 (2)	36 (2)	57 (3)
MDS	559 (9)	168 (10)	172 (8)
Other acute leukemia	96 (2)	24 (1)	44 (2)
NHL	403 (6)	98 (6)	134 (6)
Hodgkin Lymphoma	103 (2)	27 (2)	36 (2)
Plasma Cell Disorders, MM	38 (1)	12 (1)	13 (1)
Other malignancies	11 (<1)	1 (<1)	3 (<1)
SAA	97 (2)	32 (2)	49 (2)
Inherited abnormalities erythrocyte diff fxn	171 (3)	51 (3)	45 (2)
Inherited bone marrow failure syndromes	4 (<1)	3 (<1)	3 (<1)
Hemoglobinopathies	2 (<1)	1 (<1)	0
SCIDs	278 (4)	91 (5)	165 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	10 (<1)
Inherited disorders of metabolism	387 (6)	118 (7)	142 (7)
Histiocytic disorders	107 (2)	29 (2)	51 (2)
Autoimmune disorders	9 (<1)	0	6 (<1)
Other	10 (<1)	2 (<1)	9 (<1)
Disease missing	4 (<1)	3 (<1)	0
MPN	52 (1)	16 (1)	20 (1)
AML Disease status at transplant			
CR1	1222 (52)	324 (56)	350 (50)
CR2	636 (27)	149 (26)	188 (27)
CR3+	66 (3)	9 (2)	26 (4)
Advanced or active disease	422 (18)	96 (17)	138 (20)
Missing	8 (<1)	2 (<1)	4 (1)
ALL Disease status at transplant			
CR1	574 (45)	159 (43)	202 (43)
CR2	480 (38)	137 (37)	166 (35)
CR3+	148 (12)	54 (14)	61 (13)
Advanced or active disease	76 (6)	22 (6)	38 (8)
Missing	1 (<1)	1 (<1)	1 (<1)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
MDS Disease status at transplant			
Early	173 (31)	41 (24)	72 (42)
Advanced	337 (60)	113 (67)	78 (45)
Missing	49 (9)	14 (8)	22 (13)
NHL Disease status at transplant			
CR1	63 (16)	9 (9)	25 (19)
CR2	75 (19)	22 (22)	35 (26)
CR3+	45 (11)	11 (11)	12 (9)
PR	68 (17)	12 (12)	16 (12)
Advanced	149 (37)	43 (44)	42 (32)
Missing	0	1 (1)	3 (2)
Recipient age at transplant			
0-9 years	1868 (30)	612 (36)	771 (36)
10-19 years	655 (11)	158 (9)	255 (12)
20-29 years	745 (12)	152 (9)	234 (11)
30-39 years	599 (10)	150 (9)	210 (10)
40-49 years	655 (11)	172 (10)	203 (9)
50-59 years	856 (14)	210 (12)	280 (13)
60-69 years	722 (12)	212 (12)	201 (9)
70+ years	114 (2)	34 (2)	16 (1)
Median (Range)	27 (0-83)	24 (0-78)	20 (0-78)
Recipient race/ethnicity			
White	3432 (55)	996 (59)	1090 (50)
Black or African American	893 (14)	221 (13)	263 (12)
Asian	366 (6)	120 (7)	163 (8)
Native Hawaiian or other Pacific Islander	32 (1)	3 (<1)	17 (1)
American Indian or Alaska Native	45 (1)	10 (1)	19 (1)
Hispanic	1108 (18)	253 (15)	297 (14)
Missing	338 (5)	97 (6)	321 (15)
Recipient sex			
Male	3439 (55)	968 (57)	1241 (57)
Female	2775 (45)	732 (43)	929 (43)
Karnofsky score			
10-80	1647 (27)	437 (26)	556 (26)
90-100	4361 (70)	1157 (68)	1433 (66)
Missing	206 (3)	106 (6)	181 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	101 (2)	57 (4)	32 (2)
4/6	2448 (41)	557 (40)	789 (40)
5/6	2664 (45)	596 (43)	854 (43)
6/6	750 (13)	184 (13)	294 (15)
Unknown	251 (N/A)	306 (N/A)	201 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2891 (55)	569 (55)	881 (55)
6/8	1271 (24)	248 (24)	370 (23)
7/8	730 (14)	141 (14)	221 (14)
8/8	349 (7)	70 (7)	123 (8)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	973 (N/A)	672 (N/A)	575 (N/A)
HLA-DPB1 Match			
Double allele mismatch	859 (39)	99 (38)	164 (40)
Single allele mismatch	1117 (51)	136 (52)	209 (51)
Full allele matched	202 (9)	25 (10)	33 (8)
Unknown	4036 (N/A)	1440 (N/A)	1764 (N/A)
High resolution release score			
No	4674 (75)	1650 (97)	2145 (99)
Yes	1540 (25)	50 (3)	25 (1)
KIR typing available			
No	4941 (80)	1694 (>99)	2150 (99)
Yes	1273 (20)	6 (<1)	20 (1)
Graft type			
UCB	5836 (94)	1521 (89)	2034 (94)
BM+UCB	1 (<1)	0	0
PBSC+UCB	347 (6)	170 (10)	122 (6)
Others	30 (<1)	9 (1)	14 (1)
Number of cord units			
1	5200 (84)	0	1809 (83)
2	1012 (16)	0	360 (17)
3	1 (<1)	0	0
Unknown	1 (N/A)	1700 (N/A)	1 (N/A)
Conditioning regimen			
Myeloablative	4030 (65)	1076 (63)	1346 (62)
RIC/Nonmyeloablative	2168 (35)	619 (36)	807 (37)
TBD	16 (<1)	5 (<1)	17 (1)
Donor age at donation			
To Be Determined/NA	4858 (78)	646 (38)	1741 (80)
0-9 years	1081 (17)	844 (50)	348 (16)
10-19 years	58 (1)	88 (5)	17 (1)
20-29 years	65 (1)	37 (2)	15 (1)
30-39 years	57 (1)	38 (2)	21 (1)
40-49 years	46 (1)	21 (1)	11 (1)
50+ years	49 (1)	26 (2)	17 (1)
Median (Range)	4 (0-112)	5 (0-73)	4 (0-119)
Donor/Recipient CMV serostatus			
+/+	0	0	1 (<1)
-/-	0	0	1 (<1)
CB - recipient +	3888 (63)	1027 (60)	1306 (60)
CB - recipient -	2227 (36)	613 (36)	790 (36)
CB - recipient CMV unknown	99 (2)	60 (4)	72 (3)
GvHD Prophylaxis			
No GVHD prophylaxis (forms under review)	23 (<1)	8 (<1)	14 (1)
Ex vivo T-cell depletion	25 (<1)	9 (1)	8 (<1)
CD34 selection	213 (3)	100 (6)	61 (3)
Post-CY + other(s)	12 (<1)	9 (1)	13 (1)
Post-CY alone	0	0	1 (<1)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Tacrolimus + MMF +- others	1857 (30)	539 (32)	446 (21)
Tacrolimus + MTX +- others (except MMF)	216 (3)	56 (3)	78 (4)
Tacrolimus + others (except MTX, MMF)	225 (4)	64 (4)	84 (4)
Tacrolimus alone	153 (2)	45 (3)	30 (1)
CSA + MMF +- others (except Tacrolimus)	2847 (46)	683 (40)	1039 (48)
CSA + MTX +- others (except Tacrolimus, MMF)	101 (2)	29 (2)	50 (2)
CSA + others (except Tacrolimus, MTX, MMF)	341 (5)	117 (7)	223 (10)
CSA alone	52 (1)	18 (1)	70 (3)
Other GVHD prophylaxis	137 (2)	20 (1)	42 (2)
Missing	12 (<1)	3 (<1)	11 (1)
Donor/Recipient sex match			
Male-Female	0	0	1 (<1)
Female-Male	0	0	1 (<1)
CB - recipient M	3439 (55)	968 (57)	1239 (57)
CB - recipient F	2775 (45)	732 (43)	928 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	112 (2)	86 (5)	34 (2)
2006-2010	1850 (30)	426 (25)	601 (28)
2011-2015	2682 (43)	510 (30)	839 (39)
2016-2020	1341 (22)	528 (31)	547 (25)
2021-2022	228 (4)	148 (9)	144 (7)
Follow-up among survivors, Months			
N Eval	2964	887	1105
Median (Range)	64 (0-196)	49 (0-213)	43 (0-240)

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	11071	1859	851
Source of data			
CRF	3500 (32)	454 (24)	281 (33)
TED	7571 (68)	1405 (76)	570 (67)
Number of centers	93	78	63
Disease at transplant			
AML	3667 (33)	605 (33)	285 (33)
ALL	1843 (17)	362 (19)	163 (19)
Other leukemia	205 (2)	41 (2)	19 (2)
CML	337 (3)	45 (2)	24 (3)
MDS	1483 (13)	226 (12)	111 (13)
Other acute leukemia	164 (1)	33 (2)	11 (1)
NHL	936 (8)	168 (9)	76 (9)
Hodgkin Lymphoma	204 (2)	40 (2)	23 (3)
Plasma Cell Disorders, MM	257 (2)	39 (2)	23 (3)
Other malignancies	24 (<1)	0	1 (<1)
Breast cancer	1 (<1)	0	0
SAA	516 (5)	81 (4)	29 (3)
Inherited abnormalities erythrocyte diff fxn	494 (4)	72 (4)	20 (2)
Inherited bone marrow failure syndromes	16 (<1)	2 (<1)	4 (<1)
Hemoglobinopathies	111 (1)	22 (1)	8 (1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	228 (2)	36 (2)	16 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	16 (<1)	5 (<1)	2 (<1)
Histiocytic disorders	63 (1)	9 (<1)	5 (1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	16 (<1)	0	0
Disease missing	10 (<1)	4 (<1)	1 (<1)
MPN	457 (4)	69 (4)	29 (3)
AML Disease status at transplant			
CR1	2403 (66)	411 (68)	186 (65)
CR2	562 (15)	86 (14)	36 (13)
CR3+	44 (1)	14 (2)	1 (<1)
Advanced or active disease	651 (18)	90 (15)	62 (22)
Missing	7 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	1119 (61)	226 (62)	103 (63)
CR2	522 (28)	91 (25)	40 (25)
CR3+	114 (6)	19 (5)	11 (7)
Advanced or active disease	86 (5)	26 (7)	9 (6)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	2 (<1)	0	0
MDS Disease status at transplant			
Early	253 (17)	31 (14)	20 (18)
Advanced	1177 (79)	183 (81)	85 (77)
Missing	53 (4)	12 (5)	6 (5)
NHL Disease status at transplant			
CR1	174 (19)	39 (23)	16 (21)
CR2	176 (19)	34 (20)	10 (13)
CR3+	100 (11)	18 (11)	4 (5)
PR	68 (7)	13 (8)	7 (9)
Advanced	409 (44)	63 (38)	39 (51)
Missing	5 (1)	0	0
Recipient age at transplant			
0-9 years	1123 (10)	180 (10)	68 (8)
10-19 years	1071 (10)	139 (7)	63 (7)
20-29 years	1257 (11)	250 (13)	90 (11)
30-39 years	865 (8)	166 (9)	88 (10)
40-49 years	1356 (12)	218 (12)	99 (12)
50-59 years	2336 (21)	401 (22)	185 (22)
60-69 years	2583 (23)	431 (23)	226 (27)
70+ years	480 (4)	74 (4)	32 (4)
Median (Range)	49 (0-82)	49 (0-76)	51 (0-83)
Recipient race/ethnicity			
White	6869 (62)	977 (53)	514 (60)
Black or African American	1373 (12)	240 (13)	81 (10)
Asian	518 (5)	138 (7)	43 (5)
Native Hawaiian or other Pacific Islander	34 (<1)	5 (<1)	2 (<1)
American Indian or Alaska Native	47 (<1)	4 (<1)	4 (<1)
Hispanic	1677 (15)	357 (19)	151 (18)
Missing	553 (5)	138 (7)	56 (7)
Recipient sex			
Male	6513 (59)	1084 (58)	496 (58)
Female	4558 (41)	775 (42)	355 (42)
Karnofsky score			
10-80	3971 (36)	745 (40)	349 (41)
90-100	6760 (61)	1052 (57)	454 (53)
Missing	340 (3)	62 (3)	48 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	2161 (23)	346 (26)	166 (28)
4/6	636 (7)	112 (8)	65 (11)
5/6	204 (2)	37 (3)	21 (4)
6/6	6481 (68)	861 (63)	333 (57)
Unknown	1589 (N/A)	503 (N/A)	266 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2647 (29)	416 (33)	200 (38)
6/8	118 (1)	26 (2)	14 (3)
7/8	143 (2)	26 (2)	15 (3)
8/8	6262 (68)	798 (63)	296 (56)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	1901 (N/A)	593 (N/A)	326 (N/A)
HLA-DPB1 Match			
Double allele mismatch	9 (<1)	0	0
Single allele mismatch	725 (26)	8 (18)	6 (25)
Full allele matched	2072 (74)	37 (82)	18 (75)
Unknown	8265 (N/A)	1814 (N/A)	827 (N/A)
High resolution release score			
No	4655 (42)	1830 (98)	835 (98)
Yes	6416 (58)	29 (2)	16 (2)
Graft type			
Marrow	3187 (29)	431 (23)	238 (28)
PBSC	7789 (70)	1395 (75)	599 (70)
UCB	2 (<1)	14 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)
BM+UCB	30 (<1)	9 (<1)	2 (<1)
PBSC+UCB	0	0	11 (1)
Others	55 (<1)	6 (<1)	0
Conditioning regimen			
Myeloablative	6168 (56)	1021 (55)	439 (52)
RIC/Nonmyeloablative	4849 (44)	825 (44)	395 (46)
TBD	54 (<1)	13 (1)	17 (2)
Donor age at donation			
To Be Determined/NA	15 (<1)	3 (<1)	8 (1)
0-9 years	761 (7)	119 (6)	32 (4)
10-19 years	843 (8)	139 (7)	52 (6)
20-29 years	1915 (17)	319 (17)	167 (20)
30-39 years	1633 (15)	323 (17)	161 (19)
40-49 years	1796 (16)	300 (16)	115 (14)
50+ years	4108 (37)	656 (35)	316 (37)
Median (Range)	42 (0-122)	41 (0-118)	41 (0-121)
Donor/Recipient CMV serostatus			
+/+	4485 (41)	812 (44)	288 (34)
+/-	1187 (11)	151 (8)	72 (8)
-/+	2766 (25)	443 (24)	198 (23)
-/-	2371 (21)	381 (20)	162 (19)
CB - recipient +	24 (<1)	14 (1)	7 (1)
CB - recipient -	8 (<1)	9 (<1)	6 (1)
Missing	230 (2)	49 (3)	118 (14)
GvHD Prophylaxis			
No GVHD prophylaxis (forms under review)	156 (1)	35 (2)	16 (2)
Ex vivo T-cell depletion	114 (1)	31 (2)	11 (1)
CD34 selection	119 (1)	33 (2)	13 (2)
Post-CY + other(s)	3488 (32)	547 (29)	309 (36)
Post-CY alone	76 (1)	11 (1)	8 (1)
Tacrolimus + MMF +- others	794 (7)	93 (5)	26 (3)
Tacrolimus + MTX +- others (except MMF)	4050 (37)	606 (33)	309 (36)
Tacrolimus + others (except MTX, MMF)	815 (7)	292 (16)	67 (8)
Tacrolimus alone	108 (1)	22 (1)	7 (1)

Refresh date: Dec 2022

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA + MMF +- others (except Tacrolimus)	243 (2)	38 (2)	15 (2)
CSA + MTX +- others (except Tacrolimus, MMF)	719 (6)	95 (5)	43 (5)
CSA + others (except Tacrolimus, MTX, MMF)	81 (1)	11 (1)	3 (<1)
CSA alone	85 (1)	12 (1)	4 (<1)
Other GVHD prophylaxis	148 (1)	19 (1)	15 (2)
Missing	75 (1)	14 (1)	5 (1)
Donor/Recipient sex match			
Male-Male	3666 (33)	646 (35)	285 (33)
Male-Female	2322 (21)	388 (21)	182 (21)
Female-Male	2791 (25)	415 (22)	196 (23)
Female-Female	2200 (20)	374 (20)	164 (19)
CB - recipient M	21 (<1)	16 (1)	8 (1)
CB - recipient F	11 (<1)	7 (<1)	5 (1)
Missing	60 (1)	13 (1)	11 (1)
Year of transplant			
2006-2010	601 (5)	71 (4)	61 (7)
2011-2015	3701 (33)	503 (27)	203 (24)
2016-2020	5028 (45)	894 (48)	399 (47)
2021-2022	1741 (16)	391 (21)	188 (22)
Follow-up among survivors, Months			
N Eval	6629	1113	510
Median (Range)	35 (0-150)	24 (0-124)	24 (0-148)

Quality of life data on **adult** patients

Variable	**Baseline**	**30 day**	**100 day**	**6 months**	**1 year**	**2 year**	**3 year**	**4 year**	**5 year**	**≥6 year**
No. of patients	316	5	294	224	166	21	16	13	9	11
Infusion type - no. (%)										
Transplant	314 (99)	0	290 (99)	222 (99)	165 (99)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
Car-T therapy	2 (1)	5 (100)	4 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age at transplant - no. (%)										
Median (min-max)	56 (19-78)	70 (58-86)	58 (19-76)	56 (19-86)	56 (19-78)	68 (59-74)	68 (62-74)	67 (64-74)	64 (55-70)	61 (55-75)
18-29	35 (11)	0 (0)	21 (7)	20 (9)	11 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
30-39	27 (9)	0 (0)	27 (9)	20 (9)	15 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
40-49	50 (16)	0 (0)	37 (13)	31 (14)	26 (16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
50-59	87 (28)	1 (20)	87 (30)	74 (33)	48 (29)	2 (10)	0 (0)	0 (0)	3 (33)	5 (45)
60-69	102 (32)	1 (20)	96 (33)	65 (29)	55 (33)	13 (62)	13 (81)	10 (77)	6 (67)	4 (36)
70+	15 (5)	3 (60)	26 (9)	14 (6)	11 (7)	6 (29)	3 (19)	3 (23)	0 (0)	2 (18)
Gender - no. (%)										
Male	154 (49)	5 (100)	101 (34)	95 (42)	84 (51)	17 (81)	11 (69)	8 (62)	6 (67)	6 (55)
Female	111 (35)	0 (0)	74 (25)	66 (29)	70 (42)	4 (19)	5 (31)	5 (38)	3 (33)	5 (45)
Missing	51 (16)		119 (40)	63 (28)	12 (7)	0 (0)	0 (0)			
Race/Ethnicity - no. (%)										
White	235 (74)	5 (100)	162 (55)	150 (67)	125 (75)	20 (95)	14 (88)	12 (92)	9 (100)	10 (91)
Black or African American	12 (4)	0 (0)	0 (0)	2 (1)	3 (2)	0 (0)	1 (6)	1 (8)	0 (0)	0 (0)
Hispanic	7 (2)	0 (0)	4 (1)	2 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asian/Hawaiian/Pacific Islander	7 (2)	0 (0)	3 (1)	3 (1)	3 (2)	1 (5)	0 (0)	0 (0)	0 (0)	1 (9)
Unknown/Declined	2 (1)	0 (0)	2 (1)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	53 (17)		123 (42)	65 (29)	32 (19)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Indication for transplant - no. (%)										
Acute leukemia	139 (44)	0 (0)	109 (37)	87 (39)	63 (38)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Variable	Baseline	30 day	100 day	6 months	1 year	2 year	3 year	4 year	5 year	≥6 year
CML	20 (6)	0 (0)	14 (5)	14 (6)	11 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MDS/MPS	55 (17)	0 (0)	41 (14)	30 (14)	43 (26)	21 (100)	16 (100)	13 (100)	9 (100)	10 (91)
Other leukemia	20 (6)	0 (0)	15 (5)	14 (6)	10 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NHL	33 (10)	2 (40)	36 (12)	28 (12)	18 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HD	7 (2)	0 (0)	5 (2)	6 (3)	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MM/PCD	28 (9)	3 (60)	64 (22)	36 (16)	10 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nonmalignant diseases	14 (4)	0 (0)	9 (3)	9 (4)	7 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9)
Missing	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Year of transplant/CAR-T Therapy - no. (%)										
2011	25 (8)	0 (0)	12 (4)	12 (5)	12 (7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (55)
2012	185 (59)	0 (0)	121 (42)	113 (50)	94 (57)	0 (0)	0 (0)	0 (0)	0 (0)	3 (27)
2013	53 (17)	0 (0)	39 (13)	34 (15)	28 (17)	0 (0)	0 (0)	0 (0)	2 (22)	2 (18)
2014	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (31)	7 (78)	0 (0)
2015	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (19)	9 (69)	0 (0)	0 (0)
2016	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (43)	12 (75)	0 (0)	0 (0)	0 (0)
2017	0 (0)	0 (0)	0 (0)	0 (0)	11 (7)	11 (52)	1 (6)	0 (0)	0 (0)	0 (0)
2018	0 (0)	0 (0)	0 (0)	0 (0)	8 (5)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
2019	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2020	14 (4)	0 (0)	11 (4)	13 (6)	12 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2021	35 (11)	5 (100)	111 (38)	52 (23)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2022	4 (1)	0 (0)	0 (0)							
Measures completed - no. (%)										
FACT-BMT and SF-36	309 (98)	0 (0)	291 (99)	220 (98)	142 (86)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FACT-BMT only	7 (2)	0 (0)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SF-36 only	0 (0)	0 (0)	2 (1)	4 (2)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PROMIS only	0 (0)	5 (100)	0 (0)	0 (0)	19 (11)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
PROMIS + CoST	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Variable	Baseline	30 day	100 day	6 months	1 year	2 year	3 year	4 year	5 year	≥6 year
Median follow-up (range), months	95 (3-107)	N/A	71 (4-107)	93 (3-107)	95 (3-107)	37 (12-51)	49 (36-60)	63 (52-75)	73 (58-79)	96 (49-116)

Quality of life data on **pediatric** patient

Variable	**Baseline**	**100 days**	**6 months**	**1 year**
No. of patients	77	45	46	37
Median age at transplant (range), years				
Median (min-max)	7 (2-18)	7 (2-17)	8 (2-17)	7 (2-17)
2-4	24 (31)	14 (31)	13 (28)	9 (24)
5-7	21 (27)	12 (27)	11 (24)	12 (32)
8-12	18 (23)	9 (20)	10 (22)	7 (19)
13-18	14 (18)	10 (22)	12 (26)	9 (24)
Gender - no. (%)				
Male	42 (55)	28 (62)	28 (61)	21 (57)
Female	35 (45)	17 (38)	18 (39)	16 (43)
Race/Ethnicity - no. (%)				
White	67 (87)	39 (87)	41 (89)	33 (89)
Black or African American	5 (6)	3 (7)	3 (7)	2 (5)
Asian	2 (3)	1 (2)	1 (2)	1 (3)
More than one race	2 (3)	1 (2)	1 (2)	1 (3)
Not reported	1 (1)	1 (2)	0 (0)	0 (0)
Ethnicity of US residents - no. (%)				
Hispanic or Latino	5 (6)	1 (2)	3 (7)	1 (3)
Not Hispanic or Latino	72 (94)	44 (98)	43 (93)	36 (97)
Indication for transplant - no. (%)				
AML	11 (14)	7 (16)	7 (15)	4 (11)
ALL	17 (22)	10 (22)	10 (22)	10 (27)
CML	1 (1)	0 (0)	1 (2)	1 (3)
MDS/MPS	4 (5)	2 (4)	3 (7)	1 (3)
Severe aplastic anemia	6 (6)	3 (7)	3 (7)	3 (8)
Inherited abnorm. of erythrocytes	17 (22)	12 (27)	12 (26)	10 (27)
SCID & other immune disorders	10 (13)	4 (9)	4 (9)	3 (8)
Inherited disorders of metabolism	1 (1)	0 (0)	0 (0)	0 (0)
Histiocytic disorders	9 (12)	6 (13)	5 (11)	5 (14)
Autoimmune diseases	1 (1)	1 (2)	1 (2)	0 (0)
Year of transplant - no. (%)				
2011	9 (12)	4 (9)	6 (13)	5 (14)
2012	50 (65)	29 (64)	29 (63)	22 (59)
2013	18 (23)	12 (27)	11 (24)	10 (27)
Measures completed - no. (%)				
PedsQL proxy only patients (age<5)	24 (31)	14 (31)	13 (28)	9 (24)
PedsQL and proxy completed (age≥5)	49 (64)	31 (69)	33 (72)	26 (70)
Only PedsQL completed (age≥5)	3 (4)	0 (0)	0 (0)	1 (3)
Only proxy completed (age≥5)	1 (1)	0 (0)	0 (0)	1 (3)
Median follow-up (range), months	77 (6-111)	78 (6-111)	83 (6-111)	84 (39-111)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Morbidity, Recovery, and Survivorship Working Committee Members

FROM: Rachel Phelan, MD, Scientific Director for the Morbidity, Recovery, and Survivorship Working Committee

RE: Studies in Progress Summary

LE12-03: Solid organ transplant after HCT (M Gupta/PL Abt/M Levine) This study aims to report outcomes of solid organ transplantation in HCT recipients and compare survival. The data derives from both CIBMTR and OPTN (UNOS) databases. This study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE16-02b: Late effects after AlloHCT for pediatric patients with non-malignant diseases (JM Kahn/P Satwani) Manuscript Preparation
This study is analyzing new cancers and late effects in children, adolescents, and young adults undergoing allogeneic hematopoietic cell transplantation for non-malignant diseases. This study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE17-01a: Late effects after hematopoietic stem cell transplantation for sickle cell disease (E Stenger/L Krishnamurti/S Shenoy) This study aims to describe incidence of late effects after HCT for sickle cell disease (SCD) and the relationship of transplant-related factors to organ dysfunction and SCD-related complications. This study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE17-01b: Comparison of survival between transplanted and non-transplanted SCD patients. This study will compare survival of this transplanted SCD cohort to a cohort of non-transplanted SCD patients. This study is currently in data file preparation. The goal of this study is to submit December 2023.

LE18-01: Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) This study aims to evaluate trends in late mortality rates in children and young adults with hematologic malignancies. It will be presented at Tandem. The study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE18-03: Incorporating patient reported outcomes into individualized prognostication tools for survival and quality of life in transplant patients. (B Shaw) This study is designed to perform a comprehensive analysis of pre-existing PRO data collected longitudinally for individual patients in the context of seven clinical studies in HCT patients. The study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE19-01: Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) This study aims to analyze the risk for developing critical illness,

model long-term survival and analyze long-term morbidity in critically ill patients within the pediatric alloHCT population by utilizing both CIBMT and VPS (Virtual Pediatric Systems) data. The study will build on a previous CIBMTR study cohort (RT14-03) but has a different set of aims. This study is currently in analysis. The goal of this study is to submit by June 2023.

LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=50 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) This study will evaluate the incidence of late effects within the elderly population and evaluate the association between age and cGVHD with the development of late effects. This study is in analysis. The goal of this study is to submit by June 2023.

LE20-01: Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) This study will utilize linked Childhood Cancer Survivor Study (CCSS) and Center for International Blood and Marrow Transplant Research (CIBMTR) data to enrich our understanding of the relative contributions of clinical factors to cardiometabolic risk among an aging cohort of TBI-exposed HSCT survivors. This study is currently in protocol development. The goal of this study is to submit by December 2023.

LE20-02 Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) This study will investigate the role of a specific pre-transplant molecular profile in the association between PROs (global quality of life and psychosocial/mental component subscales) and clinical outcomes. This study is currently in manuscript preparation. The goal of this study is to submit by June 2023.

LE21-01 Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M-Angel Perales/A Kansagra) This study will compare the outcomes with different patients who used PTCy and who used other CNI-based prophylaxis. This study is currently in data file preparation. The goal of this study is to submit by December 2023.

RT19-01: Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler). This study aims to 1) evaluate the comorbidity-specific risk of non-relapse mortality and overall mortality within patients receiving pre-defined conditioning regimens, and 2) within patients stratified by conditioning intensity groups (myeloablative, reduced-intensity, and non-myeloablative, and 3) explore toxicities associated with specific conditioning regimen stratified by preexisting comorbidities. This study is currently in analysis. The goal of this study is to submit by June 2023.

RT19-02: Hemorrhagic cystitis (HC) as a complication of hematopoietic cell transplantation with post-transplant cyclophosphamide (PTCy)-based graft-versus-host disease prophylaxis compared to other allogeneic transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima). This study aims to determine the incidence and severity of HC in patients who received PTCy as part of GVHD prophylaxis, 2) to describe disease characteristics and pre-transplant regimens in patients that developed HC after receiving PTCy-based GVHD prophylaxis and 3) to evaluate survival outcomes in PTCy patients with HC. This study is currently in data file preparation. The goal of this study is to submit by June 2023.

RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff). This study aims to determine the incidence of organ toxicities in

older and younger adult allo transplants for hematologic malignancies, 2) to describe comorbid conditions in this population and 3) to evaluate survival, progression-free survival, and non-relapse mortality outcome. This study is currently in protocol development. The goal of this study is to submit by June 2023.

MRS22-01: Racial and socio-economic disparities in long-term survivor outcomes after allogeneic hematopoietic cell transplantation. (N Bhatt/A Sharma/L Jimenez-Kurlander/C Duncan). This study aims to compare the cumulative incidence and risks of malignant and non-malignant late effects by 1) race/ethnicity and 2) neighborhood poverty and insurance type at time of transplant in survivors of allogeneic HCT who have survived for at least 1 year. This study is currently in protocol development. The goal of this study is to submit by December 2023.

MRS22-02: Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis: A retrospective analysis from the CIBMTR database. (K Poonsombudlert/C Strouse/H Rangarajan/P Satwani/D Modi). This study aims to evaluate the incidence of ACE after use of PT-Cy compared to non-PT-Cy based GVHD prophylaxis regimen and determine pre-transplant factors associated with the development of ACE. This study also aims to evaluate overall survival, disease free survival, and non-relapse mortality in patients who developed ACE compared to patients who did not. This study is currently in protocol development. The goal of this study is to submit by December 2023.

Response Summary:

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

Q1. Study Title

Impact of melphalan dose reduction on regimen-related toxicity in multiple myeloma patients undergoing autologous transplant

Q2. Key Words

multiple myeloma, melphalan, mucositis, non-relapse mortality, frailty, autologous transplant

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Maxwell Krem, MD, PhD
Email address:	mkrem@uw.edu
Institution name:	Kansas City VA Medical Center
Academic rank:	Associate Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Charlotte Wagner, PharmD
Email address:	charlotte.wagner@hci.utah.edu
Institution name:	University of Utah Huntsman Cancer Institute
Academic rank:	Pharmacist

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Krem

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

N/A

LETTER OF COMMITMENT:

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

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

LK19-02: principal investigator. Also on writing committees and involved in numerous other CIBMTR studies.

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- Yes

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

Bipin Savani

Q15. RESEARCH QUESTION:

Does melphalan dose reduction decrease regimen-related toxicity in multiple myeloma patients undergoing autologous transplant?

Q16. RESEARCH HYPOTHESIS:

Reduced-dose melphalan (140 mg/m2, MEL140) compared to standard dose (200 mg/m2, MEL200) prior to autologous hematopoietic stem cell transplantation (auto-HCT) for multiple myeloma (MM) reduces toxicity outcomes but also correlates with frailty, demonstrated by higher pre-transplant comorbidity indices, lower Karnofsky performance status, and higher non-relapse mortality (NRM), regardless of age. However, long-term disease-control outcomes, particularly rate of relapse, are not dependent on melphalan dose.

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

Suggested word limit of 200 words:

To compare pre- and post-auto-HCT complication measures for MM patients who received reduced dose MEL140 or standard dose MEL200 from 2012 – 2020.

• Primary aim: Compare NRM, regimen-related toxicities, infections, HCT-CI, and KPS for MEL200 versus MEL140 for patients undergoing auto-HCT for treatment of MM.

• Secondary aims: Compare progression free survival (PFS), response rates, early relapse, and overall survival (OS) for MEL200 versus MEL140 for patients undergoing auto-HCT for treatment of MM

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

High-dose melphalan followed by auto-HCT is superior to conventional chemotherapy and is standard-of-care consolidation for MM.1,2 The typical dose is MEL200; however, in practice, it is often dose-reduced to MEL140 due to concerns for tolerability based on age, performance status, and organ dysfunction. Based on preliminary and previously published data, we believe that dose reduction of melphalan reduces peri-transplant non-hematologic toxicities without impairing disease response. and that OS and PFS concerns about MEL140 actually stem from higher NRM, higher HCT-CI scores, and lower KPS. This knowledge would have significant impact on clinicians' decision-making when determining which patient factors are important when taking a MM patient to auto-HCT and the impact of melphalan dose selection on patient outcomes.

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

High-dose melphalan followed by auto-HCT has been shown to improve response and survival outcomes in patients with MM compared to conventional chemotherapy1.2 .
The most common dose for auto-HCT is MEL2003. This dosing scheme was first described at the University of Arkansas4. It has been compared to both lower and higher doses of MEL. MEL200 was compared to 100 mg/m2. PFS and time to progression was superior in the patients who received MEL200. When the dose was escalated to 220 mg/m2, this larger dose was associated with higher rates of mucositis and cardiac arrhythmias6. Based on these data, MEL200 has been the standard. In current practice, clinicians often dose reduce to MEL140 in patients they deem unlikely to tolerate the higher dose. This practice is supported by retrospective studies from single institutions7,8,9. Two reported no difference in post-transplant outcomes with MEL1407,8. The largest study had 103 patients who received MEL1409. Multi-institution retrospectives in patients with renal insufficiency10 or general populations11 have established the efficacy of MEL140 in auto-HCT for MM, with survival possibly favoring MEL140 in patients who achieve very good partial response (VGPR) or better11. Notably, these studies did not focus on toxicity outcomes.
A recently published CIBMTR analysis (MM18-03 assessed outcomes in younger versus elderly MM patients undergoing auto-HCT for MM12. In a subset of elderly patients ≥ 70 years of age who received auto-HCT, the day 100 NRM was higher and OS was decreased in those who received MEL140. However, relapse was not statistically different for reduced and standard dose melphalan cohorts. Nevertheless, the purpose of MM18-03 was not to assess outcomes differences for patients based on melphalan dose.
A preliminary dataset from two institutions, including just over 200 patients, found that mucositis, grade ≥3 mucositis, diarrhea, and mean number of grade ≥3 toxicities were lower in patients who received MEL140 versus MEL20013.
A multi-institutional analysis examining the interplay of toxicity and melphalan dose in auto-HCT has not yet been performed in a large population of MM patients. This would help to define the correlation between MEL140 use and toxicity outcomes in patients undergoing auto-HCT and provide additional information and justification to guide decisions about MEL dose adjustment in melphalan auto-HCT.

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

N/A

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

Inclusion criteria:
• Adults ≥ 18 years at time of MEL auto-HCT between 2012 - 2018
• Diagnosis of MM
• Recipients of auto-HCT
• Received induction therapy with PI, IMiD, or both
• Received single-agent MEL conditioning
Exclusion criteria:
• Patients who did not consent to research
• Received a dose other than MEL200 or MEL140
• Tandem transplant recipients
• Patients with primary amyloidosis or plasma cell leukemia

Q21. Does this study include pediatric patients?

- No

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

It is rare to see multiple myeloma in pediatric patients. We could include them, but they are unlikely to comprise a significant number of patients.

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

We will collect data from standard CIBMTR forms including the following:
• Recipient baseline data (Forms 2000 and 2400)
• Post-HCT follow-up data (Form 2100)
• Multiple myeloma/plasma cell leukemia pre-HCT data (Form 2016)
• Multiple myeloma/plasma cell leukemia post-HCT data (Form 2116)
Primary outcome:
• Non-relapse mortality
Secondary outcomes:
• Mucositis requiring therapy
• Infections
• Development of grade 3 or higher infection
• Hepatotoxicity
• Other organ impairment (cardiac, pulmonary, etc.)
• Progression-free survival
• Overall survival
• Best response (including overall and VGPR or better)
• Early relapse (<24 months)
• Development of second malignancy
• Cause of death (descriptive)
Variables to be described (bolded items to be considered in multivariate analysis):
Patient-related:
• Age
• Gender (M, F)
• Race (Caucasian, African-American, Asian, Pacific Islander, Native American, other)
• Smoking history
• Karnofsky score (<90, ≥90)
• Renal function (SCr, eGFR)
• HCT-CI score (0,1,2,3+)
Disease-related:
• ISS and ISS-R stage
• Response per IMWG criteria prior to transplant
• Presence of high risk cytogenetics
• Involved M protein
• Involved light chains
Treatment/transplant-related:
• Main effect: Dose of melphalan (reduced- versus standard-dose)
• Pre-transplant treatment history (PI, IMiD, or both)
• 1st or 2nd auto-HCT
• Time from diagnosis to transplant
• Receipt of maintenance therapy after transplant
• Development of severe mucositis (CTCAE grade III – IV)

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Attal M, et al. "A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma." New England Journal of Medicine 335.2 (1996): 91-7.
2. Child JA, et al. "High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma." New England Journal of Medicine 348.19 (2003): 1875-83.
3. Rajkumar SV. "Treatment of multiple myeloma." Nature reviews Clinical oncology 8.8 (2011): 479.
4. Jagannath S, et al. "Low-risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support." Blood 80.7 (1992): 1666-72.
5. Palumbo A, Bringhen S, Bruno B, et al. Melphalan 200 mg/m2 versus melphalan 100 mg/m2 in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study. Blood. 2010;115(10):1873–9
6. Moreau P, et al. "Melphalan 220 mg/m 2 followed by peripheral blood stem cell transplantation in 27 patients with advanced multiple myeloma." Bone marrow transplantation 23.10 (1999): 1003.
7. Saunders IM, et al. "A lower dose of melphalan (140 mg/m2) as preparative regimen for multiple myeloma in patients> 65 or with renal dysfunction." (2013): 5536.
8. Ngo PT, et al. "Reduced-Dose Melphalan (140 or 100 mg/m2) Maintains Efficacy and Tolerability for Multiple Myeloma Patients with Advanced Age or Renal Impairment Undergoing Auto-HCT." Biology of Blood and Marrow Transplantation 25.3 (2019): S24-25.
9. Srour SA, et al. "Melphalan Dose Intensity for Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma." Biology of Blood and Marrow Transplantation 25.3 (2019): S21.
10. Mahindra A, et al. Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a Center for International Blood and Marrow Transplant Research Analysis. Bone Marrow Transplant 2017; 52: 1616-1622
11. Auner HW, et al. Melphalan 140 mg/m2 or 200 mg/m2 for autologous transplantation in myeloma: results from the Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study. A report by the EBMT Chronic Malignancies Working Party. Haematologica 2018; 103: 514-521
12. Munshi PN., et al. "Age no bar: A CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma." Cancer (2020).
13. Krem MM, et al. Reduced-dose melphalan (140 or 100 mg/m2) maintains efficacy and reduces toxicity for myeloma patients undergoing autologous transplant. Manuscript in preparation, 2021

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

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

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

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

N/A

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

Embedded Data:

N/A

Population characteristics for patients with Multiple Myeloma undergoing first autoHCT between 2012-2018,with MEL only conditioning at standard dose MEL140 or MEL200

Characteristic	MEL 140	MEL 200
No. of patients	981	5562
No. of centers	116	164
Chronological order of HCT - no. (%)		
1	909 (93)	5037 (91)
2	63 (6)	485 (9)
3	9 (1)	40 (1)
Type of HCT - no. (%)		
Auto-HCT	981 (100)	5562 (100)
Age at HCT - median (min-max)	67 (33-80)	60 (20-82)
Age at HCT - no. (%)		
18-29	0 (0)	13 (0)
30-39	13 (1)	163 (3)
40-49	47 (5)	751 (14)
50-59	186 (19)	1961 (35)
60-69	412 (42)	2388 (43)
>=70	323 (33)	286 (5)
Recipient sex - no. (%)		
Male	534 (54)	3010 (54)
Female	447 (46)	2552 (46)
Karnofsky Score - no. (%)		
90-100%	358 (36)	3010 (54)
<90%	577 (59)	2387 (43)
Missing	46 (5)	165 (3)
HCT-CI - no. (%)		
0	174 (18)	1685 (30)
1	87 (9)	805 (14)
2	153 (16)	879 (16)
3	164 (17)	917 (16)
4	139 (14)	522 (9)
5	91 (9)	262 (5)
6+	154 (16)	239 (4)
TBD, inconsistencies between parent and sub-questions	4 (0)	20 (0)
NA, f2400 (pre-TED) not completed	13 (1)	206 (4)
Missing	2 (0)	27 (0)
Race - no. (%)		

Characteristic	MEL 140	MEL 200
White	536 (55)	3377 (61)
Black or African American	346 (35)	1643 (30)
Asian	59 (6)	245 (4)
Native Hawaiian or other Pacific Islander	1 (0)	16 (0)
American Indian or Alaska Native	9 (1)	52 (1)
More than one race	1 (0)	29 (1)
Missing	29 (3)	200 (4)
Ethnicity - no. (%)		
Hispanic or Latino	61 (6)	378 (7)
Non Hispanic or non-Latino	838 (85)	4860 (87)
Non-resident of the U.S.	63 (6)	248 (4)
Missing	19 (2)	76 (1)
Disease status prior to HCT (MM) - no. (%)		
sCR/CR	141 (14)	847 (15)
VGPR	322 (33)	1889 (34)
PR	379 (39)	2227 (40)
SD	81 (8)	341 (6)
PD/Relapse	53 (5)	225 (4)
Missing	5 (1)	33 (1)
ISS stage at diagnosis (MM) - no. (%)		
Stage I	197 (20)	1823 (33)
Stage II	230 (23)	1551 (28)
Stage III	305 (31)	943 (17)
Missing	249 (25)	1245 (22)
Cytogenetic risk (MM) - no. (%)		
Normal	257 (26)	1399 (25)
High risk	209 (21)	1235 (22)
Standard risk	377 (38)	2141 (38)
Test not done/unknown/ No metaphases	138 (14)	787 (14)
Graft type - no. (%)		
Bone marrow	2 (0)	2 (0)
Peripheral blood	978 (100)	5556 (100)
Umbilical cord blood	0 (0)	1 (0)
BM + PB	1 (0)	2 (0)
PB + UCB	0 (0)	1 (0)
Year of HCT - no. (%)		
2008	107 (11)	641 (12)
2009	45 (5)	256 (5)

Characteristic	MEL 140	MEL 200
2010	24 (2)	225 (4)
2011	21 (2)	286 (5)
2012	20 (2)	273 (5)
2013	82 (8)	553 (10)
2014	100 (10)	524 (9)
2015	150 (15)	625 (11)
2016	134 (14)	683 (12)
2017	132 (13)	596 (11)
2018	166 (17)	900 (16)
Follow-up - median (range)	52 (2-149)	60 (0-157)

Q1. Study Title:

a) Modifying the risk and mortality of veno-occlusive disease via development of a contemporary risk assessment model.

Q2. Key Words:

veno-occlusive disease (VOD), stem cell transplantation, conditioning intensity, risk assessment

Q3. Junior Investigators:

First and last name, degree(s):	Michelle Schoettler, MD
Email address:	michelle.schoettler@emory.edu
Institution name:	Children's Healthcare of Atlanta/ Aflac Cancer and Blood Disorders Center
Academic rank:	Assistant Professor

First and last name, degree(s):	Christopher Strouse, MD
Email address:	christopher-strouse@uiowa.edu
Institution name:	University of Iowa
Academic rank:	Assistant Professor

First and last name, degree(s):	Gregory Roloff, MD
Email address:	gregory.roloff@uchospitals.edu
Institution name:	University of Chicago
Academic rank:	Senior Fellow

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

- Yes – Drs. Roloff, Strouse, and Schoettler are junior investigators

Q5. Do you identify as an underrepresented/minority?

- Dr. Schoettler: Yes
  Drs. Strouse and Roloff: No

Q6. <u>Principal Investigators (If applicable):</u>

First and last name, degree(s):	Kirsten Williams, MD
Email address:	Kirsten.marie.williams@emory.edu
Institution name:	Children's Healthcare of Atlanta/ Aflac Cancer and Blood Disorders Center
Academic rank:	Associate Professor

First and last name, degree(s):	Wendy Stock, MD
Email address:	wstock@bsd.uchicago.edu
Institution name:	University of Chicago
Academic rank:	Professor

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Christopher Strouse, MD

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

- N/A

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

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

Dr. Strouse: "Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database"

Dr. Schoettler is currently serving on working committee for consensus definitions in TA-TMA for CIBMTR, manuscript in press.

Dr. Williams is on the Advisory Committee at large for CIBMTR (2022-present). Dr. Williams is also presenting a proposal (tandem 2022) on the impact of pathogenic mutations/ likely pathogenic mutations in the donor on hematologic complications of HCT (graft failure, donor-derived leukemia etc.).

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- Yes: Mohammed Sorror, MD

Q15. RESEARCH QUESTION:

What effect do pre-transplant interventions (e.g. use of defibrotide prophylaxis, choice of reduced intensity vs myeloablative conditioning) have on the risk and severity of VOD, and can a risk score identify high-risk cohorts for these interventions?

Q16. RESEARCH HYPOTHESIS:
We hypothesize that pre-transplant patient-, disease-, and treatment-related variables influence the risk and severity of VOD and some are potentially modifiable, such as:

a) Lower likelihood of VOD with multi-organ failure in patient receiving defibrotide prophylaxis compared with those who are not

b) Lower risk of VOD in patients with history of inotuzumab exposure receiving reduced intensity conditioning compared with myeloablative conditioning

A multivariable risk score incorporating pre-transplant patient-, disease-, and treatment-related variables will identify identify patients at high risk of VOD with potential for risk modification.

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

Primary Objective: Identify patient-, disease-, and treatment-related variables associated with the incidence of veno-occlusive disease in adult and pediatric patients undergoing allogeneic transplant including but not limited to: previously described risk factors, inotuzumab ozogamcyin or gemtuzumab ozogamycin prior to HCT, number of HCTs, and defibrotide prophylaxis

Secondary Objectives:

- Perform a subanalysis of patients who received defibrotide prophyaxis compared to a propensity score matched cohort to further understand the impact of defibrotide prophylaxis on VOD incidence and multiorgan dysfunction.

- Evaluate incidence of veno-occlusive disease and treatment outcomes in patients who received inotuzumab ozogamicin therapy by transplant conditioning intensity

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

Veno-occlusive disease (VOD) is an early complication of allogeneic stem cell transplantation associated with significant morbidity and mortality. Patient and transplant related risk factors are identified and a VOD risk score has been generated previously. However, this risk score did not include recent therapies linked to VOD that are now increasingly used pre-HCT including inotuzumab ozogamycin and gemtuzumab ozogamycin, nor greater than first HCTs. With the changing landscape of therapies, updating the risk score will improve the ability to identify patients at highest risk of VOD before HCT.

We expect that many risk factors will be non-modifiable such as young age, pre-HCT therapies, prior liver toxicity, etc. Thus, we anticipate such a score would be helpful to practioners who are considering a prophylactic therapeutic or monitoring approach. Reporting real-world outcomes of defibrotide prophylaxis will help inform clinical practice for patients who are identified as high risk for developing VOD. Thus, this proposal is significant as it includes not only an updated risk score to identify patients at highest risk for VOD but also a subanalysis to determine the impact of defibrotide prophylaxis on VOD and MOD, increasing the clinical utility of the score.

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

Veno-occlusive disease (VOD) arises from damage to the hepatic sinusoidal endothelial cells sustained during hematopoietic cell transplantation (HCT), resulting in fibrin deposition, microthromi, and hepatocyte necrosis. Though the conditioning regimen plays an important role in the pathogenesis of VOD, multiple other patient-related, disease-related and treatment-related factors are important as well. Thus, it is necessary to consider a wide variety of covariates when attempting to estimate the VOD risk of a patient undergoing HCT. CIBMTR data from 2008-2013 has previously been utilized to construct a VOD risk score with a high discriminative ability (c-statistic = 0.76). The existing tool is utilized on the CIBMTR website approximately 30 times per business day. However, important changes in the field of HCT since 2013 likely alter the risk for VOD. First, agents known to impact VOD risk such as inotuzumab ozogamicin and gemtuzumab ozogamicin were not included in the earlier analysis due to the lack of prevalent use. Additionally, post-transplant cyclophosphamide was used in only 1% of cases in the data set. Its interaction with other well established risk factors for VOD is thus not known, necessitating this update. Furthermore, the incidence of post-transplant VOD in adult populations who previously received inotuzumab ozogamicin for relapsed/refractory acute lymphoblastic leukemias is as high as 20%.[1] Certain recommendations to avoid VOD have been proposed by consensus guidelines and include ursodiol prophylaxis, administration of two or fewer cycles of inotuzumab ozogamycin prior to transplant and avoidance of dual alkylating preparative regimens. Recent data suggest that reduced-intensity conditioning (RIC) is not commonly used in these populations but is becoming more acceptable in the era of novel therapies that result in high rates of undetectable minimal residual disease levels pre-transplant. Preliminary data from a small retrospective series suggests that RIC conditioning may offer opportunities for VOD mitigation.[2] These data suggest that a larger systematic analysis of the relationship between the mitigations strategies previously proposed and use of RIC transplant in INO treated patients and hepatic VOD is justified.

Defibrotide prophylaxis has been explored as a means of mitigating VOD. A randomized phase 3 clinical trial in children demonstrated a significant difference in cumulative incidence of VOD on day 30 post HCT.[3] The study was not powered to detect differences in multi-organ failure or non-relapse related mortality. A follow up randomized, open-label phase 3 multicenter trial evaluating the efficacy of VOD-free survival at day 30 in children and adults stopped accruing patients after a an interim analysis determined that the study met protocol-specified futility. Thus, it remains unclear whether defibrotide prophylaxis impacts VOD incidence or severe disease. Practices vary by institutions on the use of defibrotide prophylaxis. Given this, there is unlikely to be a follow up clinical trial. By utilizing CIBMTR data from recent years, we will build a new risk score algorithm based on contemporary standards of care, which will provide more confident estimation of the VOD risk. And, we will determine the

impact of defibrotide on VOD and multiorgan dysfunction to inform clinical strategies to utilize a risk score.

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

n/a

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

Inclusion:
- Patients of all ages who underwent allogeneic transplantation from 2013-2021

Exclusion:
- Autologous transplant

Q21. Does this study include pediatric patients?

- Yes

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

No additional data collection is necessary. Variables needed for the analysis include:

Patient-related factors:
- Age
- Sex
- Race/Ethnicity
- Karnofsky performance status
- HCT indication
- HCT Comorbidity Index
- Recipient CMV Status
- Receipient HCV status
- Recipient HBV status
- BMI
- Prior liver disease

Disease-related factors:

- Disease severity (Disease Risk Index)
- Prior lines of therapy
- Receipt of gemtuzumab ozogamicin, blinatumomab, or inotuzumab prior to HCT
- Prior HCT (yes/no)

Transplant Related factors:
- Donor type (matched related, matched unrelated, umbilical cord, haploidentical, etc.)
- HLA mismatch status
- Conditioning regimen (reduced intensity / myeloablative), including agents used
- Busulfan pharmacokinetics (if available)
- GVHD prophylaxis
- Venoocclusive disease experienced (Y/N)
- Date of venoocclusive disease onset
- Use of defibrotide (for either prophylactic or empiric purposes or direct treatment)
- Use of ursodiol
- Use of ATG
- Significant organ impairment, such as acute renal failure requiring dialysis
- ICU admission
- Date of death
- Date of last contact, if alive
- Relapse and non-relapse mortality

Q23. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.
For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Committees/wc/LateEffects/Pages/default.aspx

N/A

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

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

N/A

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

None

Q26. REFERENCES:

1. Ladha A, Mannis G, Muffly L. Hepatic veno-occlusive disease in allogeneic stem cell transplant recipients with prior exposure to gemtuzumab ozogamicin or inotuzumab ozogamicin. *Leuk Lymphoma*. Feb 2021;62(2):257-263. doi:10.1080/10428194.2020.1827247
2. Cahill K AJ, Mortel M, Dworkin E, Kosuri S, Duvall A, et al. Low incidence of hepatic veno-occlusive disease (VOD) in patients with B-cell acute lymphoblastic leukemia (B-ALL) treated with inotuzumab ozogamicin (INO) followed by allogeneic stem cell transplantation (allo-SCT). *J Clin Oncol*. 2021;39(15_suppl):e19024-e)
3. Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet*. Apr 7 2012;379(9823):1301-9. doi:10.1016/S0140-6736(11)61938-7

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

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

No

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

N/A

Population characteristics of all patients undergoing alloHCT between 2013-2019

Characteristic	N (%)
No. of patients	22605
No. of centers	278
Age at HCT - median (min-max)	50 (0-88)
Age at HCT - no. (%)	
<10	3432 (15)
10-17	1866 (8)
18-29	2263 (10)
30-39	1656 (7)
40-49	2222 (10)
50-59	3924 (17)
60-69	5716 (25)
>=70	1526 (7)
Recipient sex - no. (%)	
Male	13404 (59)
Female	9201 (41)
Karnofsky Score - no. (%)	
90-100%	14078 (62)
<90%	7998 (35)
Missing	529 (2)
HCT-CI - no. (%)	
0	7667 (34)
1	3227 (14)
2	2738 (12)
3	3488 (15)
4	2173 (10)
5	1299 (6)
6+	1771 (8)
TBD, review needed for history of malignancies	8 (0)
TBD, inconsistencies between parent and sub-questions	148 (1)
Missing	86 (0)
Race - no. (%)	
White	14977 (66)
Black or African American	2479 (11)
Asian	2409 (11)
Native Hawaiian or other Pacific Islander	152 (1)
American Indian or Alaska Native	212 (1)

Characteristic	N (%)
More than one race	220 (1)
Missing	2156 (10)
Ethnicity - no. (%)	
Hispanic or Latino	2243 (10)
Non Hispanic or non-Latino	15827 (70)
Non-resident of the U.S.	4115 (18)
Missing	420 (2)
Primary disease for HCT - no. (%)	
AML	6471 (29)
ALL	2728 (12)
Other leukemia	496 (2)
CML	454 (2)
MDS/MF	4504 (20)
Other acute leukemia	214 (1)
NHL	1090 (5)
HD	167 (1)
PCD	87 (0)
Solid tumor	17 (0)
SAA	1584 (7)
IEA	1831 (8)
IIS	884 (4)
IPA	24 (0)
IMD	246 (1)
HIS	177 (1)
AI	12 (0)
Other	25 (0)
1460	1594 (7)
Graft Type - no. (%)	
Bone Marrow	5919 (26)
Peripheral Blood	13837 (61)
Cord Blood	2849 (13)
Donor type (%dnrinfo() macro) - no. (%)	
HLA-identical sibling	5591 (25)
Twin	151 (1)
Other related	4825 (21)
Well-matched unrelated (8/8)	7336 (32)
Partially-matched unrelated (7/8)	1422 (6)
Mis-matched unrelated (<= 6/8)	83 (0)

Characteristic	N (%)
Multi-donor	28 (0)
Unrelated (matching TBD)	320 (1)
Cord blood	2849 (13)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)	
RIC/NMA	10865 (48)
MAC	11590 (51)
Missing	150 (1)
Planned GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	137 (1)
TDEPLETION alone	96 (0)
TDEPLETION +- other	168 (1)
CD34 select alone	238 (1)
CD34 select +- other	360 (2)
Cyclophosphamide alone	153 (1)
Cyclophosphamide +- others	4725 (21)
FK506 + MMF +- others	2297 (10)
FK506 + MTX +- others(not MMF)	6883 (30)
FK506 +- others(not MMF,MTX)	819 (4)
FK506 alone	342 (2)
CSA + MMF +- others(not FK506)	2428 (11)
CSA + MTX +- others(not MMF,FK506)	2767 (12)
CSA +- others(not FK506,MMF,MTX)	334 (1)
CSA alone	382 (2)
Other GVHD Prophylaxis	325 (1)
identical twin donor	125 (1)
Parent Q = yes, but no agent	12 (0)
Missing	14 (0)
Defibrotide prophylaxis - no. (%)	
No	7344 (32)
Yes	130 (1)
Missing	15131 (67)
Inotuzumab exposure - no. (%)	
Yes	111 (0)
Disease other than ALL	19877 (88)
Missing	2617 (12)
Gemtuzumab exposure - no. (%)	
No	5965 (26)
Yes	119 (1)

Characteristic	N (%)
Disease other than AML	16134 (71)
Missing	387 (2)
Hepatic, moderate / severe - no. (%)	
No	21356 (94)
Yes	725 (3)
Not done	1 (0)
Missing	341 (2)
Blank	159 (1)
Unknown	23 (0)
Veno-occlusive disease (VOD) - no. (%)	
Censoring	20268 (90)
Event	809 (4)
Missing	1528 (7)
Year of HCT - no. (%)	
2013	2824 (12)
2014	3602 (16)
2015	3548 (16)
2016	3425 (15)
2017	3194 (14)
2018	3126 (14)
2019	2886 (13)
Follow-up - median (range)	42 (0-101)

Response Summary:

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

Q1. Study Title

Updated Analysis of Long-Term Survival and Late Deaths after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies and Severe Aplastic Anemia

Q2. Key Words

N/A

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Uttam Rao, MD, MBA
Email address:	uttam.rao@hcahealthcare.com
Institution name:	St. David's South Austin Medical Center/Sarah Cannon Network
Academic rank:	N/A

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Minoo Battiwalla, MD, MS
Email address:	Minoo.Battiwalla@hcahealthcare.com
Institution name:	Sarah Cannon
Academic rank:	Director of Blood Cancer Outcomes Research

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Uttam Rao

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Late Effects and Quality of Life

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

- No

Q15. RESEARCH QUESTION:

The research question is to examine the long-term survival in 2-year survivors of allogeneic hematopoietic cell transplantation.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the probability of 2 year survivors being alive at 10 years after HCT has continued to improve.

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

Suggested word limit of 200 words:

The primary objective is to determine the probability of being alive at 10 years after HCT. Secondary objectives include: (1) an evaluation of risk factors for late mortality after HCT, (2) an evaluation of any change in late mortality over time, (3) a description of causes of late deaths, and (3) a comparison of relative mortality after HCT with that of the general population.

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

Due to the substantial advances in the field over the past decade, this updated analysis will provide new insights into long-term survival after allogeneic HCT and will reflect contemporary transplant practices such as greater use of reduced intensity conditioning regimens, transplantation in older patients, and frequent use of alternate graft sources.

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

In 1999, the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) undertook a study to determine the long-term survival of 2-year allogeneic HCT survivors and relative mortality rates compared with the general population. In that analysis of 6,691 survivors who underwent transplantation for severe aplastic anemia (SAA), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), or chronic myelogenous leukemia (CML), who were alive and free of recurrent disease at 2 years after HCT, survival at 5 years was 89% (95% CI, 88% to 90%). The risk of death of survivors who underwent transplantation for SAA had returned to that of the normal population by the sixth year but had remained higher than that of the normal population matched for age, sex, ethnicity, and nationality throughout the study (5 years later) for patients who underwent transplantation for AML, ALL, or CML. Recurrent disease was the chief cause of death for patients who underwent transplantation for leukemia, but chronic GVHD was the chief cause of death for patients who underwent transplantation for SAA. Advanced disease before transplantation and active chronic GVHD were risk factors for late death.

In 2011, another analysis was performed to investigate new insights into long-term survival after allogeneic HCT. It reported that long-term survival for 2-year survivors was excellent, and that chief risk factors for late death included older age and chronic graft-versus-host disease, while for patients who underwent HCT for malignancy, relapse was the most common cause of death. Advanced disease at transplantation was the greatest risk factor for late relapse, and that principal risk factors for non-relapse deaths were older age and GVHD. When compared with age, sex, and nationality-matched general population, late deaths remained higher than expected, although the relative risk generally receded over time. However, an additional study from CIBMTR focusing on HCT recipients with CML who had survived in remission for at least 5 years showed that the relative mortality of these survivors was similar to that of the matched general population, although the differences in the above analyses could stem from cohort selection criteria (2 year survivors vs 5 year survivors).

The field of HCT has continued to improve and change over the last decade, with older patients, reduced-intensity conditioning regiments, dramatic expansion of donor availability, greater use of alternate graft sources, improvement in control of GVHD as well as multiple agents to aid in delaying and reducing relapse. A growing focus, as highlighted by the National Institutes of Health HCT Late Effects Initiative, has emerged on late complications and their associated morbidity and mortality in HCT survivors. A specific focus on late mortality from infections, particularly in the COVID era, could help address whether SARS-CoV2 impacted early HCT survivors more than late HCT survivors. Overall, an updated analysis on long-term survival and late deaths after allogeneic HCT would be timely and useful.

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

N/A

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

Survivors of first allogeneic HCT who received myeloablative and reduced intensity conditioning regimens for hematologic malignancies (AML, ALL, MDS, MPN, MDS/MPN, Lymphoma, CML, CLL) and severe aplastic anemia Who are alive and disease free >= 2 years post HCT with follow-up data reported to the CIBMTR.
Exclusionary criteria
-Recipients of identical twin transplantations and umbilical cord blood transplantations
-Patients who experience relapse or mortality within 2 years of HCT
-Patients who undergo a second transplant

Q21. Does this study include pediatric patients?

- Yes

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

Patient variables to consider:
o Age: All age groups
o Sex
o Region of transplant centers
o Karnofsky score at HCT
o Year of transplantation
<1985, 1986-1990, 1991-1995, 1996-2000, 2001-2005, 2006-2010, 2011-2015
Disease variables
o Disease risk prior to transplantation
o Diagnosis: AML, ALL, MDS, MDS/MPN overlap, MPN, Lymphoma, CML, CLL, SAA
Conditioning regimens
o Previous analyses looked at myeloablative allogeneic transplants
o Now look at MAC as well as reduced intensity conditioning and non myeloablative
Interval from diagnosis to HCT, months
Donor type
Degree of HLA match
Graft type
GVHD prophylaxis
o Including post-transplant cyclophosphamide
T-cell depletion
Grades II to IV acute GVHD
Chronic GVHD
Time to Relapse
Follow up of survivors, months
Duration of follow up, years
Causes of death
o Recurrent or persistent disease
o GVHD
o Infection
COVID-19
o Organ failure
o Interstitial pneumonitis
o Secondary malignancy
o Hemorrhage
o Graft rejection
o Other causes
o Unknown

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, Sorror ML, Horowitz MM, Bolwell B, Rizzo JD, Socié G. J Clin Oncol. 2011 Jun 1;29(16):2230-9. doi: 10.1200/JCO.2010.33.7212. Epub 2011 Apr 4.

Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, Cahn JY, Passweg JR, Rowlings PA, Schouten HC, Kolb HJ, Klein JP. N Engl J Med. 1999 Jul 1;341(1):14-21. doi: 10.1056/NEJM199907013410103.

Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. John M Goldman, Navneet S Majhail, John P Klein, Zhiwei Wang, Kathleen A Sobocinski, Mukta Arora, Mary M Horowitz, J Douglas Rizzo. J Clin Oncol. 2010 Apr 10;28(11):1888-95. doi: 10.1200/JCO.2009.26.7757. Epub 2010 Mar 8.

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Developing Recommendations to Improve Survivorship and Long-Term Outcomes. Minoo Battiwalla, Shahrukh Hashmi, Navneet Majhail, Steven Pavletic, Bipin N Savani, Nonniekaye Shelburne. Biol Blood Marrow Transplant. 2017 Jan;23(1):6-9. doi: 10.1016/j.bbmt.2016.10.020. Epub 2016 Oct 29.

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

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

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

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

N/A

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

Embedded Data:

N/A

Population characteristics of adults undergoing first alloHCT for hematological malignancies or SAA between 2000-2015

Characteristic	N (%)
No. of patients	28589
No. of centers	376
Age at HCT - median (min-max)	47 (18-84)
Age at HCT - no. (%)	
18-29	4951 (17)
30-39	4727 (17)
40-49	6452 (23)
50-59	7544 (26)
60-69	4507 (16)
>=70	408 (1)
Sex: (2400 Q942) - no. (%)	
Male	16319 (57)
Female	12254 (43)
Missing	16 (0)
Karnofsky Score - no. (%)	
90-100%	12846 (45)
< 90%	5680 (20)
Missing	10063 (35)
HCT-CI - no. (%)	
0	6149 (22)
1	2244 (8)
2	2109 (7)
3+	4939 (17)
TBD, review needed for history of malignancies	1 (0)
TBD, inconsistencies between parent and sub-questions	39 (0)
NA, f2400 (pre-TED) not completed	12128 (42)
Missing	980 (3)
Race - no. (%)	
White	21799 (76)
Black or African American	962 (3)
Asian	1698 (6)
Native Hawaiian or other Pacific Islander	62 (0)
American Indian or Alaska Native	71 (0)
Other	691 (2)
More than one race	120 (0)

Characteristic	N (%)
Missing	3186 (11)
Ethnicity - no. (%)	
Hispanic or Latino	1813 (6)
Non Hispanic or non-Latino	16143 (56)
Non-resident of the U.S.	6728 (24)
Missing	3905 (14)
Indicate the primary disease for which the HSCT was performed: (2400 Q173) - no. (%)	
Acute myelogenous leukemia or ANLL	11399 (40)
Acute lymphoblastic leukemia	4108 (14)
Other leukemia	1483 (5)
Chronic myelogenous leukemia	3021 (11)
Myelodysplastic/myeloprolifterative disorders	3408 (12)
Other acute leukemia	353 (1)
Non-Hodgkin lymphoma	3489 (12)
Hodgkin lymphoma	172 (1)
Plasma cell disorder/Multiple Myeloma	241 (1)
Severe aplastic anemia	901 (3)
Missing	14 (0)
Graft Type - no. (%)	
Bone Marrow	6421 (22)
Peripheral Blood	22048 (77)
Missing	120 (0)
Donor type - no. (%)	
HLA-identical sibling	14232 (50)
Other related	1379 (5)
Well-matched unrelated (8/8)	7998 (28)
Partially-matched unrelated (7/8)	1896 (7)
Mis-matched unrelated (<= 6/8)	211 (1)
Multi-donor	65 (0)
Unrelated (matching TBD)	2686 (9)
Missing	122 (0)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
No drugs reported	13 (0)
MAC	9551 (33)
RIC	4388 (15)
NMA	1535 (5)
TBD	654 (2)
N/A, F2400 (pre-TED) not submitted, drug dose not available	11540 (40)

Characteristic	N (%)
N/A, not malignant disease	901 (3)
Missing	7 (0)
Planned GVHD Prophylaxis - no. (%)	
No prophylaxis	2032 (7)
T-cell depletion	761 (3)
CNIs + MMF	4714 (16)
CNIs + MTX	16964 (59)
CNIs + others	1932 (7)
CNIs alone	1297 (5)
Others	635 (2)
Missing	254 (1)
TX year - no. (%)	
2000	1741 (6)
2001	1460 (5)
2002	1616 (6)
2003	1581 (6)
2004	1446 (5)
2005	1458 (5)
2006	1515 (5)
2007	1493 (5)
2008	1727 (6)
2009	1992 (7)
2010	2231 (8)
2011	2294 (8)
2012	2449 (9)
2013	2034 (7)
2014	1671 (6)
2015	1881 (7)
Follow-up - median (range)	96 (24-250)

Response Summary:

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

Q1. Study Title

Evaluation of Total and Fractionated Total Body Irradiation Doses on Late Effects and Outcomes in Pediatric Patients with Acute Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation

Q2. Key Words

TBI, fractionated TBI, pediatric hematopoietic stem cell transplantation, late effects

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Lauren Appell MD
Email address:	leappell@uams.edu
Institution name:	University of Arkansas for Medical Sciences, Arkansas Children's Hospital
Academic rank:	Assistant Professor

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Akshay Sharma, MBBS
Email address:	Akshay.Sharma@STJUDE.ORG
Institution name:	St. Jude Children's Research Hospital, Memphis, TN
Academic rank:	Assistant Professor

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- Yes

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

Lauren Appell

Q10. 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

LETTER OF COMMITMENT:

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

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

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

Q13. PROPOSED WORKING COMMITTEE:

- **Pediatric Cancer**

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

- No

Q15. RESEARCH QUESTION:

Do different cumulative and fractionated doses of TBI impact outcomes and late effects for pediatric patients with acute leukemia undergoing hematopoietic stem cell transplantation?

Q16. RESEARCH HYPOTHESIS:

Pediatric patients with acute leukemia who receive smaller fractionated doses and lower total doses of total body irradiation (TBI) as conditioning for hematopoietic cell transplantation (HCT) have fewer late effects while maintaining similar survival outcomes compared to patients who receive higher fractionated and total doses of TBI.

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

Suggested word limit of 200 words:

1) To determine outcomes (overall survival, relapse free survival, and non-relapse mortality) for pediatric patients with acute leukemia who received lower fractionated doses and lower total doses of TBI compared to those who received higher fractionated doses and total doses of TBI.
2) To assess toxicities and late effect profiles for pediatric patients with acute leukemia who received lower fractionated doses and lower total doses of TBI compared to those who received higher fractionated doses and total doses of TBI.

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

For pediatric patients with acute leukemia who require HCT, standard conditioning therapy contains TBI (12 Gy in six/eight fractions, given twice per day).(1) However, there is a paucity of data on the outcomes of different fractionated doses and total doses other than 12Gy in pediatric patients with acute leukemia, especially lower doses. If smaller doses of TBI maintain similar survival outcomes (overall survival [OS], relapse free survival [RFS], and non-relapse mortality [NRM]) as higher doses of TBI but improve the toxicity profile and decrease late effects, then adjusting the standard dose of TBI for pediatric patients with acute leukemia is warranted.

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

TBI is an important component of conditioning regimens for a variety of malignant and non-malignant diseases requiring HCT as curative therapy, in both children and adults, due to its immunosuppressive properties, improved engraftment, efficacy against most leukemias and lymphomas, and the ability to eradicate disease in sanctuary sites.(2) In adult patients, doses >12 Gy have been associated with increased toxicity as well as higher rates of NRM without improving survival.(2,3) In pediatric patients, the concern of life-altering late effects has led to studies investigating whether TBI could be eliminated from conditioning prior to HCT, but TBI-based conditioning has proved superior to chemotherapy alone with a 2-year OS following TBI of 0.91 compared to 0.75 following chemotherapy alone conditioning.(4) Additional studies tout the superiority of TBI especially for pediatric patients with acute lymphoblastic leukemia (ALL), with one study concluding that TBI conferred significantly higher event-free survival (EFS) compared to a busulfan based regimen (3 year EFS 58% vs 29% respectively, p=0.03).(5) Several other studies found similar results showing a clear benefit of TBI-based conditioning regiments in pediatric patients with ALL.(4,6,7) Despite its benefit in improving outcomes for patients undergoing HCT, TBI has well-known late effects including growth hormone deficiency leading to shortened stature, cataracts, hypothyroidism, and increased risk of secondary malignancy.(5, 8) In order to reduce the potential late effects of TBI, fractionated TBI was investigated and showed decreased toxicity with equal or improved survival in patients.(9) This has since become standard practice in conditioning regimens, including pediatric patients. However, there is a paucity of data in pediatric patients investigating the outcomes in pediatric patients with leukemia who receive different doses of TBI. In this study we intend to investigate whether patients who receive <8Gy, 8-12Gy, and >12Gy have difference in survival or late effects. Furthermore, most pediatric conditioning protocols give fractionated doses of 150cGy, 200cGy, or 300cGy. Therefore, we also intend to investigate whether smaller fractions of TBI are better tolerated with improved late effects while maintaining OS and EFS in pediatric patients with acute leukemias.

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

N/A

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

All patients 21 years of age or younger who underwent allogeneic HCT for acute lymphoblastic leukemia registered with CIBMTR between years 2000 and 2022.

Q21. Does this study include pediatric patients?

- Yes

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

This proposed study will require no supplemental data to be collected. The current data is included in the CIBMTR collection forms for Pre-HSCT and Post-HSCT Acute Lymphoblastic Leukemia.
This study is a retrospective registry analysis of all pediatric and young adult patients who underwent allogeneic HCT for acute lymphoblastic leukemia between January 2000 and January 2022.
Baseline characteristics and known prognostic variables will be collected from CIBMTR database forms. These characteristics will include: age, sex, performance status, presence of extra-medullary disease at diagnosis (including CNS, testicular), WBC at diagnosis, immunophenotype at diagnosis, number of prior chemotherapy regimens, time from diagnosis to transplant, remission status at transplant (first remission, second remission, progressive/refractory disease), conditioning therapy (chemotherapy-based or total body irradiation based, including chemotherapy type and TBI dose), total cumulative dose of TBI, number and dose of fractionated TBI sessions, cranial and/or testicular boost given as part of conditioning regimen, GvHD prophylactic regimen, use of anti-thymocyte globulin, T-cell depletion of the graft, presence of minimal residual disease prior to transplant (molecular data or flow cytometry data), donor source (peripheral blood, cord, bone marrow), transplant type (haploidentical, 1 or 2 HLA-antigen mismatch, MUD, sibling donor, cord blood), hematopoietic cell transplantation-co-morbidity index (HCT-CI), and cytogenetics at diagnosis.
Transplant outcomes (OS, PFS, cumulative incidence (CI) NRM, and CI Relapse) and late effects will be evaluated for all patients, patients in CR1, second remission and greater (CR2+), and those with progressive/refractory disease.
Median overall survival, and progression-free survival will be calculated utilizing Kaplan-Meier analysis and compared utilizing the log-rank test. Cumulative incidences of NRM, Relapse, and GVHD (chronic and acute) will be performed utilizing the cumulative incidence procedure to account for competing risks, and comparison will be performed utilizing the Fine-Gray test.
Differences between groups will be evaluated utilizing the Chi-squared test or Fisher's exact test for categorical variables, two-sample test for proportions, or the Wilcoxon rank sum test for medians. For cumulative incidence, the Fine-Gray analysis will be utilized to compare variables with competing risks.
Outcomes will be compared between patients in CR1, CR2+, and no-remission/refractory disease. TBI-based conditioning will be compared to chemotherapy-based conditioning and TBI-based conditioning will be stratified based on a) fractionated doses and b) cumulative doses.
Prognostic variables will be evaluated for their impact on OS, PFS, NRM and Relapse utilizing univariate analysis and multivariate analysis by cox proportional hazards analysis.

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

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

N/A

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

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

No biological samples are required for this study.

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

N/A

Q26. REFERENCES:

1. Hoeben BAW, Wong JYC, Fog LS, et. al. Total Body Irradiation in Haematopoietic Stem Cell Transplantation for Paediatric Acute Lymphoblastic Leukaemia: Review of the Literature and Future Directions. Front Pediatr. 2021; 9: DOI=10.3389/fped.2021.774348.
2. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014; 124(3): 344-353.
3. Sabloff M, Chhabra S, Wang T, et. al. Comparison of High Doses of Total Body Irradiation in Myeloablative Conditioning before Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2019; 25(12): 2398-2407.
4. Peters C, Dalle J-H, Locatelli F, et. al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational Randomized, Noninferiority Phase III Study. J Clin Oncol. 2021; 39(4): 295-307.
5. Bunin N, Aplenc R, Kamani N, et. al. Randomized trial of busulfan vs total body irradiation containing pediatric regimens for children with acute lymphoblastic leukemia: A Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant. 2003; 32(6): 543-548.
6. Davies SM, Ramsay NK, Klein JP, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol. 2000; 18(2): 340–347.
7. Gupta T, Kannan S, Dantkale V, Laskar S. Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis. Hematol Oncol Stem Cell Ther. 2011; 4(1): 17–29.
8. Chemaitilly W, Boulad F, Heller G, et. al. Bone Marrow Transplant. 2007; 40(1): 29-35.
9. Cosset JM, Girinsky T, Malaise E, et. al. Clinical basis for TBI fractionation. Radiother Oncol. 1990; 18(Suppl 1): 60-67.

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

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

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

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

N/A

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

Embedded Data:

N/A

Population characteristics of patients 21 and under in research track undergoing first alloHCT for acute lymphoblastic leukemia between 2000-2019

Characteristic	N (%)
No. of patients	4109
No. of centers	259
Age at HCT - median (min-max)	10.6 (0.3-21.0)
Age at HCT - no. (%)	
<10	1936 (47.1)
10-17	1571 (38.2)
18-29	602 (14.7)
Sex - no. (%)	
Male	2599 (63.3)
Female	1510 (36.7)
Karnofsky Score - no. (%)	
90-100%	3219 (78.3)
<90%	660 (16.1)
Not reported	230 (5.6)
HCT-CI - no. (%)	
0	1096 (26.7)
1	240 (5.8)
2	102 (2.5)
3+	239 (5.8)
TBD, inconsistencies between parent and sub-questions	1 (0.0)
NA, f2400 (pre-TED) not completed	2349 (57.2)
Missing	82 (2.0)
Race - no. (%)	
White	2966 (72.2)
Black or African American	302 (7.3)
Asian	301 (7.3)
Native Hawaiian or other Pacific Islander	19 (0.5)
American Indian or Alaska Native	24 (0.6)
Other	165 (4.0)
More than one race	89 (2.2)
Not reported	243 (5.9)
Ethnicity - no. (%)	
Hispanic or Latino	880 (21.4)
Non Hispanic or non-Latino	1931 (47.0)
Non-resident of the U.S.	885 (21.5)

Characteristic	N (%)
Not reported	413 (10.1)
Primary disease - no. (%)	
ALL-acute lymphoblastic leukemia	4109 (100)
Graft Type - no. (%)	
Bone Marrow	1765 (43.0)
Peripheral Blood	931 (22.7)
Cord Blood	1410 (34.3)
Not reported	3 (0.1)
Donor type - no. (%)	
HLA-identical sibling	795 (19.3)
Twin	20 (0.5)
Other related	358 (8.7)
Well-matched unrelated (8/8)	826 (20.1)
Partially-matched unrelated (7/8)	445 (10.8)
Mis-matched unrelated (<= 6/8)	193 (4.7)
Multi-donor	7 (0.2)
Unrelated (matching TBD)	55 (1.3)
Cord blood	1410 (34.3)
Conditioning regimen intensity - no. (%)	
MAC	3733 (90.8)
RIC	97 (2.4)
NMA	47 (1.1)
TBD	54 (1.3)
Missing	178 (4.3)
TBI usage - no. (%)	
TBI regimen	
TBI > 800 cGy	3210 (78.1)
TBI <= 800 cGy	216 (5.3)
Non-TBI regimen	683 (16.6)
GVHD prophylaxis - no. (%)	
No GVHD prophylaxis	49 (1.2)
Ex-vivo T-cell depletion	262 (6.4)
CD34 selection	79 (1.9)
Post-CY + other(s)	142 (3.5)
Post-CY alone	1 (0.0)
TAC + MMF +- other(s) (except post-CY)	248 (6.0)
TAC + MTX +- other(s) (except MMF, post-CY)	615 (15.0)
TAC + other(s) (except MMF, MTX, post-CY)	84 (2.0)

Characteristic	N (%)
TAC alone	33 (0.8)
CSA + MMF +- other(s) (except post-CY)	556 (13.5)
CSA + MTX +- other(s) (except MMF, post-CY)	1277 (31.1)
CSA + other(s) (except MMF, MTX, post-CY)	428 (10.4)
CSA alone	147 (3.6)
Other(s)	38 (0.9)
Not reported	150 (3.7)
TX year - no. (%)	
2000	299 (7.3)
2001	291 (7.1)
2002	299 (7.3)
2003	291 (7.1)
2004	322 (7.8)
2005	294 (7.2)
2006	312 (7.6)
2007	298 (7.3)
2008	247 (6.0)
2009	188 (4.6)
2010	120 (2.9)
2011	95 (2.3)
2012	103 (2.5)
2013	143 (3.5)
2014	151 (3.7)
2015	174 (4.2)
2016	153 (3.7)
2017	114 (2.8)
2018	113 (2.8)
2019	102 (2.5)
Follow-up - median (range)	78.1 (0.0-249.9)

Response Summary:

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

Q1. Study Title

Prediction of non-relapse mortality by EASIX and HCT-CI scores in patients with chronic myelomonocytic leukemia undergoing allogeneic stem cell transplant.

Q2. Key Words

CMML, EASIX, HCT-CI, non-relapse mortality

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hassan Alkhateeb, MD
Email address:	Alkhateeb.hassan@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Assistant professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Anmol Baranwal, MBBS
Email address:	Baranwal.anmol@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	N/A

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Hassan Alkhateeb, MD

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- No

Q15. RESEARCH QUESTION:

To determine if the Endothelial Activation and Stress Index (EASIX) score can predict non-relapse mortality (NRM) in patients with chronic myelomonocytic leukemia (CMML) undergoing allogeneic stem cell transplantation (alloSCT).

Q16. RESEARCH HYPOTHESIS:

Allogeneic stem cell transplant (alloSCT) is the only curative treatment option in patients with CMML. The EASIX score has been shown to predict non-relapse mortality (NRM) in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). We hypothesize that the EASIX score can predict NRM in patients with CMML undergoing alloSCT.

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

Suggested word limit of 200 words:

Specific aims:
1. To investigate whether the EASIX score can predict non-relapse mortality in patients with CMML undergoing alloSCT.
2. To analyze if EASIX is a better predict of NRM compared to the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) scoring system.

Definitions and Study End Points:
Primary study end-points are-
1. 3-year non-relapse mortality (NRM) and overall survival (OS).

Secondary study-endpoints are-
1. Non-relapse mortality (NRM) at day 100, 1-year and 3-years post-transplant
2. 3-year cumulative incidence of relapse
3. Time to neutrophil recovery
4. Time to platelet recovery
5. Cumulative incidence of acute GVHD grades 2-4
6. Cumulative incidence of chronic GVHD

Definitions:
1. Relapse: Disease recurrence. This event will be summarized by cumulative incidence estimate with TRM as the competing risk.
2. RFS: Survival without disease progression or relapse; patients alive without disease progression or relapse will be censored at the time of last follow-up.
3. NRM: Time to death without the evidence of disease relapse. This event will be summarized as cumulative incidence estimate with relapse as competing risk.
4. OS: Time to death, patients censored at last follow-up.
5. Time to neutrophil recovery: First of the 3 consecutive days with absolute neutrophil count of ≥ 500 neutrophils/mL post-transplant
6. Time to platelet recovery: First of the 3 consecutive days with platelet count of ≥ 20,000 x 109/L post-transplant, in the absence of platelet transfusion within the last 7 days
7. GVHD: Grades 2- 4 acute GVHD and chronic GVHD as defined by Glucksberg and NIH criteria.

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

This study will help to evaluate patients with CMML before alloSCT and determine if they are at a high risk of non-relapse mortality after undergoing allogeneic stem cell transplant. Therefore, the study will help in reducing non-relapse mortality in patients with CMML undergoing alloSCT.

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

Chronic myelomonocytic leukemia (CMML) is a chronic, clonal disorder, of monocytes. A diagnosis of CMML requires that monocytes comprise at least 10% of the peripheral blood white blood cell (WBC) differential with a sustained absolute monocyte count of ≥ 1 x 109 cells/L, and the absence of other disease-defining genetic abnormalities, such as BCR-ABL1, PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2 fusions (1). Because the 1994 French-American-British classification for chronic myeloid leukemias subclassified CMML into dysplastic and proliferative types based on WBC counts of < 13 x 10^9 cells/L or ≥ 13 x 10^9 cells/L at diagnosis, respectively, the 2016 WHO classification of myeloid malignancies describes CMML as a myelodysplastic/myeloproliferative neoplasm (1,2). Subsequently it was shown that the proliferative subtypes of CMML had worse overall survival compared to the dysplastic subtype, and CMML was further subclassified into CMML-0, CMML-1 and CMML-2 depending on bone marrow and peripheral blood and blast counts (3).

A risk-adapted therapy is typically pursued in CMML, and allogeneic stem cell transplant (alloSCT) remains the only potentially curative option for these patients. Studies have shown that the post-alloSCT treatment-related mortality in patients with CMML ranges from 12% to 52% (4–10). Several prognostic scoring systems have been developed (11–18). Padron et al., showed that all these CMML prognostic models have comparable performance (19). For instance, Liu et al showed that while a high CPSS score was associated with increased mortality in patients who had relapsed, it was not associated with non-relapse mortality, and the 3 year treatment-related mortality was 20% in the low/intermediate-1 risk group and 21% in the intermediate-2/high risk group (20). Kerbauy et al showed that the MD Anderson scoring system in CMML was not associated with post-transplant outcomes (21). Similarly, Gagelman et al. recently proposed a model incorporating ASXL1 and NRAS to predict survival in patients with CMML undergoing alloSCT (18).

The EASIX score has been shown to predict mortality in patients with AML and MDS (22). Recent data shows that a pre-conditioning EASIX score can predict non-relapse mortality in patients with CMML undergoing alloSCT (23). It was found that patients with CMML having a high pre-conditioning log2 EASIX score, defined as a log2 EASIX score ≥ 2.32, had a significantly higher incidence of NRM at 3 years after alloSCT (52.9% vs. 17.9%, P = 0.003). Accordingly, patients with a high log2 EASIX score had significantly lower overall survival (OS) at 3 years after alloSCT (57.4% vs. 29.4%, P = 0.017) (23).

These studies are, however, limited by small sample size and patient accrual over a long period of time. Given the rarity of CMML, these limitations are expected for single-center studies. Furthermore, single center analyses are prone to institutional biases and are unlikely to provide meaningful guidance. Given the robust database of clinical information of the CIBMTR, we believe this will be the most comprehensive study evaluating the role of EASIX score in patients with CMML and to compare the accuracy of EASIX and HCT-CI scoring systems in predicting non-relapse mortality in patients with CMML undergoing alloSCT. Overall, the proposed study has a potential to advance the field and provide guidance to future transplants in this rare and challenging population.

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

N/A

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

Inclusion criteria: The study will include all patients with chronic myelomonocytic leukemia (CMML) undergoing first allogeneic stem cell transplant between January 2011 and December 2021.

Exclusion criteria: All patients age less than 18 years should be excluded.

Q21. Does this study include pediatric patients?

- No

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

CMML is primarily a disease involving adult patients, and the EASIX and HCT-CI scores have primarily been evaluated in adult patients undergoing allogeneic stem cell transplant.

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

Variables to Be Analyzed:
Patient related variables:
1. Age at diagnosis
2. Sex: Female vs. male
3. Age at the time of transplantation
4. Karnofsky performance score (< 70 vs. ≥ 70)
5. Hematopoietic stem cell transplant comorbidity index (HCT-CI)
6. Pre-transplant lactate dehydrogenase (LDH)
7. Pre-transplant creatinine
8. Pre-transplant platelet count

Disease related variables at diagnosis and pre-transplant treatment
1. Date of diagnosis of hematologic malignancy
2. Complete blood count (WBC, blasts in blood, hemoglobin, absolute neutrophil count, and platelet) at diagnosis
3. Cytogenetics at diagnosis (karyotype or FISH)
4. Extramedullary disease yes or no
5. Bone marrow blast count
6. Molecular studies
7. Systemic therapy given prior to allogeneic stem cell transplant
8. Disease status after systemic therapy
9. Best response to the systemic therapy prior to allogeneic stem cell transplant

Disease related variables prior to transplant (before initiation of conditioning regimen)
1. Disease status at stem cell transplantation; CR1 vs CR2, vs active disease.

Transplant related variables:
1. Donor type
2. Conditioning regimen
3. Graft source – bone marrow (BM) vs. peripheral blood stem cell (PBSC)
4. Graft manipulation, if any
5. Donor and recipient CMV serologic status
6. HCT CI score
7. EASIX score [determined from pre-transplant lactate dehydrogenase (LDH), creatinine and platelet count using the formula LDH (U/L) × Creatinine (mg/dL) / platelet count (10^9/L)]

Study variables post-transplant:
8. Time to neutrophil recovery
9. Time to platelet recovery
10. Chimerism studies
11. Acute GVHD – grade 0-I vs. grade II-IV
12. Chronic GVHD – yes vs. no
13. Relapse – yes vs. no
14. Time to relapse from the date of alloSCT
15 Survival status – alive vs. dead
16. Time to death from the date of alloSCT
17. Primary cause of death

Data forms needed for the study:
Pre-TED (2400), Comprehensive Baseline (2000), Post-TED (2450), Form 2402, Form 2900, Form 2006.

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

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

NA

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

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

NA

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

NA

Q26. REFERENCES:

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391–405.
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22. Luft T, Benner A, Terzer T, Jodele S, Dandoy CE, Storb R, et al. EASIX and mortality after allogeneic stem cell transplantation. Bone Marrow Transplant. 2020 Mar 26;55(3):553–61.
23. Baranwal A, Mangaonkar A, Shah M v., Litzow MR, Hogan WJ, Patnaik MM, et al. High EASIX score is an independent predictor of non-relapse mortality in patients with CMML undergoing allogeneic stem cell transplant. Bone Marrow Transplant. 2022 Sep 21.

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

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

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

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

N/A

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Prediction of non-relapse mortality by EASIX and HCT-CI scores in patients with AML and MDS receiving post-transplant cyclophosphamide based GVHD prophylaxis.

Q2. Key Words

AML/MDS, EASIX, HCT-CI, PT-Cy

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hassan Alkhateeb, MD
Email address:	Alkhateeb.hassan@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Assistant Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Anmol Baranwal, MBBS
Email address:	Baranwal.anmol@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	N/A

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Hassan Alkhateeb, MD

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

N/A

LETTER OF COMMITMENT:

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

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

NA

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- No

Q15. RESEARCH QUESTION:

Can the Endothelial Activation and Stress Index (EASIX) score predict non-relapse mortality in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who receive a post-transplant cyclophosphamide (PT-Cy) based GVHD prophylaxis after alloSCT?

Q16. RESEARCH HYPOTHESIS:

While the Endothelial Activation and Stress Index (EASIX) has been shown to predict non-relapse mortality (NRM), its ability to predict NRM in patients receiving post-transplant cyclophosphamide (PT-Cy) after alloSCT remains unknown. We hypothesize that the EASIX score can predict non-relapse mortality in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who receive a PT-Cy based GVHD prophylaxis after alloSCT.

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

Suggested word limit of 200 words:

Specific Aims:
1. To investigate whether the EASIX can predict non-relapse mortality in patients with AML and MDS undergoing alloSCT and receiving PT-Cy based GVHD prophylaxis.
2. To analyze if EASIX is a better predict of NRM compared to the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) scoring system in this cohort.

Definitions and Study End Points:
Primary study end-points are-
1. 3-year non-relapse mortality (NRM) and overall survival (OS).

Secondary study-endpoints are-
1. Non-relapse mortality (NRM) at day 100, 1-year and 3-years post-transplant
2. 3-year cumulative incidence of relapse
3. Time to neutrophil recovery
4. Time to platelet recovery
5. Cumulative incidence of acute GVHD grades 2-4
6. Cumulative incidence of chronic GVHD

Definitions:
1. Relapse: Disease recurrence. This event will be summarized by cumulative incidence estimate with NRM as the competing risk.
2. RFS: Survival without disease progression or relapse; patients alive without disease progression or relapse will be censored at the time of last follow-up.
3. NRM: Time to death without the evidence of disease relapse. This event will be summarized as cumulative incidence estimate with relapse as competing risk.
4. OS: Time to death, patients censored at last follow-up.
5. Time to neutrophil recovery: First of the 3 consecutive days with absolute neutrophil count of ≥ 500 neutrophils/mL post-transplant
6. Time to platelet recovery: First of the 3 consecutive days with platelet count of ≥ 20,000 x 109/L post-transplant, in the absence of platelet transfusion within the last 7 days
7. GVHD: Grades 2- 4 acute GVHD and chronic GVHD as defined (15,16).

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

This study will help determine patients with AML/MDS who receive a PT-Cy based GVHD prophylaxis and are at a high risk of non-relapse mortality after transplant. After completion of the study, the EASIX score may be used to prognosticate these patients and thereby reduce non-relapse mortality.

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

The Endothelial Activation and Stress Index (EASIX) score was first proposed by Luft et al. as a marker of endothelial pathology (1). It was shown that the post-alloSCT EASIX score calculated at the onset of GVHD can predict survival after GVHD.

Thereafter, studies evaluated the role of pre-conditioning EASIX score in predicting post-transplant mortality (2–4). Luft et al. evaluated the association of pre-conditioning EASIX score with post-transplant non-relapse mortality in patients with hematologic malignancies. Because a definite cut-off for EASIX score could not be determined in the study, the EASIX score was analyzed on a continuous scale. It was shown that an increasing pre-conditioning EASIX score was significantly associated with post-transplant non-relapse mortality (HR 1.23, 95% CI 1.10 – 1.38, $p < 0.001$). Shouval et al. further validated and showed that the pre-conditioning EASIX score can predict NRM in patients with hematologic malignancies (4). However, the number of patients receiving PT-Cy based GVHD prophylaxis in either of these studies is not known.

O'Donnell et al. in 2002 showed that cyclophosphamide added on days -5 and -6 to fludarabine and TBI based conditioning followed by post-transplant cyclophosphamide (PTCy) on day +3 along with tacrolimus and mycophenolate mofetil led to improved engraftment compared to patients received cyclophosphamide in the post-transplant setting alone (5). Subsequent trials showed that post-transplant cyclophosphamide on days +3 and +4 lead to lower incidences of GVHD and primary graft failure, and improved overall survival and event free survival (6–8). Cyclophosphamide, however, has been shown to cause endothelial injury (9–12). More recently, PT-Cy based GVHD prophylaxis was shown to be associated with early cardiac events (13).

Because the EASIX score is a marker of endothelial dysfunction and cyclophosphamide has been associated with endothelial injury, we hypothesize that the EASIX score can predict non-relapse mortality in patients with AML and MDS who undergo alloSCT and receive a PT-Cy based GVHD prophylaxis.

In the study by Sorror et al. evaluating the HCT-CI scoring system, none of the patients received a PT-Cy based GVHD prophylaxis (14). Given that PT-Cy has significantly decreased the incidence of post-alloSCT GVHD and thereby NRM, the ability of HCT-CI score to predict NRM in patients receiving PT-CY based GVHD prophylaxis remains unknown.

In their validation study across multiple scoring systems, Shouval et al. mention, "individual prediction remains a challenge" (4). This challenge is likely because of the inhomogeneity among the various hematological malignancies. Therefore, there currently exists a need of the validation of these prognostic scoring systems in more homogenous cohorts. Given the robust database of clinical information of the CIBMTR, we believe this will be the most comprehensive study evaluating the role of EASIX score in patients with AML and MDS who receive a PT-Cy based GVHD prophylaxis, and to compare the accuracy of EASIX and HCT-CI scoring systems in predicting non-relapse mortality in this homogenous cohort. Overall, the proposed study has a potential to advance the field and provide guidance to future transplants in this rare and challenging population.

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

N/A

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

Inclusion criteria: The study will include all patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) undergoing first allogeneic stem cell transplant between January 2011 and December 2021.

Exclusion criteria: All patients age less than 18 years should be excluded.

Q21. Does this study include pediatric patients?

- No

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

The aim of this study is to provide guidance for adult patients with AML/MDS who receive a PT-Cy based GVHD prophylaxis. Moreover, the EASIX and HCT-CI scores have primarily been evaluated in adult patient population.

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

Variables to Be Analyzed:
Patient related variables:
1. Age at diagnosis
2. Sex: Female vs. male
3. Age at the time of transplantation
4. Karnofsky performance score (< 70 vs. ≥ 70)
5. Hematopoietic stem cell transplant comorbidity index (HCT-CI)
6. Pre-transplant lactate dehydrogenase (LDH)
7. Pre-transplant creatinine
8. Pre-transplant platelet count

Disease related variables at diagnosis and pre-transplant treatment
1. Date of diagnosis of AML or MDS
2. De novo or therapy related AML/MDS (t-AML/MDS)
3. Complete blood count (WBC, blasts in blood, hemoglobin, absolute neutrophil count, and platelet) at diagnosis
4. Cytogenetics at diagnosis (karyotype or FISH)
5. Extramedullary disease yes or no
6. Bone marrow blast count
7. Molecular studies
8. Systemic therapy given prior to allogeneic stem cell transplant
9. Disease status after systemic therapy
10. Best response to the systemic therapy prior to allogeneic stem cell transplant

Disease related variables prior to transplant (before initiation of conditioning regimen)
1. Disease status at stem cell transplantation; CR1 vs CR2, vs active disease.

Transplant related variables:
1. Donor type
2. Conditioning regimen
3. Graft source – bone marrow (BM) vs. peripheral blood stem cell (PBSC)
4. Graft manipulation, if any
5. Donor and recipient CMV serologic status
6. HCT CI score
7. EASIX score [determined from pre-transplant lactate dehydrogenase (LDH), creatinine and platelet count using the formula LDH (U/L) × Creatinine (mg/dL) / platelet count (10^9/L)]

Study variables post-transplant:
1. Time to neutrophil recovery
2. Time to platelet recovery
3. Chimerism studies
4. Acute GVHD – grade 0-I vs. grade II-IV
5. Chronic GVHD – yes vs. no
6. Relapse – yes vs. no
7. Time to relapse after alloSCT
8. Survival status – alive vs. dead
9. Time to death from the date of alloSCT
10. Primary cause of death

Data Requirements:
Form 2010, Form 2110, Pre-TED (2400), Comprehensive Baseline (2000), Post-TED (2450), Form 2402, Form 2900, Form 2006.

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

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

NA

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

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

NA

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

NA

Q26. REFERENCES:

1. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol. 2017 Sep;4(9):e414–23.
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4. Shouval R, Fein JA, Shouval A, Danylesko I, Shem-Tov N, Zlotnik M, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. Blood Adv [Internet]. 2019 Jun 25;3(12):1881–90. Available from: https://ashpublications.org/bloodadvances/article/3/12/1881/261336/External-validation-and-comparison-of-multiple
5. O'Donnell PV, Luznik L, Jones RJ, Vogelsang GB, Leffell MS, Phelps M, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. Biology of Blood and Marrow Transplantation. 2002 Jul;8(7):377–86.
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9. DeJarnett N, Conklin DJ, Riggs DW, Myers JA, O'Toole TE, Hamzeh I, et al. Acrolein Exposure Is Associated With Increased Cardiovascular Disease Risk. J Am Heart Assoc. 2014 Aug 15;3(4).
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12. Taniguchi I. Clinical Significance of Cyclophosphamide-induced Cardiotoxicity. Internal Medicine. 2005;44(2):89–90.
13. Duléry R, Mohty R, Labopin M, Sestili S, Malard F, Brissot E, et al. Early Cardiac Toxicity Associated With Post-Transplant Cyclophosphamide in Allogeneic Stem Cell Transplantation. JACC CardioOncol. 2021 Jun;3(2):250–9.
14. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 Oct 15;106(8):2912–9.
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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

Population characteristics for patients undergoing first alloHCT for AML or MDS (with CMML patients subsetted) between 2011-2019

Characteristic	AML/Other MDS	CMML
No. of patients	39438	1141
No. of centers	346	178
Type of HCT - no. (%)		
Allo-HCT	39438 (100)	1141 (100)
Age at HCT - median (min-max)	57 (18-88)	63 (18-78)
Age at HCT - no. (%)		
18-29	3429 (9)	8 (1)
30-39	3816 (10)	37 (3)
40-49	5698 (14)	91 (8)
50-59	10302 (26)	296 (26)
60-69	13154 (33)	577 (51)
>=70	3039 (8)	132 (12)
Recipient sex - no. (%)		
Male	21929 (56)	771 (68)
Female	17509 (44)	370 (32)
Karnofsky score - no. (%)		
90-100%	23353 (59)	678 (59)
<90%	15354 (39)	444 (39)
Missing	731 (2)	19 (2)
HCT-CI - no. (%)		
0	9962 (25)	288 (25)
1	5507 (14)	153 (13)
2	5328 (14)	162 (14)
3	6563 (17)	199 (17)
4	4210 (11)	145 (13)
5	2616 (7)	63 (6)
6+	3498 (9)	96 (8)
TBD, review needed for history of malignancies	9 (0)	0 (0)
TBD, inconsistencies between parent and sub-questions	252 (1)	10 (1)
Missing	1493 (4)	25 (2)
LDH levels pre-HCT known? - no. (%)		
No	29859 (76)	643 (56)
Yes	9579 (24)	498 (44)
Serum creatinine levels pre-HCT known? - no. (%)		

Characteristic	AML/Other MDS	CMML
Yes	8205 (21)	423 (37)
No	31223 (79)	718 (63)
Platelet levels pre-HCT known? - no. (%)		
Yes	8135 (21)	423 (37)
No	31303 (79)	718 (63)
Race - no. (%)		
White	29310 (74)	912 (80)
Black or African American	1753 (4)	48 (4)
Asian	2589 (7)	52 (5)
Native Hawaiian or other Pacific Islander	124 (0)	3 (0)
American Indian or Alaska Native	114 (0)	0 (0)
More than one race	106 (0)	0 (0)
Missing	5442 (14)	126 (11)
Ethnicity - no. (%)		
Hispanic or Latino	2534 (6)	67 (6)
Non Hispanic or non-Latino	28618 (73)	876 (77)
Non-resident of the U.S.	7665 (19)	177 (16)
Missing	621 (2)	21 (2)
Graft Type - no. (%)		
Bone Marrow	4881 (12)	124 (11)
Peripheral Blood	32477 (82)	983 (86)
Cord Blood	2077 (5)	34 (3)
Missing	3 (0)	0 (0)
Donor type (%dnrinfo() macro) - no. (%)		
HLA-identical sibling	11524 (29)	302 (26)
Twin	51 (0)	2 (0)
Other related	4869 (12)	143 (13)
Well-matched unrelated (8/8)	14636 (37)	497 (44)
Partially-matched unrelated (7/8)	2606 (7)	74 (6)
Mis-matched unrelated (<= 6/8)	145 (0)	2 (0)
Multi-donor	84 (0)	4 (0)
Unrelated (matching TBD)	3263 (8)	83 (7)
Cord blood	2077 (5)	34 (3)
Missing	183 (0)	0 (0)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)		
RIC/NMA	18587 (47)	692 (61)
MAC	20431 (52)	437 (38)

Characteristic	AML/Other MDS	CMML
Missing	420 (1)	12 (1)
Planned GVHD prophylaxis - no. (%)		
No GvHD Prophylaxis	173 (0)	5 (0)
TDEPLETION alone	44 (0)	2 (0)
TDEPLETION +- other	165 (0)	2 (0)
CD34 select alone	298 (1)	7 (1)
CD34 select +- other	439 (1)	10 (1)
Cyclophosphamide alone	249 (1)	5 (0)
Cyclophosphamide +- others	5710 (14)	209 (18)
FK506 + MMF +- others	3834 (10)	106 (9)
FK506 + MTX +- others(not MMF)	14194 (36)	457 (40)
FK506 +- others(not MMF,MTX)	2120 (5)	72 (6)
FK506 alone	690 (2)	17 (1)
CSA + MMF +- others(not FK506)	3753 (10)	94 (8)
CSA + MTX +- others(not MMF,FK506)	5537 (14)	115 (10)
CSA +- others(not FK506,MMF,MTX)	374 (1)	7 (1)
CSA alone	1050 (3)	16 (1)
Other GVHD Prophylaxis	710 (2)	14 (1)
identical twin donor	36 (0)	1 (0)
Parent Q = yes, but no agent	24 (0)	0 (0)
Missing	38 (0)	2 (0)
Year of HCT - no. (%)		
2011	3930 (10)	84 (7)
2012	4116 (10)	85 (7)
2013	4373 (11)	94 (8)
2014	4269 (11)	113 (10)
2015	4218 (11)	118 (10)
2016	4359 (11)	140 (12)
2017	4764 (12)	176 (15)
2018	4782 (12)	139 (12)
2019	4627 (12)	192 (17)
Follow-up - median (range)	47 (0-125)	42 (0-123)

Study title: Incidence, risk factors, and characteristics of secondary malignancies following CAR-T therapy and its impact on survival

Proposed working committee: Late Effects

Research question: Defining the incidence, risk factors, and pattern of second primary malignancies (SPM) and second hematological malignancies (SHM) following CAR-T therapy and its impact on progression-free (PFS) and overall survival (OS).

Research hypothesis:

1. Patient- and disease-related factors available prior to CAR-T therapy predicts the risk for second primary neoplasm developing after CAR-T therapy.
2. Patients with cytopenia persisting beyond day +100 are at a higher risk of a subsequent therapy-related myeloid neoplasm (t-MN), resulting in an inferior progression-free (PFS) and overall survival (OS).
3. A higher grade of inflammatory complications such as cytokine release syndrome or neurotoxicity are associated with increased risk for t-MN post CAR-T.

Specific objectives/outcomes to be investigated:

Primary:

1. To characterize the cumulative incidence of second primary malignancy (SPM) or second hematological malignancy (SHM) following CAR-T therapy

Secondary:

1. Impact of SPM/SHM development on PFS and OS
2. Identify pre- and post-CAR-T therapy related factors associated with a higher risk of developing SPM/SHM
3. Identify the pattern of cytopenia associated with a higher risk of developing t-MN.

Scientific impact: CAR-T cell therapy is currently FDA approved for relapsed, refractory B-cell non-Hodgkin Lymphoma (NHL), multiple myeloma (MM), and B-cell acute lymphoblastic leukemia (B-ALL). SPM/SHM developing after day +100 are a significant deterrent to life expectancy and/or quality of life—even more so in whom CART therapy is 'successful.' The rationale for our approach is as follows.

Second primary malignancies and second hematological malignancies: Multiple studies indicate higher-than-expected incidences of SPM, SHM, and t-MN following CAR-T therapy. For example, Cordeiro *et al* (Transplant and Cellular Therapy, 2020) reported a 15% incidence of SPM that included 7% non-melanoma skin cancer, 5% myelodysplastic syndrome (MDS), 1% melanoma, 1% non-invasive bladder cancer, and 1% MM. In a cohort of 189 patients treated with commercially available CAR-T therapy for relapsed/refractory NHL, 10 (5.3%) patients developed t-MN (Alkhateeb *et al*, Blood Cancer Journal, 2022). Median time to develop t-MN was 9.1 months and 6 (60%) patient developing t-MN within 1 year from CAR-T. At t-MN diagnosis 4 (40%) patient had complex karyotype and *TP53* mutation. When compared to t-MN developing after autologous stem cell transplant, there was short latency of post CAR-T t-MN as median MN free survival was 22 *vs.* 44 months (p=0.01), and post CAR-T t-MN continues to have comparable worse survival compared to t-MN following other forms of therapy (9 *vs.* 16 months, p=0.11). Finally, MD Anderson/Moffitt groups also noted a 2-year cumulative incidence of 12% (Saini *et al*, Blood Cancer Discovery, 2022). The presence of clonal hematopoiesis prior to CAR-T therapy was associated with a higher incidence of t-MN (19% *vs*. 4.2%).

In contrast, the reported incidence of SPM varies widely among clinical trials. For example, in the CARTITUDE-1 study (Martin *et al*, Journal of Clinical Oncology, 2022), 20 SPM were reported in 16 patients. Nine patients had SHM, including one case of low-grade B-cell lymphoma, 6 MDS, and 3 acute myeloid leukemia (AML). Four patients had squamous cell carcinoma; one of these also had basal cell carcinoma. One patient each had malignant melanoma, adenocarcinoma, or myxofibrosarcoma, and one patient had prostate cancer in addition to his squamous cell carcinoma and AML reported above. Whereas the pivotal CAR-T studies in NHL including ZUMA-7, TRANSFORM, and BELINDA did not report the development of SPM including t-MN.

Long-term cytopenia, defined as persistence of profound cytopenia beyond day +90/+100 is the most common hematological toxicity of CART therapy. Single-institution studies have reported that a wide range (16-41%) of

CART treated patients suffer from long-term cytopenia without any clear explanation (Cordeiro *et al* 2020, Jain *et al* 2020, Sharma *et al* 2022). Cytopenia have a potential to profoundly impact survivorship following CAR-T therapy. Specifically, the presence of cytopenia may lead to transfusion dependency and related complications, infections, the inability to pursue maintenance or salvage therapies—ultimately leading to a significant morbidity and mortality. Whether the presence of cytopenia and its pattern can predict the development of a subsequent t-MN is not known.

In summary, while CAR-T therapy is a life-saving option for many patients, unique and serious adverse events are being recognized with longer follow up. This CIBMTR database will allow us to comprehensively characterize the burden of secondary malignancies in CAR T cell recipients. As the utilization of CAR-T therapy is expected to rise exponentially, it is critical to further our understanding of long-term complications, which will inform the choice and sequencing of therapies and monitoring.

Patient selection criteria:

1. All patients who underwent CAR-T therapy for NHL and MM
2. Achieved remission at day+100
3. Subsequently diagnosed with a malignancy unrelated to the primary indication for CAR-T therapy including—
    a. solid malignancies
    b. unrelated hematological malignancies including therapy-related myeloid neoplasms

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.

<u>Patient and disease related (at baseline):</u>

- Age at CAR-T, as a categorical variable (18-60, 60-70, and >70)
- Performance status - KPS prior to CAR-T therapy
- HCT-CI (if available for most)
- Sex
- Ethnicity
- Indication for CAR-T therapy
- Disease status at CART infusion
- If prior alloSCT (then CART for consolidation Vs relapse)
- Prior lines of therapy
    - Use of alkylator (yes *vs*. no)
    - Use of nucleoside analogue (yes *vs*. no)
    - Use of radiation (yes *vs*. no)
    - Use of immunosuppressive therapy (yes *vs*. no)
- Prior autologous stem cell transplant (yes vs. no)
    - Type of conditioning chemotherapy
- Prior allogeneic stem cell transplant (yes vs. no)
    - Type of conditioning chemotherapy
- Prior malignancy (yes *vs*. no)
    - If yes, type (SPM, SHM other than t-MN, t-MN)
- Ferritin
- LDH
- C-reactive protein

<u>CAR-T related:</u>

- Bridging chemotherapy utilized (yes *vs*. no)
- Lymphodepletion chemotherapy (drug and dose)
- CAR-T Product name and construct
- Time from collection to infusion

- Time to neutrophil and platelet recovery
-
- Max grade of cytokine release syndrome (CRS) and neurotoxicity grade (using immune effector cell-associated neurotoxicity syndrome or ICANS score)
- Use of immunosuppressive therapy to treat CRS/neurotoxicity (steroids vs tocilizumab vs. anakinra vs. others)

Long-term complication related:

- CBC at day +100, 6 months, and 1 year
- Diagnosis and type of SPM
- Time to develop SPM/SHM
- Interventions for t-MN
    - Unconditioned or $CD34^+$ selected therapy (yes *vs*. no, as a surrogate for stem cell boost)
    - Autologous SCT (yes *vs*. no)
    - Allogeneic SCT (yes *vs*. no)
- Vital status at last follow-up
- Primary cause of death

Study population: Patients who underwent first CAR-T therapy for any approved indication (relapsed/refractory lymphomas including diffuse large B-cell lymphoma, transformed low-grade lymphomas, high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma; relapsed/refractory multiple myeloma; or relapsed/refractory acute lymphoblastic leukemia/lymphoma who achieved remission and were alive at +100 days after CAR-T therapy.

Statistical analysis: The study population will be summarized using descriptive statistics. While the cumulative incidence of LPD and MM appears to be similar; the patient, disease, and treatment related factors are likely different. For that reason, we will analyze the risk factors for SPM/SHM development as stratified by the primary indication (LPD *vs*. MM).

For the purpose of this study, SPM will be defined as any solid tumor malignancy that develops >3 months from CAR-T infusion. SHM will defined as the development of an unrelated hematological malignancy that develops >3 months from CAR-T infusion. Finally, therapy-related myeloid neoplasms will be defined as the development of MDS, AML, or MDS/MPN malignancy that develops >3 months from CAR-T infusion per 2016 WHO criteria.

Cumulative incidence of SPM/SHM will be calculated using landmark analysis from day +100 to the development of the first SPM/SHM with death as a competing risk. The incidence of SPM/SHM will be stratified according to the diagnosis before or after the relapse of the primary malignancy. Kaplan-Meier method and log-rank testing for univariate comparisons will be used to determine probabilities of OS and PFS. Multivariate analysis (MVA) will be performed using a Cox proportional hazards regression model using both the variables as time-dependent covariates to determine the impact of SPM and SHM on PFS or OS. Uni- and multivariate Cox regression model will be performed using patient, disease, and CAR-T related variables for the development of SPM/SHM. A stepwise model building approach will be adopted and variables that attain a *P*-value <5% were retained in the final model.

Population Characteristics for recipients of first CAR-T therapy for NHL, having achieved CR at 100 days

Characteristic	N(%)
No. of patients	2514
No. of centers	116
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	64.5 (18.2-86.8)
18-29	44 (1.8)
30-39	86 (3.4)
40-49	183 (7.3)
50-59	548 (21.8)
60-69	946 (37.6)
70+	707 (28.1)
Recipient Sex - no. (%)	
male	1543 (61.4)
female	969 (38.5)
NA	2 (0.1)
Recipient race - no. (%)	
White	2058 (81.9)
Black or African American	106 (4.2)
Asian	119 (4.7)
Native Hawaiian or other Pacific Islander	5 (0.2)
American Indian or Alaska Native	6 (0.2)
More than one race	9 (0.4)
Unknown	99 (3.9)
Not reported	112 (4.5)

Characteristic	N(%)
Recipient ethnicity - no. (%)	
Hispanic or Latino	246 (9.8)
Non Hispanic or non-Latino	2050 (81.5)
Non-resident of the U.S.	128 (5.1)
Unknown	87 (3.5)
Not reported	3 (0.1)
Performance score prior to CT - no. (%)	
90-100%	1134 (45.1)
80%	734 (29.2)
<80%	370 (14.7)
Not reported	276 (11.0)
ECOG performance status prior to CT - no. (%)	
0	1134 (45.1)
90-100	1057 (42.0)
70-80	43 (1.7)
50-60	4 (0.2)
Not reported	276 (11.0)
CT-CI - no. (%)	
0	749 (29.8)
1	529 (21.0)
2	328 (13.0)
3+	860 (34.2)
TBD	13 (0.5)
Not reported	35 (1.4)
Disease related	
IPI at initial diagnosis of the primary disease - no. (%)	

Characteristic	N(%)
Low	89 (3.5)
Low intermediate	152 (6.0)
High intermediate	150 (6.0)
High	160 (6.4)
Not reported	1963 (78.1)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I - Involvement of a single lymph node region or of a single extralymphatic organ or site	198 (7.9)
II - Involvement of two or more lymph node regions on same side of diaphragm or localized invol...	259 (10.3)
III - Involvement of lymph node regions on both sides of diaphragm, which may also ...	508 (20.2)
IV - Diffuse or disseminated involvement of one or more extralymphatic organs in tissues with...	1010 (40.2)
Not reported	539 (21.4)
Disease Status (LYM) - no. (%)	
CR	193 (7.7)
PR	564 (22.4)
Resistant	1451 (57.7)
Untreated	194 (7.7)
Unknown	109 (4.3)
Not reported	3 (0.1)
Prior lines of therapies - no. (%)	
No	10 (0.4)
Yes	712 (28.3)
1	27 (1.1)
Not reported	685 (27.2)
Not reported	1792 (71.3)
Prior radiation therapy - no. (%)	
Not reported	2514 (100)

Characteristic	N(%)
Prior HCT - no. (%)	
No	1716 (68.3)
Yes	712 (28.3)
Prior allo-HCT	34 (1.4)
Prior auto-HCT	651 (25.9)
Prior auto and allo-HCT	11 (0.4)
Not reported	16 (0.6)
Not reported	86 (3.4)
Time from HCT to CT, months - median (min-max)	22.3 (3.2-268.7)
CAR-T cell related	
Year of CT - no. (%)	
2017	1 (0.0)
2018	251 (10.0)
2019	450 (17.9)
2020	541 (21.5)
2021	879 (35.0)
2022	392 (15.6)
Product - no. (%)	
Kymriah	448 (17.8)
Yescarta	1649 (65.6)
Tecartus	277 (11.0)
Breyanzi	140 (5.6)
Time from diagnosis to CT - no. (%)	
Median (min-max)	20.6 (1.3-446.7)
0-6 months	242 (9.6)
6 months-1 year	498 (19.8)

Characteristic	N(%)
1-2 years	626 (24.9)
2+ years	1145 (45.5)
Not reported	3 (0.1)
Bridging therapy - no. (%)	
Not reported	2514 (100)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	4 (0.2)
Yes	2509 (99.8)
Bendamustine only	74 (2.9)
Flu+Cy only	2401 (95.5)
Other	33 (1.3)
None selected	1 (0.0)
Not reported	1 (0.0)
None selected	1 (0.0)
Outcomes	
Indication of the 1st subsequent neoplasm during the follow-up for this CT - no. (%)	
Other leukemia	2 (0.1)
Acute myeloid leukemia (AML/ANLL):	7 (0.3)
Breast cancer:	1 (0.0)
Central nervous system (CNS) malignancy:	1 (0.0)
Clonal cytogenetic abnormality without leukemia or MDS:	1 (0.0)
Gastrointestinal malignancy (GI):	5 (0.2)
Genitourinary malignancy (GU):	2 (0.1)
Hodgkin disease:	1 (0.0)
Lung cancer:	3 (0.1)
Melanoma:	7 (0.3)

Characteristic	N(%)
Myelodysplasia (MDS)/Myeloproliferative (MPS) disorder:	5 (0.2)
Oropharyngeal cancer:	1 (0.0)
Thyroid cancer:	2 (0.1)
Other malignancy:	8 (0.3)
Myelodysplasia (MDS)	46 (1.8)
Non-Hodgkin Lymphoma	3 (0.1)
Basal cell skin malignancy	14 (0.6)
Squamous cell skin malignancy	23 (0.9)
Other	1 (0.0)
Not reported	2381 (94.7)
Time from CT to occurance of the 1st subsequent neoplasm, days - median (min-max)	363.0 (11.0-1555.0)
Follow-up, in months - median (range)	12.4 (1.0-52.1)