Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Salt Lake City, Utah
Monday, April 25, 2022, 12:15 pm – 1:45 pm

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1. **Introduction**

   a. Minutes and Overview Plan from February 2021 meeting (Attachment 1)

2. **Accrual summary** (Attachment 2)

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

   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. ***Oral presentation, Tandem Meetings 2022.***

4. Studies in progress (Attachment 3)

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**

5. Future/proposed studies

a. **PROP 2110-27** Bladder cancer incidence and mortality after hematopoietic cell transplantation. (Megan Herr/Theresa Hahn) (Attachment 4)
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*) (Attachment 5)
c. **PROP 2110-74** Cumulative Incidence and Risk Factors for Breast Cancer after Allogeneic Hematopoietic Cell Transplant. *(Kareem Jamani/K. Scott Baker)* (Attachment 6)
d. **PROP 2110-240** The Role of Poverty in Late Effects Following Hematopoietic Cell Transplantation. (*Christine Duncan/Lauren Jimenez-Kurlander*) (Attachment 7)
e. **PROP 2110-299** Risk of secondary colorectal cancer development after allogeneic hematopoietic stem cell transplantation (HCT) (*Jed Calata MD/Larisa Broglie MD*) (Attachment 8)

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

f. **PROP 2110-145** Impact of Socioeconomic Factors on Outcomes in Autologous Stem Cell Transplant. *(Audrey M Sigmund/Nidhi Sharma/Yvonne A Efebera/Don Benson/Samantha Jaglowski)* (Attachment 9)

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.*

6. Other Business

a. Update on PROs data at CIBMTR (Rachel Cusatis) (Attachment 10)

b. HCT Survivorship Guidelines (Seth Rotz)

c. EBMT/CIBMTR Late Effects Systematic Reviews

d. PROP 2110-145 Impact of Socioeconomic Factors on Outcomes in Autologous Stem Cell Transplant. (Audrey M Sigmund/Nidhi Sharma/Yvonne A Efebera/Don Benson/Samantha Jaglowski) (Attachment
7) will being presented at Collaborative Study Proposal Session (Attachment 9)

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

INTRODUCTION:

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

GENERAL REMINDERS:

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

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

PRESENTATIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLOSING:

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

APPENDICES:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

chemotherapy as a confounder in the time delay?

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

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

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

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

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

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

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

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

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

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

Follow-up of **adult** patients (age≥18) after **allogeneic** transplant reported to CIBMTR, 1990-2021

Variable	TED	CRF
All patients	189028	63888
3 year survivors	61510	20434
5 year survivors	42470	14237
10 year survivors	17048	6192
15 year survivors	6725	2209
Acute Myelogenous Leukemia	69051	21007
3 year survivors	20646	6482
5 year survivors	13714	4498
10 year survivors	4886	1799
Acute Lymphoblastic Leukemia	26314	7863
3 year survivors	7690	2253
5 year survivors	5003	1525
10 year survivors	1713	633
Chronic Myelogenous Leukemia	24707	9141
3 year survivors	10162	3179
5 year survivors	7872	2504
10 year survivors	4295	1482
Myelodysplastic/Myeloproliferative Diseases	28651	12140
3 year survivors	8287	3696
5 year survivors	5241	2280
10 year survivors	1751	785
Multiple Myeloma/Plasma Cell Disorders	3402	1143
3 year survivors	1141	350
5 year survivors	786	235
10 year survivors	334	82
Lymphoma	17402	5461
3 year survivors	6273	1847
5 year survivors	4675	1381
10 year survivors	2073	703

Variable	TED	CRF
Other Malignant	9231	3137
3 year survivors	3131	1062
5 year survivors	2195	728
10 year survivors	776	287
Severe Aplastic Anemia	7302	2952
3 year survivors	3132	1204
5 year survivors	2292	846
10 year survivors	993	336
Immune deficiencies	413	123
3 year survivors	155	44
5 year survivors	85	27
10 year survivors	10	5
Other Non-malignant	2380	921
3 year survivors	859	317
5 year survivors	584	213
10 year survivors	203	80

Follow-up of **pediatric** patients (age<18) after **allogeneic** transplant reported to CIBMTR, 1990-2021

Variable	TED	CRF
All patients	56603	22995
3 year survivors	24306	9813
5 year survivors	18015	7376
10 year survivors	8111	3697
15 year survivors	3080	1233
Acute Myelogenous Leukemia	10372	3928
3 year survivors	3908	1490
5 year survivors	2870	1127
10 year survivors	1386	559
Acute Lymphoblastic Leukemia	14795	5668
3 year survivors	5665	2110
5 year survivors	4223	1587
10 year survivors	1985	817
Chronic Myelogenous Leukemia	2219	863
3 year survivors	1035	405
5 year survivors	807	330
10 year survivors	407	186
Myelodysplastic/Myeloproliferative Diseases	3131	1315
3 year survivors	1352	578
5 year survivors	1052	462
10 year survivors	491	271
Multiple Myeloma/Plasma Cell Disorders	28	4
3 year survivors	9	1
5 year survivors	6	0
10 year survivors	4	0
Lymphoma	1218	439
3 year survivors	433	143
5 year survivors	323	113
10 year survivors	137	49

Variable	TED	CRF
Other Malignant	1117	421
3 year survivors	428	177
5 year survivors	309	141
10 year survivors	137	67
Severe Aplastic Anemia	5458	2206
3 year survivors	2809	1099
5 year survivors	2094	790
10 year survivors	917	357
Immune deficiencies	5514	2537
3 year survivors	2667	1309
5 year survivors	1948	1013
10 year survivors	864	511
Other Non-malignant	12722	5614
3 year survivors	5990	2501
5 year survivors	4404	1813
10 year survivors	1783	880

Follow-up of **adult** patients (age≥18) after **autologous** transplant reported to CIBMTR, 1990-2021

Variable	TED	CRF
All patients	242774	35832
3 year survivors	114759	16473
5 year survivors	75055	10327
10 year survivors	24796	3457
15 year survivors	8433	837
Acute Myelogenous Leukemia	7182	1336
3 year survivors	2548	428
5 year survivors	1861	296
10 year survivors	978	127
Acute Lymphoblastic Leukemia	1151	208
3 year survivors	293	41
5 year survivors	197	26
10 year survivors	102	11
Chronic Myelogenous Leukemia	662	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	106496	15048
3 year survivors	54832	8435
5 year survivors	33688	5202
10 year survivors	7906	1573
Lymphoma	93594	11211
3 year survivors	43682	5005
5 year survivors	30379	3381
10 year survivors	11548	1327

Variable	TED	CRF
Other Malignant	31991	7633
3 year survivors	12607	2381
5 year survivors	8378	1298
10 year survivors	4012	362
Severe Aplastic Anemia	14	3
3 year survivors	3	1
5 year survivors	2	1
10 year survivors	0	0
Immune deficiencies	14	2
3 year survivors	7	1
5 year survivors	2	1
10 year survivors	0	0
Other Non-malignant	1312	136
3 year survivors	333	61
5 year survivors	240	53
10 year survivors	102	31

Follow-up of **pediatric** patients (age<18) after **autologous** transplant reported to CIBMTR, 1990-2021

Variable	TED	CRF
All patients	16784	2819
3 year survivors	6984	1128
5 year survivors	4809	746
10 year survivors	1968	358
15 year survivors	737	95
Acute Myelogenous Leukemia	985	248
3 year survivors	394	50
5 year survivors	305	29
10 year survivors	162	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	104	3
3 year survivors	18	2
5 year survivors	12	2
10 year survivors	4	1
Lymphoma	2924	356
3 year survivors	1295	168
5 year survivors	912	117
10 year survivors	348	37

Variable	TED	CRF
Other Malignant	12047	2015
3 year survivors	5032	855
5 year survivors	3411	570
10 year survivors	1377	302
Severe Aplastic Anemia	7	3
3 year survivors	4	2
5 year survivors	4	2
10 year survivors	1	0
Immune deficiencies	62	45
3 year survivors	29	22
5 year survivors	15	11
10 year survivors	0	0
Other Non-malignant	193	19
3 year survivors	58	9
5 year survivors	45	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	44543	15903	8657
Source of data			
CRF	24072 (54)	6924 (44)	4451 (51)
TED	20471 (46)	8979 (56)	4206 (49)
Number of centers	258	232	351
Disease at transplant			
AML	15294 (34)	5896 (37)	2918 (34)
ALL	6535 (15)	2123 (13)	1370 (16)
Other leukemia	1408 (3)	385 (2)	249 (3)
CML	3509 (8)	1045 (7)	695 (8)
MDS	6346 (14)	2568 (16)	1072 (12)
Other acute leukemia	462 (1)	185 (1)	106 (1)
NHL	4032 (9)	1194 (8)	710 (8)
Hodgkin Lymphoma	917 (2)	220 (1)	160 (2)
Plasma Cell Disorders, MM	892 (2)	270 (2)	159 (2)
Other malignancies	59 (<1)	13 (<1)	18 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1428 (3)	485 (3)	344 (4)
Inherited abnormalities erythrocyte diff fxn	727 (2)	251 (2)	157 (2)
Inherited bone marrow failure syndromes	9 (<1)	9 (<1)	11 (<1)
Hemoglobinopathies	8 (<1)	6 (<1)	4 (<1)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	4 (<1)	0
SCIDs	780 (2)	280 (2)	253 (3)
Inherited abnormalities of platelets	40 (<1)	14 (<1)	11 (<1)
Inherited disorders of metabolism	292 (1)	79 (<1)	95 (1)
Histiocytic disorders	376 (1)	107 (1)	94 (1)
Autoimmune disorders	22 (<1)	12 (<1)	5 (<1)
Other	51 (<1)	21 (<1)	19 (<1)
MPN	1347 (3)	733 (5)	204 (2)
Disease missing	1 (N/A)	0 (N/A)	2 (N/A)
AML Disease status at transplant			
CR1	8061 (53)	3434 (58)	1439 (49)
CR2	2975 (19)	1072 (18)	590 (20)
CR3+	330 (2)	95 (2)	67 (2)
Advanced or active disease	3783 (25)	1262 (21)	767 (26)
Missing	145 (1)	33 (1)	55 (2)
ALL Disease status at transplant			
CR1	3206 (49)	1180 (56)	585 (43)
CR2	1873 (29)	548 (26)	393 (29)
CR3+	558 (9)	157 (7)	139 (10)
Advanced or active disease	852 (13)	222 (10)	217 (16)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	46 (1)	16 (1)	36 (3)
MDS Disease status at transplant			
Early	1380 (22)	488 (19)	256 (24)
Advanced	4003 (63)	1854 (72)	592 (55)
Missing	963 (15)	226 (9)	224 (21)
NHL Disease status at transplant			
CR1	556 (14)	205 (17)	90 (13)
CR2	741 (18)	223 (19)	117 (17)
CR3+	345 (9)	102 (9)	66 (9)
PR	439 (11)	110 (9)	76 (11)
Advanced	1866 (47)	531 (45)	346 (49)
Missing	65 (2)	15 (1)	12 (2)
Recipient age at transplant			
0-9 years	3829 (9)	1110 (7)	1068 (12)
10-19 years	3937 (9)	1138 (7)	978 (11)
20-29 years	4617 (10)	1454 (9)	981 (11)
30-39 years	5099 (11)	1604 (10)	1015 (12)
40-49 years	6813 (15)	2184 (14)	1294 (15)
50-59 years	9175 (21)	3138 (20)	1573 (18)
60-69 years	9168 (21)	4145 (26)	1465 (17)
70+ years	1905 (4)	1130 (7)	283 (3)
Median (Range)	47 (0-84)	52 (0-82)	43 (0-81)
Recipient race/ethnicity			
Caucasian, non-Hispanic	36965 (83)	13172 (83)	6184 (71)
African-American, non-Hispanic	2018 (5)	651 (4)	388 (4)
Asian, non-Hispanic	1027 (2)	498 (3)	331 (4)
Pacific islander, non-Hispanic	55 (<1)	25 (<1)	23 (<1)
Native American, non-Hispanic	168 (<1)	66 (<1)	33 (<1)
Hispanic	2662 (6)	861 (5)	468 (5)
Missing	1648 (4)	630 (4)	1230 (14)
Recipient sex			
Male	25968 (58)	9313 (59)	5132 (59)
Female	18575 (42)	6590 (41)	3525 (41)
Karnofsky score			
10-80	15260 (34)	5968 (38)	2755 (32)
90-100	27634 (62)	9412 (59)	5408 (62)
Missing	1649 (4)	523 (3)	494 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	28 (<1)	37 (<1)	3 (<1)
4/6	235 (1)	102 (1)	45 (1)
5/6	6059 (14)	1819 (13)	1217 (15)
6/6	37443 (86)	12508 (86)	6817 (84)
Unknown	778 (N/A)	1437 (N/A)	575 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	884 (2)	102 (1)	45 (1)
6/8	1724 (4)	139 (1)	152 (3)
7/8	8420 (20)	1863 (16)	1254 (22)
8/8	31783 (74)	9524 (82)	4335 (75)
Unknown	1732 (N/A)	4275 (N/A)	2871 (N/A)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
HLA-DPB1 Match			
Double allele mismatch	10933 (29)	1275 (23)	590 (26)
Single allele mismatch	20128 (54)	2834 (51)	1199 (52)
Full allele matched	6179 (17)	1427 (26)	512 (22)
Unknown	7303 (N/A)	10367 (N/A)	6356 (N/A)
High resolution release score			
No	9149 (21)	15838 (>99)	8450 (98)
Yes	35394 (79)	65 (<1)	207 (2)
KIR typing available			
No	30764 (69)	15880 (>99)	8609 (99)
Yes	13779 (31)	23 (<1)	48 (1)
Graft type			
Marrow	16082 (36)	4740 (30)	3436 (40)
PBSC	28404 (64)	11007 (69)	5187 (60)
BM+PBSC	11 (<1)	7 (<1)	3 (<1)
PBSC+UCB	27 (<1)	137 (1)	5 (<1)
Others	19 (<1)	12 (<1)	26 (<1)
Conditioning regimen			
Myeloablative	27651 (62)	8835 (56)	5389 (62)
RIC/Nonmyeloablative	16685 (37)	7019 (44)	3146 (36)
TBD	207 (<1)	49 (<1)	122 (1)
Donor age at donation			
To Be Determined/NA	410 (1)	1434 (9)	126 (1)
0-9 years	8 (<1)	36 (<1)	3 (<1)
10-19 years	1223 (3)	550 (3)	184 (2)
20-29 years	20165 (45)	7124 (45)	3529 (41)
30-39 years	12640 (28)	3985 (25)	2591 (30)
40-49 years	7729 (17)	2111 (13)	1682 (19)
50+ years	2368 (5)	663 (4)	542 (6)
Median (Range)	30 (0-69)	29 (0-109)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	11076 (25)	4431 (28)	2157 (25)
+/-	5279 (12)	2016 (13)	1101 (13)
-/+	14617 (33)	4780 (30)	2679 (31)
-/-	12957 (29)	4204 (26)	2327 (27)
CB - recipient +	3 (<1)	17 (<1)	0
CB - recipient -	1 (<1)	8 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	610 (1)	446 (3)	393 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	146 (<1)	65 (<1)	45 (1)
TDEPLETION alone	100 (<1)	31 (<1)	31 (<1)
TDEPLETION +- other	1068 (2)	278 (2)	261 (3)
CD34 select alone	272 (1)	129 (1)	62 (1)
CD34 select +- other	881 (2)	628 (4)	194 (2)
Cyclophosphamide alone	785 (2)	676 (4)	226 (3)
Cyclophosphamide +- others	2016 (5)	1404 (9)	426 (5)
FK506 + MMF +- others	4990 (11)	1515 (10)	694 (8)
FK506 + MTX +- others(not MMF)	18673 (42)	6475 (41)	2380 (27)

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

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	5894	1566	1557
Source of data			
CRF	4361 (74)	1124 (72)	947 (61)
TED	1533 (26)	442 (28)	610 (39)
Number of centers	152	138	201
Disease at transplant			
AML	2221 (38)	529 (34)	505 (32)
ALL	1222 (21)	344 (22)	347 (22)
Other leukemia	93 (2)	30 (2)	27 (2)
CML	128 (2)	35 (2)	38 (2)
MDS	523 (9)	151 (10)	119 (8)
Other acute leukemia	93 (2)	26 (2)	28 (2)
NHL	394 (7)	89 (6)	100 (6)
Hodgkin Lymphoma	97 (2)	27 (2)	27 (2)
Plasma Cell Disorders, MM	37 (1)	12 (1)	11 (1)
Other malignancies	11 (<1)	1 (<1)	1 (<1)
SAA	93 (2)	31 (2)	27 (2)
Inherited abnormalities erythrocyte diff fxn	165 (3)	50 (3)	33 (2)
Inherited bone marrow failure syndromes	2 (<1)	2 (<1)	1 (<1)
Hemoglobinopathies	1 (<1)	0	0
SCIDs	262 (4)	87 (6)	122 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	7 (<1)
Inherited disorders of metabolism	361 (6)	105 (7)	105 (7)
Histiocytic disorders	105 (2)	27 (2)	38 (2)
Autoimmune disorders	9 (<1)	0	2 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
MPN	46 (1)	13 (1)	14 (1)
AML Disease status at transplant			
CR1	1147 (52)	287 (54)	241 (48)
CR2	608 (27)	139 (26)	139 (28)
CR3+	62 (3)	8 (2)	22 (4)
Advanced or active disease	398 (18)	93 (18)	101 (20)
Missing	6 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	550 (45)	146 (42)	146 (42)
CR2	451 (37)	124 (36)	125 (36)
CR3+	143 (12)	51 (15)	48 (14)
Advanced or active disease	77 (6)	21 (6)	28 (8)
Missing	1 (<1)	2 (1)	0
MDS Disease status at transplant			
Early	163 (31)	41 (27)	52 (44)
Advanced	315 (60)	95 (63)	48 (40)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	45 (9)	15 (10)	19 (16)
NHL Disease status at transplant			
CR1	60 (15)	6 (7)	18 (18)
CR2	74 (19)	20 (22)	31 (31)
CR3+	44 (11)	10 (11)	9 (9)
PR	67 (17)	12 (13)	11 (11)
Advanced	146 (37)	40 (45)	28 (28)
Missing	0	1 (1)	2 (2)
Recipient age at transplant			
0-9 years	1776 (30)	580 (37)	578 (37)
10-19 years	776 (13)	175 (11)	211 (14)
20-29 years	556 (9)	110 (7)	131 (8)
30-39 years	569 (10)	141 (9)	153 (10)
40-49 years	623 (11)	154 (10)	144 (9)
50-59 years	803 (14)	190 (12)	184 (12)
60-69 years	683 (12)	188 (12)	145 (9)
70+ years	108 (2)	28 (2)	11 (1)
Median (Range)	27 (0-83)	22 (0-76)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3254 (55)	917 (59)	834 (54)
African-American, non-Hispanic	841 (14)	204 (13)	176 (11)
Asian, non-Hispanic	340 (6)	107 (7)	105 (7)
Pacific islander, non-Hispanic	30 (1)	3 (<1)	16 (1)
Native American, non-Hispanic	42 (1)	9 (1)	18 (1)
Hispanic	1054 (18)	229 (15)	209 (13)
Missing	333 (6)	97 (6)	199 (13)
Recipient sex			
Male	3249 (55)	892 (57)	879 (56)
Female	2645 (45)	674 (43)	678 (44)
Karnofsky score			
10-80	1563 (27)	400 (26)	391 (25)
90-100	4149 (70)	1075 (69)	1056 (68)
Missing	182 (3)	91 (6)	110 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	97 (2)	38 (3)	12 (1)
4/6	2341 (41)	537 (40)	555 (39)
5/6	2550 (45)	566 (42)	647 (46)
6/6	718 (13)	191 (14)	202 (14)
Unknown	188 (N/A)	234 (N/A)	141 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2777 (55)	537 (56)	609 (54)
6/8	1193 (24)	228 (24)	279 (25)
7/8	701 (14)	129 (13)	166 (15)
8/8	333 (7)	70 (7)	79 (7)
Unknown	890 (N/A)	602 (N/A)	424 (N/A)
HLA-DPB1 Match			
Double allele mismatch	815 (39)	97 (43)	109 (39)
Single allele mismatch	1065 (51)	108 (48)	145 (51)
Full allele matched	199 (10)	21 (9)	28 (10)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	3815 (N/A)	1340 (N/A)	1275 (N/A)
High resolution release score			
No	4378 (74)	1500 (96)	1539 (99)
Yes	1516 (26)	66 (4)	18 (1)
KIR typing available			
No	4634 (79)	1560 (>99)	1545 (99)
Yes	1260 (21)	6 (<1)	12 (1)
Graft type			
UCB	5557 (94)	1429 (91)	1472 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	307 (5)	137 (9)	78 (5)
Others	29 (<1)	0	7 (<1)
Number of cord units			
1	4944 (84)	0	1310 (84)
2	946 (16)	0	247 (16)
3	2 (<1)	0	0
Unknown	2 (N/A)	1566 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3852 (65)	1008 (64)	978 (63)
RIC/Nonmyeloablative	2029 (34)	554 (35)	570 (37)
TBD	13 (<1)	4 (<1)	9 (1)
Donor age at donation			
To Be Determined/NA	209 (4)	113 (7)	120 (8)
0-9 years	5183 (88)	1205 (77)	1316 (85)
10-19 years	296 (5)	141 (9)	70 (4)
20-29 years	65 (1)	35 (2)	11 (1)
30-39 years	56 (1)	34 (2)	18 (1)
40-49 years	39 (1)	17 (1)	8 (1)
50+ years	46 (1)	21 (1)	14 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-69)
Donor/Recipient CMV serostatus			
+/+	1338 (23)	309 (20)	307 (20)
+/-	573 (10)	148 (9)	145 (9)
-/+	1084 (18)	283 (18)	267 (17)
-/-	724 (12)	195 (12)	201 (13)
CB - recipient +	1253 (21)	336 (21)	339 (22)
CB - recipient -	828 (14)	238 (15)	238 (15)
CB - recipient CMV unknown	94 (2)	57 (4)	60 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	21 (<1)	8 (1)	9 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	5 (<1)
CD34 select alone	0	2 (<1)	2 (<1)
CD34 select +- other	287 (5)	136 (9)	84 (5)
Cyclophosphamide alone	0	0	2 (<1)
Cyclophosphamide +- others	47 (1)	27 (2)	53 (3)
FK506 + MMF +- others	1622 (28)	415 (27)	260 (17)
FK506 + MTX +- others(not MMF)	214 (4)	56 (4)	71 (5)
FK506 +- others(not MMF,MTX)	221 (4)	63 (4)	65 (4)

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

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

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

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
0-9 years	659 (7)	89 (6)	28 (4)
10-19 years	983 (10)	140 (9)	56 (9)
20-29 years	1354 (14)	231 (15)	97 (15)
30-39 years	1382 (14)	246 (16)	121 (19)
40-49 years	1574 (16)	258 (17)	88 (14)
50+ years	3727 (38)	581 (37)	255 (39)
Median (Range)	43 (0-82)	43 (0-79)	43 (1-76)
Donor/Recipient CMV serostatus			
+/+	3949 (41)	706 (45)	248 (38)
+/-	1079 (11)	127 (8)	60 (9)
-/+	2411 (25)	368 (24)	163 (25)
-/-	2115 (22)	325 (21)	151 (23)
CB - recipient +	0	3 (<1)	0
CB - recipient -	0	0	3 (<1)
Missing	141 (1)	26 (2)	21 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	103 (1)	14 (1)	6 (1)
TDEPLETION alone	40 (<1)	17 (1)	4 (1)
TDEPLETION +- other	63 (1)	19 (1)	7 (1)
CD34 select alone	77 (1)	20 (1)	6 (1)
CD34 select +- other	371 (4)	86 (6)	47 (7)
Cyclophosphamide alone	261 (3)	50 (3)	24 (4)
Cyclophosphamide +- others	2500 (26)	360 (23)	176 (27)
FK506 + MMF +- others	690 (7)	73 (5)	19 (3)
FK506 + MTX +- others(not MMF)	3524 (36)	478 (31)	233 (36)
FK506 +- others(not MMF,MTX)	713 (7)	253 (16)	49 (8)
FK506 alone	67 (1)	9 (1)	3 (<1)
CSA + MMF +- others(not FK506)	223 (2)	33 (2)	12 (2)
CSA + MTX +- others(not MMF,FK506)	666 (7)	83 (5)	33 (5)
CSA +- others(not FK506,MMF,MTX)	80 (1)	10 (1)	1 (<1)
CSA alone	76 (1)	9 (1)	3 (<1)
Other GVHD Prophylaxis	136 (1)	16 (1)	12 (2)
Missing	105 (1)	25 (2)	11 (2)
Donor/Recipient sex match			
Male-Male	3212 (33)	546 (35)	222 (34)
Male-Female	2068 (21)	313 (20)	136 (21)
Female-Male	2436 (25)	350 (23)	150 (23)
Female-Female	1934 (20)	317 (20)	125 (19)
CB - recipient M	24 (<1)	15 (1)	8 (1)
CB - recipient F	16 (<1)	6 (<1)	5 (1)
Missing	5 (<1)	8 (1)	0
Year of transplant			
2006-2010	604 (6)	72 (5)	38 (6)
2011-2015	3665 (38)	491 (32)	181 (28)
2016-2020	4930 (51)	874 (56)	361 (56)
2021	496 (5)	118 (8)	66 (10)
Follow-up among survivors, Months			
N Eval	5758	893	368
Median (Range)	37 (1-150)	29 (0-124)	27 (2-143)

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Late Effects and Quality of Life Working Committee Members

FROM: Rachel Phelan, MD, Scientific Director for the Late Effects and Quality of Life 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 2022.

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 2022.

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 2022.

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 June 2022.

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 analysis. The goal of this study is to submit by June 2022.

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 2022.

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 December 2022.

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 data file preparation. The goal of this study is to submit by December 2022

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 data file preparation. The goal of this study is to submit by June 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 analysis. The goal of this study is to submit by December 2022.

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 2022.

Response Summary:

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

Q1. Study Title

Bladder cancer incidence and mortality after hematopoietic cell transplantation

Q2. Key Words

Bladder cancer
cyclophosphamide

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Megan Herr, Phd
Email address:	megan.herr@roswellpark.org
Institution name:	Roswell Park Comprehensive Cancer Center
Academic rank:	Assistant Professor of Oncology

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):	Theresa Hahn, PhD
Email address:	Theresa.Hahn@RoswellPark.org
Institution name:	Roswell Park Comprehensive Cancer Center
Academic rank:	Professor of Oncology

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:

Megan Herr

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.

PI: IN20-01
CO-I: CT20-01, CT19-01, SC17-07, IN19-01, LE17-01, LE18-01, LE20-02, IB19-02, CV20-04b

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:

Has bladder cancer incidence and mortality following hematopoietic cell transplantation (HCT) increased due to post-transplant cyclophosphamide and have the risk factors for bladder cancer changed over time?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that bladder cancer incidence has increased due to increased exposure to post-transplant cyclophosphamide for graft-versus-host disease prophylaxis

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

Suggested word limit of 200 words:

Aim 1a: assess bladder cancer incidence and mortality rate after HCT
Aim 1b: identify risk factors for bladder cancer after HCT
Primary outcome: bladder cancer incidence
Secondary outcome: survival after bladder cancer diagnosis compared to other second solid neoplasms, second hematologic malignancies, and no second neoplasm.
Using TED level data, we will assess the rate of bladder cancer incidence and identify the risk factors for bladder cancer after HCT
Aim 2: In a subset analysis, identify risk factors for bladder cancer after HCT using dose-level data for cyclophosphamide
Outcome: bladder cancer
Exposure of interest: cyclophosphamide used as pre-HCT therapy, conditioning regimens and GvHD prophylaxis
Using CRF level data, we will identify risk factors for bladder cancer including cyclophosphamide dosing for pre-HCT treatment and GvHD prophylaxis.

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.

Treatment with cyclophosphamide is common for induction and salvage treatment of hematologic malignancies and for HCT as part of the conditioning regimen and graft-versus-host disease prophylaxis. Unfortunately, cyclophosphamide is associated with an increased risk of bladder cancer. HCT patients are already monitored for second cancers, but the identification of additional risk factors may help detect patients at higher risk who should be more closely monitored.

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.

Cyclophosphamide is commonly used as a chemotherapeutic agent in hematologic malignancies, as well as for the conditioning regimen and graft-versus-host disease prophylaxis. The carcinogenic effects of cyclophosphamide result in elevated cases of bladder cancer, secondary myelodysplastic syndromes and acute leukemias, and skin cancers (Emadi et al. 2009). A strong dose-dependent association exists between cyclophosphamide and bladder cancer with risk rising substantially between a cumulative total dose of >20g to >100g (Chou et al. 2021). Many of the hematologic patients receive cyclophosphamide during their initial therapy and then again for transplant. For example, a non-Hodgkin lymphoma patient who received 6 cycles of RCHOP would have initial received 4.5 g/m2 of cyclophosphamide (approximately 9g of cyclophosphamide for a patient who has a BSA of 2.0). This patient could then have received an autologous HCT with CBV for conditioning, resulting in another 11g of cyclophosphamide, or a haploidentical HCT resulting in another 9-16g (weight dependent) of cyclophosphamide. This repeated cumulative exposure to cyclophosphamide exceeds 20g which increases HCT patient's risk of bladder cancer.
Other risk factors include length of cyclophosphamide administration, hemorrhagic cystitis, age >60 years, >30 pack-years of smoking, history of prior malignancy, and radiation to the pelvic region. The median latency from time of cyclophosphamide administration to bladder cancer diagnosis was 7-10 years, and 33% of bladder cancer cases died of bladder cancer (Chou et al. 2021, Emadi et al. 2009).
Compared to de novo bladder cancer, second bladder cancers were more likely to be evenly distributed between genders, younger in age (55 years compared to 73 years), and had diagnoses of leiomyosarcoma and squamous cell carcinoma (Chou et al. 2021). The high grade at diagnosis (58%) was similar to what was reported in de novo bladder cancers (21-67%).

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

N/A

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

• Patients who received first HCT (autos and allos) between 2000 and 2018 with ≥5 years of follow-up
• ≥18 years of age at time of HCT

Q21. Does this study include pediatric patients?

- No

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

De novo and second bladder cancers are extremely rare in the pediatric population and including pediatric patients would only inflate the denominator.

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.

Because bladder cancer is reported as "genitourinary cancer" on CIBMTR forms, pathology reports will need to be reviewed to distinguish bladder cancer from other GU cancers. This will limit our study to patients who have a second GU cancer and a pathology report. We are aware of the time commitment this review requires and are willing to participate in the review and adjudication of pathology reports.
Additionally, for centers that reported second genitourinary cancers, we would like to request additional data. If the centers claim the second cancer is bladder cancer, we would like to request supporting documentation. This documentation could be a pathology report, but if that is not available, any information in support of bladder cancer; for example, if there was a clinic note describing treatment for bladder cancer, we could use that as support.

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

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

None

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

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

None

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

None

Q26. REFERENCES:

1. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641-650.
2. Chou WH, McGregor B, Schmidt A, et al. Cyclophosphamide-associated bladder cancers and considerations for survivorship care: A systematic review. Urologic Oncology: Seminars and Original Investigations. 2021;39(10):678-685.
3. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nature reviews Clinical oncology. 2009;6(11):638-647.

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Table 1. Baseline characteristics for all disease patients receiving first HCT between 2000 and 2016 with ≥5 years of follow-up

Characteristic	N (%)
No. of patients	52398
No. of centers	298
TED vs. CRF - no. (%)	
TED	41913 (80)
CRF	10485 (20)
Transplant type - no. (%)	
Allo	17083 (33)
Auto	35315 (67)
Age at HCT - median (min-max)	56 (18-84)
Age at HCT - no. (%)	
18-29	4449 (8)
30-39	4423 (8)
40-49	8314 (16)
50-59	16079 (31)
60-69	16194 (31)
>=70	2939 (6)
Recipient sex - no. (%)	
Male	30133 (58)
Female	22265 (42)
KPS - no. (%)	
90-100	33712 (64)
< 90	17179 (33)
Missing	1507 (3)
HCT-CI - no. (%)	
0	19334 (37)
1	7373 (14)
2	7791 (15)
3	7929 (15)
4	4159 (8)
5	2240 (4)
6	2188 (4)
TBD, review needed for history of malignancies	6 (0)
TBD, inconsistencies between parent and sub-questions	161 (0)
NA, f2400 (pre-TED) not completed	15 (0)
Missing	1202 (2)
Race - no. (%)	
White	42006 (80)

Characteristic	N (%)
Black or African American	5242 (10)
Asian	1581 (3)
Native Hawaiian or other Pacific Islander	134 (0)
American Indian or Alaska Native	184 (0)
More than one race	135 (0)
Missing	3116 (6)
Ethnicity - no. (%)	
Hispanic or Latino	4026 (8)
Non-Hispanic or non-Latino	44683 (85)
Non-resident of the U.S.	3116 (6)
Missing	573 (1)
Primary disease for HCT - no. (%)	
Acute myelogenous leukemia	6968 (13)
Acute lymphoblastic leukemia	2544 (5)
Other leukemia	908 (2)
Chronic myelogenous leukemia	792 (2)
Myelodysplastic/myeloprolifterative disorders	2124 (4)
Acute leukemias of ambiguous lineage and other myeloid neoplasms	228 (0)
Non-Hodgkin lymphoma	11746 (22)
Hodgkin lymphoma	3530 (7)
Plasma cell disorder/Multiple Myeloma	21236 (41)
Other Malignancies	459 (1)
Breast Cancer	8 (0)
Severe aplastic anemia	691 (1)
Inherited abnormalities erythrocyte differention or functuntion	183 (0)
SCID and other immune system disorders	72 (0)
Inherited abnormalities of platelets	1 (0)
Inherited disorders of metabolism	10 (0)
Histiocytic disorders	38 (0)
Autoimmune Diseases	72 (0)
Other, specify	19 (0)
Myeloproliferative Neoplasms	769 (1)
Graft type - no. (%)	
Bone marrow	2984 (6)
Peripheral blood	48569 (93)
Umbilical cord blood	835 (2)
Missing	10 (0)
Donor type - no. (%)	
HLA-identical sibling	6551 (13)
Twin	155 (0)
Other related	997 (2)

Characteristic	N (%)
Well-matched unrelated (8/8)	6314 (12)
Partially matched unrelated (7/8)	1202 (2)
Mis-matched unrelated (<= 6/8)	54 (0)
Multi-donor	11 (0)
Unrelated (matching TBD)	883 (2)
Cord blood	915 (2)
Missing	1 (0)
N/A, Auto-HCT	35315 (67)
Conditioning intensity (MAC vs. RIC/NMA) - no. (%)	
RIC/NMA	6733 (13)
MAC	10224 (20)
Missing	126 (0)
N/A, Auto-HCT	35315 (67)
GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	62 (0)
TDEPLETION alone	18 (0)
TDEPLETION +- other	109 (0)
CD34 select alone	146 (0)
CD34 select +- other	189 (0)
Cyclophosphamide alone	167 (0)
Cyclophosphamide +- others	827 (2)
FK506 + MMF +- others	1927 (4)
FK506 + MTX +- others(not MMF)	7243 (14)
FK506 +- others(not MMF,MTX)	1232 (2)
FK506 alone	327 (1)
CSA + MMF +- others(not FK506)	1562 (3)
CSA + MTX +- others(not MMF,FK506)	2546 (5)
CSA +- others(not FK506,MMF,MTX)	144 (0)
CSA alone	214 (0)
Other GVHD Prophylaxis	220 (0)
Identical twin donor	141 (0)
Missing	9 (0)
N/A, Auto-HCT	35315 (67)
Second neoplasms - no. (%)	
Yes	6441 (12)
No	45860 (88)
Missing	97 (0)
Year of HCT - no. (%)	
2008	4620 (9)
2009	5687 (11)
2010	6244 (12)

Characteristic	N (%)
2011	6713 (13)
2012	7143 (14)
2013	7209 (14)
2014	7275 (14)
2015	5839 (11)
2016	1668 (3)
Follow-up - median (range)	93 (60-163)

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

Racial/ Ethnic Disparities in Long-Term Health Outcomes Among Survivors of Allogeneic Hematopoietic Cell Transplant Performed in Childhood

Q2. Key Words

Disparities, Survivorship, Long-term Health Outcomes

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

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

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

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

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:

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

CV20-04b: COVID-19 in Pediatric HCT Recipients
I am one of the PIs of this project and will be "co-first author" on soon to be submitted manuscript.

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:

Are there any differences in long-term health outcomes of survivors of allogeneic hematopoietic cell transplant performed in childhood according to survivors' race/ ethnicity?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that Hispanic or Latino and Non-Hispanic Black survivors have increased likelihood of adverse long-term health outcomes compared to Non-Hispanic White survivors.

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

Suggested word limit of 200 words:

1. To determine the effect of race/ ethnicity on the incidence of non-malignant late effects among survivors of allogeneic hematopoietic cell transplant performed during childhood.
2. To investigate the differences in the risk of developing subsequent neoplasms by race/ ethnicity among survivors of allogeneic hematopoietic cell transplant performed during childhood

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.

Racial/ ethnic disparities in healthcare continues to be a significant challenge. Within the field of hematopoietic cell transplant (HCT), the impact of race/ ethnicity is multi-fold, as several prior studies have shown its association with donor availability, access to HCT, and overall survival.1 The underlying reasons for these differences are unclear, but theories attributing the role of social determinants have been postulated.1 The impact of race/ ethnicity on long-term survivors' health outcomes is unknown. It is possible that the inequalities in socio-economic status or insurance coverage could subsequently impact survivors' lifestyle, health behaviors, ability to access healthcare, and follow recommended surveillance guidelines post-HCT, eventually leading to long-term adverse health outcomes. Additionally, differences in disease biology or stage at diagnosis and prior comorbidities may also be playing a role in impacting the outcomes.1 Assessing the long-term health outcomes in relation to the race/ ethnicity among HCT survivors would the first step in understanding the burden of chronic health conditions among racial/ ethnic minorities. The findings of our study may help determine the need for resource allocation and inform future guidelines for long-term surveillance for this population.

Reference:

1. Majhail NS, Nayyar S, Santibanez ME, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. Bone Marrow Transplant. 2012;47(11):1385-1390.

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

The use of allogeneic hematopoietic cell transplant (HCT) as a curative option for malignant and non-malignant diseases has increased over time.2 Similarly, survival rates after HCT have also gradually improved due to several factors, including better donor availability, improvements in HLA typing techniques, and supportive care.3,4 Despite improving survival rates, significant racial/ ethnic disparities in HCT outcomes still exist and several investigators have shown worse outcomes among Black and Hispanic HCT recipients. Using the Center for International Blood and Marrow Transplant Research (CIBMTR) data, Baker and colleagues showed that African American HCT recipients had worse overall survival (Relative risk [RR] 1.5; 95% confidence interval [CI] 1.3-1.7).5 Transplant-related mortality was also higher among African American and Hispanic recipients. Ballen and colleagues studied the relationship of race/ ethnicity with outcomes of umbilical cord blood transplant and found that Black recipients had inferior overall survival (RR 1.3; 95% CI 1.0-1.7, P=0.02) compared to Whites. 6 Other studies have also shown disparities when assessing treatment failure7 and graft vs. host disease.8

While these studies assessed the impact of racial/ ethnic variations on immediate post-HCT outcomes, its effect on long-term health outcomes among HCT survivors is unclear. A prior study focusing on adult survivors of childhood cancer assessed the race/ ethnicity-specific risks of adverse outcomes.9 The authors found that non-Hispanic Black survivors had a higher prevalence of hypertension and obesity, which translated into higher severe cardiovascular conditions. Additionally, Hispanic and Non-Hispanic Black survivors were more likely to report diabetes mellitus, the reason for which remained unclear. Another study focusing on survivors of breast cancer found that Black patients had a higher rate of cardiotoxicity (24%; 95% CI 12-34%) compared to White patients (7%; 95% CI 3-11%).10 The authors also found that the occurrence of cardiotoxicity correlated with a higher probability of not completing therapy among Black patients.

HCT survivors remain at a life-long increased risk of late effects impacting organ function compared to non-HCT conventional therapy survivors and/ or the general population and require longitudinal surveillance for prevention and early detection of late effects.11-13 It is important to assess the impact of race/ ethnicity on these outcomes among HCT survivors in order to better allocate resources and inform the long-term follow-up guidelines. To address this knowledge gap, we aim to examine the differences in the incidence of malignant and non-malignant adverse health outcomes between groups defined by race/ ethnicity in the Center for International Blood and Marrow Transplant Research (CIBMTR) cohort.

References:

2. D'Souza A, Fretham C, Lee SJ, et al. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant. 2020;26(8):e177-e182.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091-2101.
4. Majhail NS, Tao L, Bredeson C, et al. Prevalence of hematopoietic cell transplant survivors in the United States. Biology of Blood and Marrow Transplantation. 2013;19(10):1498-1501.
5. Baker KS, Davies SM, Majhail NS, et al. Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(12):1543-1554.
6. Ballen KK, Klein JP, Pedersen TL, et al. Relationship of race/ethnicity and survival after single umbilical cord blood transplantation for adults and children with leukemia and myelodysplastic syndromes. Biol Blood Marrow Transplant. 2012;18(6):903-912.
7. Baker KS, Loberiza FR, Jr., Yu H, et al. Outcome of ethnic minorities with acute or chronic leukemia treated with hematopoietic stem-cell transplantation in the United States. J Clin Oncol. 2005;23(28):7032-7042.
8. Mielcarek M, Gooley T, Martin PJ, et al. Effects of race on survival after stem cell transplantation. Biol Blood Marrow Transplant. 2005;11(3):231-239.
9. Liu Q, Leisenring WM, Ness KK, et al. Racial/Ethnic Differences in Adverse Outcomes Among Childhood Cancer Survivors: The Childhood Cancer Survivor Study. J Clin Oncol. 2016;34(14):1634-1643.
10. Litvak A, Batukbhai B, Russell SD, et al. Racial disparities in the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer. Cancer. 2018;124(9):1904-1911.
11. Armenian SH, Sun CL, Kawashima T, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). Blood. 2011;118(5):1413-1420.
12. Chow EJ, Cushing-Haugen KL, Cheng GS, et al. Morbidity and Mortality Differences Between Hematopoietic Cell Transplantation Survivors and Other Cancer Survivors. J Clin Oncol. 2017;35(3):306-313.
13. Yen HJ, Eissa HM, Bhatt NS, et al. Patient-reported outcomes in survivors of childhood hematologic malignancies with hematopoietic stem cell transplant. Blood. 2020;135(21):1847-1858.

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.

We will include all pediatric patients (<18 years of age at HCT) who received first allogeneic HCT between January 1, 1995 and December 31, 2019 and were alive and relapse-free, at least one year following HCT. All disease diagnoses, donor types/ graft sources, and conditioning regimens will be included (Limiting the year range to 1995 has been determined based on CIBMTR forms availability to allow collection of long-term health outcomes data. Two prior CIBMTR analyses have used similar timeline14,15)

References:

14. Buchbinder D, Nugent DJ, Brazauskas R, et al. Late effects in hematopoietic cell transplant recipients with acquired severe aplastic anemia: a report from the late effects working committee of the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2012;18(12):1776-1784.

15. Vrooman LM, Millard HR, Brazauskas R, et al. Survival and Late Effects after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancy at Less than Three Years of Age. Biol Blood Marrow Transplant. 2017;23(8):1327-1334.

Q21. Does this study include pediatric patients?

- Yes

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

Variables to be described and analyzed:

Main effect variable:

• Race/ ethnicity: Non-Hispanic White vs Non-Hispanic Black vs Hispanic vs Asian vs Others

Patient related

• Patient age at transplant (0-4, 5-9, 10-14, 15-17)

• Patient sex

• Karnofsky performance at transplant: <80% vs >=80%

Disease/Transplant Related

• Disease diagnoses (malignant vs non-malignant)

• Conditioning intensity (myeloablative vs reduced intensity/non-ablative)

• TBI-based conditioning (yes vs no)

• Donor type: HLA-identical vs. matched related vs haplo-identical (≥ 2 Ag/allele mismatch) vs matched unrelated vs mismatched unrelated vs cord

• Stem cell source: peripheral blood vs bone marrow vs cord

• GVHD prophylaxis

• Year of transplant: continuous

Post-HCT

• Acute GVHD: yes vs no and grade

• Chronic GVHD: yes vs no and grade

• Relapse: yes vs. no

• Overall survival

Outcomes (Yes/ No and date of onset):

• Avascular necrosis

• Cataracts

- Congestive heart failure
- Diabetes mellitus
- Gonadal dysfunction/ infertility requiring hormone replacement
- Growth hormone deficiency/ disturbance
- Hemorrhagic cystitis
- Hypothyroidism
- Myocardial infarction
- Pancreatitis
- Thrombotic thrombocytopenic purpura/ Hemolytic uremic syndrome
- Renal failure warranting dialysis
- Stroke/ Seizures
- Bronchiolitis obliterans
- Pulmonary hemorrhage
- Cryptogenic organizing pneumonia
- Interstitial pneumonitis/ Idiopathic pneumonia syndrome
- Non-infectious liver toxicity (Cirrhosis)
- New malignancy

Study design:

Patient-, disease- and transplant- related factors will be described as frequency (percentage) for categorical variables and median (range) for non-categorical variables and time dependent outcomes. Data will be stratified by recipients' race/ ethnicity.

Aim 1: Prevalence of non-malignant late effects will be estimated. Cumulative incidence of non-malignant late effects will be evaluated at 2-, 5-, and 10-years post-HCT, treating death as a competing risk and comparing survivors by race/ ethnicity. Survivors will be censored at relapse or second HCT. Cox regression models will be used to compare the hazards of frequently occurred (at least 5 events in each group) non-malignant late effects in Non-White survivors (Non-Hispanic Black, Hispanic) to white survivors, adjusted for age at HCT, sex, and diagnosis. Additional adjustment in the models will be made according to transplant characteristics (donor/ graft source, TBI use, and GVHD). Stepwise selection will be used to identify covariates to be included in the final models. In addition to the above analyses of specific non-malignant late effects, occurrence of more than two non-malignant late effects will be examined in the same fashion.

Aim 2: Cumulative incidence of subsequent neoplasms with death as a competing risk event will be estimated by survivors' race/ ethnicity. For each survivor, the number of person-years at risk will be calculated from the date of transplant until the date of last contact, death, or diagnosis of new cancer, whichever occurs first. Incidence rates of all invasive cancers in the general population will be obtained from selected registries.16 Age-, sex-, calendar year-, and region-specific incidence rates for all invasive cancers will be applied to the appropriate person-years at risk to compute the expected numbers of cancers. Observed–to–expected (O/E) ratios, also called standardized incidence ratios, will be calculated, and the exact Poisson distribution will be used to calculate 95% confidence intervals (CIs). Multivariable analyses will be conducted to compare the risks of subsequent neoplasms by race/ ethnicity using the above-mentioned covariates.

(Of note, an ongoing CIBMTR study (HS18-02) aims to determine the association of race/ ethnicity and socioeconomic status on overall survival, non-relapse mortality, and relapse among 1-year survivors of adult allogeneic HCT, who underwent transplant for hematologic malignancies between 2007-2017. That ongoing study specifically excludes pediatric HCT recipients, which remains a major unmet need in the field. Since we are only focusing on pediatric HCT survivors and on malignant and non-malignant late effects, we do not anticipate an overlap with this ongoing analysis.)

Reference:

16. Cuardo MP, Edwards B, Shin HR, et al. Cancer incidence in five continents. Vol. IX. Lyon, France: IARC Press, International Agency for Research on Cancer; 2007.

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

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

None

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

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

None

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

None

Q26. REFERENCES:

1. Majhail NS, Nayyar S, Santibanez ME, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. Bone Marrow Transplant. 2012;47(11):1385-1390.
2. D'Souza A, Fretham C, Lee SJ, et al. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant. 2020;26(8):e177-e182.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091-2101.
4. Majhail NS, Tao L, Bredeson C, et al. Prevalence of hematopoietic cell transplant survivors in the United States. Biology of Blood and Marrow Transplantation. 2013;19(10):1498-1501.
5. Baker KS, Davies SM, Majhail NS, et al. Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(12):1543-1554.
6. Ballen KK, Klein JP, Pedersen TL, et al. Relationship of race/ethnicity and survival after single umbilical cord blood transplantation for adults and children with leukemia and myelodysplastic syndromes. Biol Blood Marrow Transplant. 2012;18(6):903-912.
7. Baker KS, Loberiza FR, Jr., Yu H, et al. Outcome of ethnic minorities with acute or chronic leukemia treated with hematopoietic stem-cell transplantation in the United States. J Clin Oncol. 2005;23(28):7032-7042.
8. Mielcarek M, Gooley T, Martin PJ, et al. Effects of race on survival after stem cell transplantation. Biol Blood Marrow Transplant. 2005;11(3):231-239.
9. Liu Q, Leisenring WM, Ness KK, et al. Racial/Ethnic Differences in Adverse Outcomes Among Childhood Cancer Survivors: The Childhood Cancer Survivor Study. J Clin Oncol. 2016;34(14):1634-1643.
10. Litvak A, Batukbhai B, Russell SD, et al. Racial disparities in the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer. Cancer. 2018;124(9):1904-1911.
11. Armenian SH, Sun CL, Kawashima T, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). Blood. 2011;118(5):1413-1420.
12. Chow EJ, Cushing-Haugen KL, Cheng GS, et al. Morbidity and Mortality Differences Between Hematopoietic Cell Transplantation Survivors and Other Cancer Survivors. J Clin Oncol. 2017;35(3):306-313.
13. Yen HJ, Eissa HM, Bhatt NS, et al. Patient-reported outcomes in survivors of childhood hematologic malignancies with hematopoietic stem cell transplant. Blood. 2020;135(21):1847-1858.
14. Buchbinder D, Nugent DJ, Brazauskas R, et al. Late effects in hematopoietic cell transplant recipients with acquired severe aplastic anemia: a report from the late effects working committee of the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2012;18(12):1776-1784.
15. Vrooman LM, Millard HR, Brazauskas R, et al. Survival and Late Effects after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancy at Less than Three Years of Age. Biol Blood Marrow Transplant. 2017;23(8):1327-1334.
16. Cuardo MP, Edwards B, Shin HR, et al. Cancer incidence in five continents. Vol. IX. Lyon, France: IARC Press, International Agency for Research on Cancer; 2007.

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1A. Baseline characteristics for all disease patients receiving alloHCT during 1995-2015 all pediatric patients

Characteristic	N (%)
No. of patients	10148
No. of centers	220
TED vs. CRF track - no. (%)	
TED	6635 (65)
CRF	3513 (35)
Age at HCT - median (min-max)	8 (0-18)
Age at HCT - no. (%)	
<10	6412 (63)
10-17	3736 (37)
Recipient sex - no. (%)	
Male	6025 (59)
Female	4123 (41)
KPS - no. (%)	
90-100	8347 (82)
< 90	1524 (15)
Missing	277 (3)
HCT-CI - no. (%)	
0	6912 (68)
1	995 (10)
2	381 (4)
3	480 (5)
4	184 (2)
5	69 (1)
6	86 (1)
TBD, review needed for history of malignancies	1 (0)
TBD, inconsistencies between parent and sub-questions	3 (0)
NA, f2400 (pre-TED) not completed	11 (0)
Missing	1026 (10)
Race - no. (%)	
White	5540 (55)
Black or African American	1001 (10)
Asian	1043 (10)
Native Hawaiian or other Pacific Islander	54 (1)
American Indian or Alaska Native	95 (1)
More than one race	159 (2)
Missing	2256 (22)
Ethnicity - no. (%)	
Hispanic or Latino	1453 (14)

Characteristic	**N (%)**
Non-Hispanic or non-Latino	6106 (60)
Non-resident of the U.S.	2469 (24)
Missing	120 (1)
Primary disease for HCT - no. (%)	
Acute myelogenous leukemia	1395 (14)
Acute lymphoblastic leukemia	2012 (20)
Other leukemia	7 (0)
Chronic myelogenous leukemia	161 (2)
Myelodysplastic/myeloprolifterative disorders	498 (5)
Acute leukemias of ambiguous lineage and other myeloid neoplasms	169 (2)
Non-Hodgkin lymphoma	171 (2)
Hodgkin lymphoma	51 (1)
Plasma cell disorder/Multiple Myeloma	1 (0)
Other Malignancies	22 (0)
Severe aplastic anemia	1190 (12)
Inherited abnormalities erythrocyte differention or functuntion	2108 (21)
SCID and other immune system disorders	1361 (13)
Inherited abnormalities of platelets	67 (1)
Inherited disorders of metabolism	502 (5)
Histiocytic disorders	398 (4)
Autoimmune Diseases	16 (0)
Myeloproliferative Neoplasms	19 (0)
Graft type - no. (%)	
Bone marrow	6316 (62)
Peripheral blood	1822 (18)
Umbilical cord blood	2009 (20)
Other, specify	1 (0)
Donor type - no. (%)	
HLA-identical sibling	3803 (37)
Twin	28 (0)
Other related	878 (9)
Well-matched unrelated (8/8)	1718 (17)
Partially-matched unrelated (7/8)	611 (6)
Mis-matched unrelated (<= 6/8)	43 (0)
Multi-donor	18 (0)
Unrelated (matching TBD)	912 (9)
Cord blood	2100 (21)
Missing	37 (0)
Conditioning intensity - no. (%)	
RIC/NMA	2079 (20)
MAC	7827 (77)

Characteristic	**N (%)**
Missing	242 (2)
GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	111 (1)
TDEPLETION alone	45 (0)
TDEPLETION +- other	149 (1)
CD34 select alone	99 (1)
CD34 select +- other	144 (1)
Cyclophosphamide alone	19 (0)
Cyclophosphamide +- others	209 (2)
FK506 + MMF +- others	531 (5)
FK506 + MTX +- others(not MMF)	1356 (13)
FK506 +- others(not MMF,MTX)	138 (1)
FK506 alone	125 (1)
CSA + MMF +- others(not FK506)	1645 (16)
CSA + MTX +- others(not MMF,FK506)	3774 (37)
CSA +- others(not FK506,MMF,MTX)	747 (7)
CSA alone	739 (7)
Other GVHD Prophylaxis	213 (2)
Identical twin donor	20 (0)
Missing	84 (1)
Year of HCT - no. (%)	
2008	1059 (10)
2009	1265 (12)
2010	1272 (13)
2011	1301 (13)
2012	1263 (12)
2013	1330 (13)
2014	1292 (13)
2015	1366 (13)
Follow-up - median (range)	69 (0-159)

Table 1B. Baseline characteristics for all disease patients receiving alloHCT during 1995-2015 all pediatric patients (CRF)

Characteristic	N (%)
No. of patients	3513
No. of centers	134
Age at HCT - median (min-max)	6 (0-18)
Age at HCT - no. (%)	
<10	2422 (69)
10-17	1091 (31)
Recipient sex - no. (%)	
Male	2052 (58)
Female	1461 (42)
KPS - no. (%)	
90-100	2878 (82)
< 90	544 (15)
Missing	91 (3)
HCT-CI - no. (%)	
0	2462 (70)
1	412 (12)
2	138 (4)
3	204 (6)
4	74 (2)
5	40 (1)
6	34 (1)
TBD, inconsistencies between parent and sub-questions	2 (0)
NA, f2400 (pre-TED) not completed	11 (0)
Missing	136 (4)
Race - no. (%)	
White	2225 (63)
Black or African American	472 (13)
Asian	272 (8)
Native Hawaiian or other Pacific Islander	35 (1)
American Indian or Alaska Native	38 (1)
More than one race	92 (3)
Missing	379 (11)
Ethnicity - no. (%)	
Hispanic or Latino	629 (18)
Non-Hispanic or non-Latino	2185 (62)
Non-resident of the U.S.	642 (18)
Missing	57 (2)
Primary disease for HCT - no. (%)	

Characteristic	**N (%)**
Acute myelogenous leukemia	523 (15)
Acute lymphoblastic leukemia	558 (16)
Other leukemia	3 (0)
Chronic myelogenous leukemia	34 (1)
Myelodysplastic/myeloprolifterative disorders	176 (5)
Acute leukemias of ambiguous lineage and other myeloid neoplasms	60 (2)
Non-Hodgkin lymphoma	59 (2)
Hodgkin lymphoma	12 (0)
Plasma cell disorder/Multiple Myeloma	1 (0)
Other Malignancies	3 (0)
Severe aplastic anemia	369 (11)
Inherited abnormalities erythrocyte differention or functuntion	666 (19)
SCID and other immune system disorders	598 (17)
Inherited abnormalities of platelets	27 (1)
Inherited disorders of metabolism	258 (7)
Histiocytic disorders	152 (4)
Autoimmune Diseases	4 (0)
Myeloproliferative Neoplasms	10 (0)
Graft type - no. (%)	
Bone marrow	1598 (64)
Peripheral blood	408 (19)
Umbilical cord blood	1507 (17)
Donor type - no. (%)	
HLA-identical sibling	795 (23)
Twin	13 (0)
Other related	294 (8)
Well-matched unrelated (8/8)	624 (18)
Partially-matched unrelated (7/8)	208 (6)
Mis-matched unrelated (<= 6/8)	16 (0)
Multi-donor	1 (0)
Unrelated (matching TBD)	16 (0)
Cord blood	1546 (44)
Conditioning intensity - no. (%)	
RIC/NMA	795 (23)
MAC	2628 (75)
Missing	90 (3)
GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	28 (1)
TDEPLETION alone	22 (1)
TDEPLETION +- other	45 (1)
CD34 select alone	41 (1)

Characteristic	**N (%)**
CD34 select +- other	50 (1)
Cyclophosphamide alone	3 (0)
Cyclophosphamide +- others	81 (2)
FK506 + MMF +- others	286 (8)
FK506 + MTX +- others(not MMF)	473 (13)
FK506 +- others(not MMF,MTX)	57 (2)
FK506 alone	33 (1)
CSA + MMF +- others(not FK506)	920 (26)
CSA + MTX +- others(not MMF,FK506)	805 (23)
CSA +- others(not FK506,MMF,MTX)	438 (12)
CSA alone	168 (5)
Other GVHD Prophylaxis	50 (1)
Identical twin donor	12 (0)
Missing	1 (0)
Year of HCT - no. (%)	
2008	569 (16)
2009	536 (15)
2010	301 (9)
2011	214 (6)
2012	231 (7)
2013	404 (12)
2014	576 (16)
2015	682 (19)
Follow-up - median (range)	72 (1-158)

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

Cumulative Incidence and Risk Factors for Breast Cancer after Allogeneic Hematopoietic Cell Transplant.

Q2. Key Words

subsequent malignancy, breast cancer, late effects, late toxicity, survivorship

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Kareem Jamani, MD MPH
Email address:	kareem.jamani@ahs.ca
Institution name:	Alberta Blood & Marrow Transplant Program/University of Calgary
Academic rank:	Clinical Assistant Professor

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	K. Scott Baker, MD MSc
Email address:	ksbaker@fredhutch.org
Institution name:	Fred Hutchinson Cancer Research Center/University of Washington
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:

Kareem Jamani

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.

One of many coauthors on male fertility/reproductive system late effects review paper (was involved in literature review and summary for the fertility section).

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:

What is the cumulative incidence of and what are the risk factors for breast cancer after all-HCT? Particularly, what is the association between TBI dose/fractionation and breast cancer?

Q16. RESEARCH HYPOTHESIS:

Breast cancer is a known late complication of allo-HCT. While consensus guidelines for breast cancer screening after allo-HCT exist, the recommendations are largely extrapolated from the Hodgkin lymphoma literature. There is a paucity of literature on the risk of breast cancer after allo-HCT and the existing literature does not examine how 1) variations in modern conditioning regimens (particularly variations in TBI dosing and fractionation), and 2) age at allo-HCT and time post allo-HCT, independent of conditioning, impact risk of subsequent breast cancer. We hypothesize that discrete risk factors for the occurrence of breast cancer after allo-HCT will be identified in this proposed registry study that will contain larger numbers of patients and longer follow-up than previous studies. Specifically, we hypothesize that total body irradiation (TBI) as part of conditioning will be associated with occurrence of breast cancer, with the magnitude of the association modulated by the total dose and fractionation of the TBI. Additionally, we hypothesize that younger age at transplant and greater number of years since transplant will be associated with occurrence of breast cancer, independent of receipt of TBI. The results of the study will inform future breast cancer screening guidelines for allo-HCT recipients.

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

Suggested word limit of 200 words:

1. Estimate the cumulative incidence of breast cancer after allo-HCT.
2. Elucidate risk factors for the occurrence of breast cancer after allo-HCT, particularly the association between breast cancer and TBI (at varying dose and fractionation), age at allo-HCT and time post allo-HCT.
3. Estimate the excess risk of breast cancer in allo-HCT recipients as compared to 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.

The current consensus guidelines for screening and preventive practices after HCT emphasize the importance of early initiation of screening mammography for women exposed to total body irradiation (TBI) as part of HCT conditioning.1 Specifically, for women exposed to >8 Gy screening is recommended to begin at the later of 8 years post-HCT (but no later than age 40) or age 25, whichever occurs later. While these recommendations have served as an important guide for clinicians, they are currently inadequate because: 1) they are largely extrapolated from the Hodgkin lymphoma survivorship literature, and 2) there have since been significant changes in HCT conditioning. Importantly, higher dose TBI (typically considered to be >6-8 Gy) is now typically fractionated, the use of low dose TBI (typically considered to be 2-4.5 Gy) has become relatively common, and there are now multitudes of HCT conditioning regimens that do not include TBI. It is currently unclear, for example, whether those patients who received low dose TBI or those who received a non-TBI conditioning regimen at a young age should begin screening mammography earlier than general population guidelines. The proposed study aims to harness CIBMTR registry data to provide the HCT community with an updated analysis of risk factors for breast cancer with the primary purpose of informing future screening guidelines for breast cancer after allo-HCT.

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.

Subsequent malignancies (SM) are a known late complication of allo-HCT that contribute significantly to morbidity and non-relapse mortality, and thus are a major focus of post-transplant survivorship care.2, 3 The cumulative incidence of SMs increases in the decades after transplant with no discernable plateau.4, 5 As compared to the general population, allo-HCT survivors develop SMs at a rate that is at least double the population rate in the first decade after transplant and at least triple the population rate beyond the first decade.2 Risk factors for the development of SM reported in the literature to date include receipt of TBI-based conditioning, younger age at transplant, and occurrence of acute (a lesser factor) and chronic GVHD, among others.4

Advances in allo-HCT conditioning over the last decades have led to various levels of conditioning-related exposure: conditioning may be of varying intensity with or without TBI. If TBI is used, it may be used in fractionated high doses or in lower doses. These varying levels of exposure likely lead to varying risks of SM. Recently, two single center studies found that the risk of SM in those exposed to low dose TBI as part of conditioning (2-4.5 Gy) was similar to those conditioned with chemotherapy alone.6, 7 Additionally, a single fraction of high dose TBI was associated with greater risk of SM as compared to fractionated high dose TBI.6

However, risk factors also vary for the specific type of SM being studied,4 emphasizing the importance of studying individual SMs in an effort to identify sub-groups of survivors who will benefit from screening practices. Breast cancer, a common malignancy in the general population and among survivors of allo-HCT, is a malignancy with an effective screening modality in the form of breast imaging. While recommendations for breast cancer screening in HCT survivors exist, they are based on data extrapolated from the Hodgkin lymphoma literature. The current screening recommendations focus specifically on exposure to >8 Gy TBI and do not make specific recommendations for other groups of allo-HCT survivors (for example, those exposed to low dose TBI or those who received allo-HCT at a young age with non-TBI based conditioning). The reason for these limited screening guidelines is a paucity of literature specifically examining the risk of breast cancer after allo-HCT.

Two prior studies have examined risk factors for breast cancer after allo-HCT, although neither have examined the association between breast cancer and dose and fraction of TBI. In a FHCRC/EBMT collaborative study of 3337 female survivors of allo-HCT (transplanted 1969-2000), 52 developed breast cancer at a median follow-up of 12.5 years post-transplant.8 Increased risk of breast cancer was associated with longer time since transplant, use of TBI and younger age at transplant. Notably, dose and fractionation of TBI were not included in the multivariable model. More recently, the Bone Marrow Transplant Survivor Study analyzed 37 cases of breast cancer among 1464 allo- and auto-HCT survivors.9 Among the 19 cases of breast cancer in those who received allo-HCT, receipt of TBI was associated with breast cancer. However, >90% of patients in the cohort received ≥12 Gy TBI, thus the impact of TBI dose could not be adequately analyzed. Additionally, the effect of fractionation of TBI was not examined.

As these data continue to mature and further conditioning regimens are examined, we expect novel insights to be gleaned to guide clinical practice: a recent FHCRC analysis of 2091 female survivors of allo-HCT (transplanted 1969-2014) revealed that standardized incidence ratios (SIRs) for breast cancer were similar for those receiving conditioning with chemotherapy only, low dose TBI and high dose fractionated TBI (all in the 10.5-11.8 range) (K.S. Baker, unpublished data). Additionally, the SIR for current age 21-50 was 17.6, and SIRs for breast cancer increased with decreasing age at time of transplant (26.2 for those <20 years old) and with increasing years since transplant (16.2 for those >30 years post-transplant). The 80 observed cases of breast cancer in this analysis were spread thin across multiple covariate categories, making multivariable analysis unreliable. Importantly, these data suggest that risk factors for breast cancer after allo-HCT may extend beyond high dose TBI. Those who received chemotherapy only or low dose TBI conditioning, those who were transplanted at a young age and those who are very late post-transplant, may not fit into current guidelines for breast cancer screening after allo-HCT (particularly those in the 21-50 year old current age group), yet may be at significant risk of breast cancer.

The relatively small numbers of breast cancer cases in the above-mentioned studies highlight the need to harness registry data to maximize the number of cases available for analysis to ensure a robust multivariable analysis is possible. The long latency of SMs after allo-HCT renders a retrospective study attractive. The use the CIBMTR registry to successfully explore risk factors for a specific malignancy after allo-HCT was recently demonstrated for melanoma.10

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 female recipients of a first allo-HCT reported to CIBMTR through 2016 who survived until at least one year post-transplant without developing breast cancer will be included. Patients who received allo-HCT for Fanconi anemia, primary immunodeficiency or breast cancer will be excluded. Patients who have a known history of breast cancer that predates allo-HCT will also be excluded (history obtained from Pre-TED form or AML/MDS pre-infusion forms indicating therapy-related disease with prior breast cancer).

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.

Pre-HCT Data: age at transplant, race, primary disease, conditioning regimen (chemotherapy only vs. TBI groups: low dose (200-450 cGy), single dose 600-1000 cGy, fractionated 600-1200 cGy, fractionated 1320-1400 cGy, fractionated >1400 cGy), stem cell source (BM vs. PBSC vs. cord), donor type (matched related, haploidentical, matched unrelated, mismatched unrelated), T-cell depletion (in-vivo or ex-vivo).
Post-HCT Data: occurrence of breast cancer, date of breast cancer, death, date of death, second allo-HCT, date of second allo-HCT, grade II-IV aGVHD, date of onset of grade II-IV aGVHD, moderate-severe NIH or clinically extensive cGVHD, date of onset of moderate-severe NIH or clinically extensive cGVHD, date of last follow-up or death, age at last follow-up or death.

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

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

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. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012;18:348-371.
2. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009;113:1175-1183.
3. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood. 2007;110:3784-3792.
4. Inamoto Y, Shah NN, Savani BN, et al. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50:1013-1023.
5. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. N Engl J Med. 1997;336:897-904.
6. Baker KS, Leisenring WM, Goodman PJ, et al. Total body irradiation dose and risk of subsequent neoplasms following allogeneic hematopoietic cell transplantation. Blood. 2019;133:2790-2799.
7. Nunez L, Abedin T, Naqvi S, et al. Cumulative Incidence of subsequent malignancy after allo-HCT conditioned with or without low dose total body irradiation. Blood Advances. 2021. In Press.
8. Friedman DL, Rovo A, Leisenring W, et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. Blood. 2008;111:939-944.
9. McDonald AM, Chen Y, Wu J, et al. Total body irradiation and risk of breast cancer after blood or marrow transplantation: a blood or marrow transplantation survivor study report. J Clin Oncol. 2020;38:2872-2882.
10. Herr MM, Curtis RE, Tucker MA, et al. Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation. J Am Acad Dermatol. 2020;83:762-772.

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Baseline characteristics for malignant or non-malignant diseases female patients receiving first alloHCT through 2006

Characteristic	N (%)
No. of patients	25107
No. of centers	357
TED vs. CRF track - no. (%)	
TED	18278 (72.8)
CRF	6829 (27.2)
Age at HCT - median (min-max)	45.3 (0.2-83.5)
Age at HCT - no. (%)	
<10	2378 (9.5)
10-17	1853 (7.4)
18-29	3192 (12.7)
30-39	3055 (12.2)
40-49	4229 (16.8)
50-59	5767 (23.0)
60-69	4196 (16.7)
>=70	437 (1.7)
KPS - no. (%)	
90-100	17300 (68.9)
< 90	7193 (28.6)
Not reported	614 (2.4)
HCT-CI - no. (%)	
0	10023 (39.9)
1	3021 (12.0)
2	2625 (10.5)
3+	6981 (27.9)
Missing	2457 (9.8)
Race - no. (%)	
White	16787 (66.9)
African American	1517 (6.0)
Asian	2196 (8.7)
Pacific Islander	91 (0.4)
Native American	123 (0.5)
More than one race	1 (0.0)
Unknown	136 (0.5)
Not reported	4256 (17.0)
Ethnicity - no. (%)	
Hispanic or Latino	2344 (9.3)
Non-Hispanic or non-Latino	17372 (69.2)
N/A - Not a resident of the U.S.	5135 (20.5)

Characteristic	**N (%)**
Not reported	256 (1.0)
Primary disease for HCT - no. (%)	
Acute myelogenous leukemia	9926 (39.5)
Acute lymphoblastic leukemia	4110 (16.4)
Other leukemia	617 (2.5)
Chronic myelogenous leukemia	879 (3.5)
Myelodysplastic/myeloprolifterative disorders	2669 (10.6)
Acute leukemias of ambiguous lineage and other myeloid neoplasms	317 (1.3)
Non-Hodgkin lymphoma	1971 (7.9)
Hodgkin lymphoma	592 (2.4)
Plasma cell disorder/Multiple Myeloma	652 (2.6)
Other Malignancies	28 (0.1)
Severe aplastic anemia	1416 (5.6)
Inherited abnormalities erythrocyte differention or functuntion	1118 (4.5)
Inherited abnormalities of platelets	38 (0.2)
Autoimmune Diseases	13 (0.1)
MPN	761 (3.0)
Product type - no. (%)	
BM	6069 (24.2)
PB	17216 (68.6)
UCB	1819 (7.2)
Other	1 (0.0)
Not reported	2 (0.0)
Donor type - no. (%)	
HLA-identical sibling	9775 (38.9)
Twin	157 (0.6)
Other related	1820 (7.2)
Well-matched unrelated (8/8)	6638 (26.4)
Partially-matched unrelated (7/8)	1479 (5.9)
Mis-matched unrelated (<= 6/8)	83 (0.3)
Multi-donor	70 (0.3)
Unrelated (matching TBD)	2956 (11.8)
Cord blood	1819 (7.2)
Not reported	310 (1.2)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)	
RIC/NMA	9698 (38.6)
MAC	15166 (60.4)
Not reported	243 (1.0)
Planned GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	98 (0.4)
TDEPLETION alone	42 (0.2)

Characteristic	**N (%)**
TDEPLETION +- other	161 (0.6)
CD34 select alone	194 (0.8)
CD34 select +- other	225 (0.9)
Cyclophosphamide alone	158 (0.6)
Cyclophosphamide +- others	1284 (5.1)
FK506 + MMF +- others	2238 (8.9)
FK506 + MTX +- others(not MMF)	7599 (30.3)
FK506 +- others(not MMF,MTX)	1222 (4.9)
FK506 alone	424 (1.7)
CSA + MMF +- others(not FK506)	2761 (11.0)
CSA + MTX +- others(not MMF,FK506)	5713 (22.8)
CSA +- others(not FK506,MMF,MTX)	576 (2.3)
CSA alone	1545 (6.2)
Other GVHD Prophylaxis	632 (2.5)
Identical twin donor	139 (0.6)
Not reported	96 (0.4)
Number of breast SNs - no. (%)	120 (0.5)
Year of HCT - no. (%)	
2008	2271 (9.0)
2009	2644 (10.5)
2010	2835 (11.3)
2011	2826 (11.3)
2012	2950 (11.7)
2013	2933 (11.7)
2014	2854 (11.4)
2015	2818 (11.2)
2016	2976 (11.9)
Follow-up - median (range)	70.4 (0.0-159.0)

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

The Role of Poverty in Late Effects Following Hematopoietic Cell Transplantation

Q2. Key Words

Poverty, allogeneic transplant, late effects, long-term toxicity

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Christine Duncan, MD
Email address:	christine_duncan@dfci.harvard.edu
Institution name:	Dana-Farber Cancer Institute
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):	Lauren Jimenez-Kurlander, MD
Email address:	LaurenS_Jimenez-Kurlander@DFCI.HARVARD.EDU
Institution name:	Dana-Farber Cancer Institute
Academic rank:	Fellow

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:

Christine Duncan

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:

- Health Services and International Studies

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:

Rachel Phelan

Q15. RESEARCH QUESTION:

This proposal seeks to determine if adult and pediatric survivors of allogeneic hematopoietic cell transplant who from areas of high neighborhood poverty levels have a greater incidence of transplant late effects and higher transplant related mortality.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that survivors of transplant from areas of high neighborhood level poverty and those with Medicaid/Medicare insurance will have a greater incidence of late effects due that may be due to biologic and social determinants.

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

Suggested word limit of 200 words:

Specific Aims
Primary Aim: To compare the cumulative incidence of organ toxicity and mental health late effects in adult and pediatric survivors of allogeneic HCT from areas of low to those from high-neighborhood poverty
Secondary Aim 1: To determine how various patient and treatment-related factors influence the development of late transplant organ toxicity and mental health diagnoses in patients from areas of low versus high-neighborhood poverty
Secondary Aim 2: To report the overall survival and transplant related mortality along with cause of death, when applicable, in adult and pediatric survivors of allogeneic HCT coming from areas of low versus high-neighborhood poverty
Secondary Aim 3: To compare the cumulative incidence of organ toxicity and mental health late effects in adult and pediatric survivors of allogeneic HCT in patients with private insurance to those with Medicaid/Medicare insurance coverage

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.

Data from the 2019 United States Census reported that 10.5% of Americans were living below the poverty threshold. Single center data from the Dana-Farber Cancer Institute showed 40% of pediatric families surveyed reported pre-HCT incomes ≤200% the Federal Poverty Level, 38% of families experienced material hardship, and that low-income families reported disproportionate transplantation-related income losses. This data indicated that poverty may be more prevalent in transplant patients than the general population. We do not understand how poverty affects the development of transplant late effects. Identifying differences in late toxicity in patients from high-poverty areas would enable to tailoring of screening, support, education, and therapy and impact survival for this population.

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.

Social determinants of health, including poverty, contribute significantly to health outcomes in the United States; however, their impact on hematopoietic cell transplantation (HCT) outcomes is incompletely understood. Recent work from the CIBMTR investigated the potential association of neighborhood poverty and overall outcomes in pediatric patients who received allogeneic transplantation between 2006 and 2015. (Bona, 2021) That study of 2053 children and young adults demonstrated that neighborhood poverty was associated with an increased risk of transplant related mortality (TRM) in patients transplanted for a malignant disease. Neighborhood poverty was not associated with inferior overall survival (OS). A secondary finding was that children with Medicaid insurance experienced inferior OS and increased TRM compared with those with private insurance in children with malignant disease. These data were not identified in patients with nonmalignant disease. Additionally, a study of outcomes in children transplanted for nonmalignant disease did not identify associations of socioeconomic status and outcome. (Harney SM, 2020) Conclusions from these studies were that further investigations of the role of poverty in transplant outcomes are needed. Poverty is associated with chronic medical conditions in the general population, but has not been extensively explored in transplant patients. This proposal investigates the potential association of poverty in long-term health conditions/late effects in adult and pediatric survivors of HCT. (Reisinger Walker, 2017)

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
1. Patients who have survived disease-free two year or greater following allogeneic HCT
2. Adult and pediatric patients included
3. All stem cell sources and conditioning regimens
4. Transplanted at a center in the United States
5. Follow-up data available regarding survival, disease status, and transplant late effects

Exclusion
1. Patients with primary residence outside the United States

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.

Variable Form Question
Age in years at time of transplant 2006 R5.0 Q94
Sex 2804 R6.0 Q7
Race 2804 R6.0 Q9
Ethnicity 2804 R6.0 Q8
Underlying disease
Health insurance at HCT & most recent follow-up 2000 R6.0 Q111
Type of health insurance at time of transplant 2000 R6.0 Q112-114
Household income 2000 R6.0 Q115
Zip or postal code of residence at time of transplant 2400 R8.0 Q11
Co-existing disease impairment 2400 R8.0 Q96
Performance score at HCT & most recent follow-up 2400 R8.0 Q84-85
Year of transplant 2006 R5.0 Q94
Donor type 2450 Q19,37
Conditioning regimen 2400 R8.0 Q120,126
Acute/Chronic GVHD status 2100 R7.0 Q91,131
Anxiety requiring therapy 2100 R7.0 Q280
Other non-infectious pulmonary abnormality 2100 R7.0 Q252-253
Post-traumatic stress disorder requiring therapy 2100 R7.0 Q280
Depression requiring therapy 2100 R7.0 Q280
Non-infectious liver toxicity 2100 R7.0 Q264-265
Thrombotic microangiopathy 2100 R7.0 Q268
Other organ impairment 2100 R7.0 Q280-281
Solid organ transplant 2100 R7.0 Q305-309
New malignancy 2100 R7.0 Q310
Current or most recent work status 2100 R7.0 Q330
Did the recipient claim medical disability 2100 R7.0 Q334

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

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

No PRO requirements

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 sample requirements

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.

No CIBMTR Data Source

Q26. REFERENCES:

Bona, K. et al. Prevalence and impact of financial hardship among New England pediatric stem cell transplantation families. Biol Blood and Marrow Tranplant. 2015. 21(2):312-8.
Bona K, et al. Neighborhood poverty and pediatric allogeneic hematopoietic cell transplantation outcomes: a CIBMTR analysis. Blood. 2021,137(4): 556-568.
Harney SM, K. J. Race and socioeconomic status in pediatric allogeneic hematopoietic cell transplantation for nonmalignant conditions. Pediatr Blood Cancer. 2020 Sep;67(9):e28367
Reisinger Walker, E. Cumulative burden of comborid mental disorders, substance use disorders, chronic medical conditions, and poverty on health among adults in the U.S.A. Psychol Health Med. 2017. 6, 727-735.

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Baseline characteristics for all disease patients receiving alloHCT in US

Characteristic	N (%)
No. of patients	46008
No. of centers	196
TED vs. CRF track - no. (%)	
TED	30047 (65)
CRF	15961 (35)
Age at HCT - median (min-max)	47 (0-84)
Age at HCT - no. (%)	
<10	6059 (13)
10-17	3720 (8)
18-29	5358 (12)
30-39	4330 (9)
40-49	5860 (13)
50-59	9455 (21)
60-69	9381 (20)
>=70	1845 (4)
Recipient sex - no. (%)	
Male	26478 (58)
Female	19530 (42)
KPS - no. (%)	
90-100	30603 (67)
<90	14254 (31)
Missing	1151 (3)
HCT-CI - no. (%)	
0	15947 (35)
1	6845 (15)
2	6355 (14)
3	7247 (16)
4	4255 (9)
5	2289 (5)
6	2700 (6)
TBD, review needed for history of malignancies	9 (0)
TBD, inconsistencies between parent and sub-questions	198 (0)
NA, f2400 (pre-TED) not completed	155 (0)
Missing	8 (0)
Race - no. (%)	
White	37138 (81)
Black or African American	4011 (9)
Asian	2002 (4)
Native Hawaiian or other Pacific Islander	140 (0)

Characteristic	N (%)
American Indian or Alaska Native	263 (1)
More than one race	422 (1)
Missing	2032 (4)
Ethnicity - no. (%)	
Hispanic or Latino	6099 (13)
Non-Hispanic or non-Latino	38449 (84)
Non-resident of the U.S.	444 (1)
Missing	1016 (2)
Primary disease for HCT - no. (%)	
Acute myelogenous leukemia	15308 (33)
Acute lymphoblastic leukemia	7099 (15)
Other leukemia	1076 (2)
Chronic myelogenous leukemia	1436 (3)
Myelodysplastic/myeloprolifterative disorders	5676 (12)
Acute leukemias of ambiguous lineage and other myeloid neoplasms	629 (1)
Non-Hodgkin lymphoma	4132 (9)
Hodgkin lymphoma	899 (2)
Plasma cell disorder/Multiple Myeloma	647 (1)
Other Malignancies	29 (0)
Severe aplastic anemia	2535 (6)
Inherited abnormalities erythrocyte differention or functuntion	2239 (5)
SCID and other immune system disorders	1637 (4)
Inherited abnormalities of platelets	78 (0)
Inherited disorders of metabolism	583 (1)
Histiocytic disorders	483 (1)
Autoimmune Diseases	45 (0)
MPN	1477 (3)
Graft type - no. (%)	
Bone marrow	12325 (26)
Peripheral blood	30105 (65)
Umbilical cord blood	3576 (8)
Other, specify	2 (0)
Donor type - no. (%)	
HLA-identical sibling	13704 (30)
Twin	234 (1)
Other related	5841 (13)
Well-matched unrelated (8/8)	18337 (40)
Partially-matched unrelated (7/8)	3387 (7)
Mis-matched unrelated (<= 6/8)	199 (0)
Multi-donor	92 (0)
Unrelated (matching TBD)	316 (1)

Characteristic	N (%)
Cord blood	3894 (8)
Missing	4 (0)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)	
RIC/NMA	19801 (43)
MAC	25887 (56)
Missing	320 (1)
Planned GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	254 (1)
TDEPLETION alone	173 (0)
TDEPLETION +- other	416 (1)
CD34 select alone	516 (1)
CD34 select +- other	658 (1)
Cyclophosphamide alone	361 (1)
Cyclophosphamide +- others	6935 (15)
FK506 + MMF +- others	4795 (10)
FK506 + MTX +- others(not MMF)	18174 (40)
FK506 +- others(not MMF,MTX)	2917 (6)
FK506 alone	908 (2)
CSA + MMF +- others(not FK506)	4214 (9)
CSA + MTX +- others(not MMF,FK506)	3652 (8)
CSA +- others(not FK506,MMF,MTX)	710 (2)
CSA alone	310 (1)
Other GVHD Prophylaxis	666 (1)
Identical twin donor	206 (0)
Missing	143 (0)
Year of HCT - no. (%)	
2008	2249 (5)
2009	2556 (6)
2010	2841 (6)
2011	3163 (7)
2012	3315 (7)
2013	3520 (8)
2014	3483 (8)
2015	3781 (8)
2016	3989 (9)
2017	4133 (9)
2018	4405 (10)
2019	4760 (10)
2020	3298 (7)
2021	515 (1)
Follow-up - median (range)	55 (0-159)

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

Risk of secondary colorectal cancer development after allogeneic hematopoietic stem cell transplantation (HCT)

Q2. Key Words

colon cancer, rectal cancer, stem cell transplant, GVHD, late effects, secondary malignancies

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Jed Calata MD
Email address:	jcalata@mcw.edu
Institution name:	Medical College of Wisconsin
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?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Larisa Broglie MD
Email address:	lbroglie@mcw.edu
Institution name:	Medical College of Wisconsin
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?

- 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:

Jed Calata

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.

None

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.

- Yes

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

Rachel Phelan

Q15. RESEARCH QUESTION:

Does GVHD increase risk of developing secondary colorectal cancer after allogeneic HCT?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that colorectal cancer after allogeneic hematopoietic stem cell transplantation is highest among patients who developed GVHD.

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

Suggested word limit of 200 words:

Primary Objective: To assess whether the development of secondary colorectal cancer is associated with a prior history of GVHD after alloHCT.
Secondary Objectives:
- To describe the cumulative incidence of secondary Colorectal cancer in allogeneic HCT patients and compare to the general population
- To describe the time to development of colorectal cancer diagnoses in relation to prior allogeneic HCT.
- To assess survival of patients who developed colorectal cancer after allogeneic HCT and compare to the survival in the general population with colorectal cancer

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.

Secondary malignancies remain a concern after allogeneic HCT, including colorectal cancers. Current recommendations for colorectal cancer screening after allogeneic HCT are similar to the general population. However, if our hypothesis is correct, patients with a history of GVHD would warrant earlier colorectal cancer screening to identify and treat pre-cancerous lesions/polyps. This would help prevent secondary development of colorectal cancer in high-risk transplant survivors.

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.

Advances in allogeneic hematopoietic stem cell transplantation therapy has allowed this therapy to become more widely utilized1; there are a growing number of long-term survivors of HCT2. Despite its many benefits, patients receiving allogeneic HCT have a substantial risk of developing secondary solid organ cancers. Although colorectal cancer after HCT have been shown to be more prevalent compared to the general population, risk factors associated with the development of colorectal cancer remain unclear3,4. Screening guideline recommendations for HCT patients remain the same as for the general population3.
Overall, colorectal Cancer incidence and mortality in the US has been declining with aggressive screening and improving treatments5. However, despite success in decreasing colorectal cancer rates, the incidence of early-onset colorectal cancer has increased markedly5. In fact, the US preventative services task force recently lowered the age of recommended colorectal cancer screening from age 50 to age 45 in response to this growing trend6 Newer studies are investigating the role of diet, microbiome, and inflammation as potential risk factors.
It is well known that chronic gastrointestinal inflammatory processes increase a patient's risk of developing colorectal cancer. Patients with inflammatory bowel disease have a significantly higher risk of developing colorectal cancer7. It is estimated that 8% of patients with ulcerative colitis will develop colorectal cancer within 10 year of diagnosis7. This has led to screening recommendations that patients with inflammatory bowel disease undergo aggressive colorectal cancer screening8. Survivors of allogeneic HCT have also been shown to present with polyps, suggesting a potentially similar pathophysiology to that seen in other inflammatory bowel diseases9.
Previous studies have shown that GVHD in HCT patients is a risk factor for development of oral and esophageal cancer4. Although its role in colorectal cancer has also been suggested, the effect of GVHD on the development of colorectal cancer after alloHCT has not been studied. This is important given the trend of early-onset colorectal cancer in the US. Additional understanding of the risks of prior HCT and, in particular, the role of GVHD in development of colorectal cancer will help to better stratify patients and identify patients that require closer screening.

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:
- Patients that received first allogeneic HCT from 1990-2015
- Transplant indication for malignant or non-malignant diseases
- Any donor or graft type
- Any conditioning intensity

Exclusion
- None

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.

- Age at transplant (0-10y, 11-20y, 21-40y, 40-60y, >60y)
- Ethnicity (Caucasian, African American, Hispanic v Other)
- Gender (Male v female)
- Indication for transplant (ALL, AML, other leukemia, lymphoma, other malignant, non-malignant disease)
- Year of transplant (1990-2000, 2001-2010, 2011-2015)
- History of Inflammatory Bowel Disease (only collected after 2008)
- Donor (matched related, matched unrelated, mismatched unrelated, mismatched related/haploidentical, cord)
- Graft source (BM, peripheral blood, cord)
- Conditioning Intensity (myeloablative v reduced intensity/non-myeloablative)
- TBI (yes v no)
- TBI >800cGy (yes v no)
- GVHD prophylaxis (ex vivo T-cell depletion, CNI+MMF, CNI+MTX, CNI alone, PT-Cy, other)
- Secondary gastrointestinal malignancy (yes v no)
- aGVHD (yes v no)
- aGVHD max grade (none v I-II v III-IV)
- aGVHD lower intestinal stage (if available from CRF)
- cGVHD (yes v no)
- cGVHD max grade (none v limited v extensive)
- cGVHD severity (none v mild v moderate v severe) (if available from CRF)
- cGVHD gastrointestinal tract involvement (yes v no) (if available from CRF)

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:

. D'Souza A, Fretham C, Lee SJ et al. "Current use of and trends in hematopoietic cell transplantation in the United States". Biol Blood Marrow Transplant. 2020; 26(8):2177-e182.
2. Majhail NS, Rizzo, JD, Lee SJ et al. "Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation". 2012; 18(3):348-371.
3. Inamoto Y, Shah NN, Savani BN. "Secondary solid caner screening following hematopoietic cell transplantation". Bone Marrow Transplant. 2015; 50(8):1013-1023.
4. Tanaka Y, Kurosawa S, Tajima K et al. "Increased incidence of oral and gastrointestinal secondary cancer after allogeneic hematopoietic stem cell transplantation." Bone Marrow Transplant. 2017; 52(5):789-791.
5. Loomans-Kropp HA and Umar A. "Increasing incidence of colorectal cancer in young adults". J Cancer Epidemiol. 2019; 2019:9841295.
6. US Preventative Services Task Force et al. "Screening for colorectal cancer: US preventive services task force recommendation statement". JAMA. 2021; 325(19):1965-1977.
7. Dyson JK and Rutter MD. "Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk?" World J Gastroenterol. 2012; 18(29):3839-3848.
8. Wijnands AM, Mahmoud R, Lutgens MWMD, Oldenburg B. "Surveillance and management of colorectal dysplasia and cancer in inflammatory bowel disease: current practice and future perspectives". Eur J Intern Med. 2021. PMID: 34481721.
9. Knight B, Anderson L, Lerner D, Phelan R, Thakar MS. "Case series: development of polyps as a late effect after total body irradiation-based hematopoietic cell transplantation in children with high-risk leukemia". J Pediatr Hematol Oncol. 2021. PMID: 33828034

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Baseline characteristics for malignant or non-malignant diseases patients receiving first alloHCT during 1990-2015

Characteristic	N (%)
No. of patients	78122
No. of centers	376
TED vs. CRF track - no. (%)	
TED	54957 (70)
CRF	23165 (30)
Age at HCT - median (min-max)	47 (0-84)
Age at HCT - no. (%)	
<10	8879 (11)
10-17	5599 (7)
18-29	9364 (12)
30-39	7956 (10)
40-49	11805 (15)
50-59	17849 (23)
60-69	14759 (19)
>=70	1911 (2)
Recipient sex - no. (%)	
Male	45697 (58)
Female	32425 (42)
KPS - no. (%)	
90-100	52630 (67)
< 90	23546 (30)
Missing	1946 (2)
HCT-CI - no. (%)	
0	31611 (40)
1	9493 (12)
2	7959 (10)
3	9650 (12)
4	5380 (7)
5	2943 (4)
6	3536 (5)
TBD, review needed for history of malignancies	13 (0)
TBD, inconsistencies between parent and sub-questions	181 (0)
NA, f2400 (pre-TED) not completed	417 (1)
Missing	6939 (9)
Race - no. (%)	
White	54388 (70)
Black or African American	4397 (6)
Asian	5871 (8)

Characteristic	N (%)
Native Hawaiian or other Pacific Islander	291 (0)
American Indian or Alaska Native	370 (0)
Other	1 (0)
More than one race	440 (1)
Missing	12364 (16)
Ethnicity - no. (%)	
Hispanic or Latino	7134 (9)
Non-Hispanic or non-Latino	55836 (71)
Non-resident of the U.S.	14463 (19)
Missing	689 (1)
Primary disease for HCT - no. (%)	
AML	27386 (35)
ALL	12026 (15)
Other leukemia	2694 (3)
CML	2666 (3)
MDS	9112 (12)
Other acute leukemia	959 (1)
NHL	7503 (10)
HD	1662 (2)
PCD	2037 (3)
Solid tumor	113 (0)
Breast cancer	4 (0)
SAA	3499 (4)
IEA	2897 (4)
IIS	1891 (2)
IPA	80 (0)
IMD	707 (1)
HIS	675 (1)
AI	49 (0)
MPN	2162 (3)
Graft type - no. (%)	
BM	17783 (23)
PB	53132 (68)
UCB	7200 (9)
Other	2 (0)
Missing	5 (0)
Donor type - no. (%)	
HLA-identical sibling	28253 (36)
Twin	341 (0)
Other related	5597 (7)
Well-matched unrelated (8/8)	20924 (27)

Characteristic	**N (%)**
Partially-matched unrelated (7/8)	5525 (7)
Mis-matched unrelated (<= 6/8)	364 (0)
Multi-donor	205 (0)
Unrelated (matching TBD)	8952 (11)
Cord blood	7200 (9)
Missing	761 (1)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)	
RIC/NMA	30896 (40)
MAC	46297 (59)
Missing	929 (1)
Planned GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	386 (0)
TDEPLETION alone	129 (0)
TDEPLETION +- other	620 (1)
CD34 select alone	625 (1)
CD34 select +- other	760 (1)
Cyclophosphamide alone	483 (1)
Cyclophosphamide +- others	3297 (4)
FK506 + MMF +- others	7798 (10)
FK506 + MTX +- others(not MMF)	23061 (30)
FK506 +- others(not MMF,MTX)	3627 (5)
FK506 alone	1400 (2)
CSA + MMF +- others(not FK506)	9726 (12)
CSA + MTX +- others(not MMF,FK506)	16573 (21)
CSA +- others(not FK506,MMF,MTX)	2456 (3)
CSA alone	4575 (6)
Other GVHD Prophylaxis	2036 (3)
Identical twin donor	290 (0)
Missing	280 (0)
Number of GI SNs - no. (%)	210 (0)
Year of HCT - no. (%)	
2008	8106 (10)
2009	9311 (12)
2010	9866 (13)
2011	10158 (13)
2012	10348 (13)
2013	10466 (13)
2014	10031 (13)
2015	9836 (13)
Follow-up - median (range)	72 (0-159)

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 Socioeconomic Factors on Outcomes in Autologous Stem Cell Transplant

Q2. Key Words

Race, Geographic area of residence,

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Audrey M Sigmund, MD
Email address:	audrey.sigmund@osumc.edu
Institution name:	The Ohio State University
Academic rank:	Fellow

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):	Nidhi Sharma, Ph.D, MS; Yvonne A Efebera, MD, MPH; Don Benson, MD, PhD; Samantha Jaglowski, MD
Email address:	Nidhi.Sharma@osumc.edu; Yvonne.Efebbera@ohiohealth.com;Don.Benson@osumc.edu;Samantha.Jaglowski@osumc.edu;
Institution name:	The Ohio State University (OSU);OhioHealth, OSU, OSU
Academic rank:	Research Specialist; Professor; Professor; Associate professor

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

- No

Q8. Do you identify as an underrepresented/minority?

N/A

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

Nidhi Sharma

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

N/A

LETTER OF COMMITMENT:

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

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

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:

To evaluate the impact of socioeconomic and demographic factors on outcomes of auto-SCT.

Q16. RESEARCH HYPOTHESIS:

Socioeconomic and demographic factors such as race, income, education, location of residence, and health insurance have been demonstrated to impact medical treatment received by patients and health outcomes. We hypothesize that though underserved or minority populations are less likely to undergo autologous hematopoietic stem cell transplant, when they do, outcomes are similar to non-minority populations.

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

Suggested word limit of 200 words:

Primary aim:

- To assess the impact of race, income, education, health insurance, and location of residence on outcomes of patients undergoing auto-HCT.

Secondary aims:

- Comparison of progression free survival (PFS) and overall survival (OS) among different races and location of residences.
- Assess differences in non-relapse mortality among the groups.

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.

Autologous hematopoietic stem cell transplant (auto-HCT) plays a key role in the treatment of many patients with hematologic malignancies including multiple myeloma and a variety of lymphomas. However, auto-HCT is a costly procedure and requires highly specialized care that is only accessible in select centers across the country. Due to its cost and limited availability, minority populations are at risk for healthcare disparities in access to and outcomes of auto-HCT (Majhail 2010). We propose a study that will utilize the CIBMTR database to evaluate the effect of health disparities on outcomes of auto-HCT. This analysis would have a significant impact in understanding the disparities that underserved populations face when undergoing auto-SCT transplant. If factors relating to poor outcomes are identified, our hope would be for institutions to work towards providing equitable care to patients with health disparities. Furthermore, if patients undergoing auto-HCT with disparities are shown to have similar outcomes to the general population, we would encourage providers to refer them for auto-HCT as aggressively as non-minority patients.

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

Prior studies have focused on the impact of health disparities, including race, and geographic residence at time of transplant on the utilization and access to auto-SCT with the majority showing decreased rates of auto-SCT in these populations (Scriber, 2017; Costa, 2015). An analysis using the CIBMTR database for patients from 2008 to 2014 of patients undergoing auto-SCT for multiple myeloma showed significant differences in utilization by race with lowest utilization in Hispanics followed by blacks and non-hispanic white. Prior studies have also focused on the impact of these factors on transplant outcomes with the majority showing no significant difference in outcomes based on race (Verma, 2008; Schriber, 2017) but some have suggested differences based on other socioeconomic factors such as area of primary residence and socioeconomic status (Hong, 2016; Rao 2007). Given these variable results, we believe that conducting a large multi-center study would provide greater insight into identifying key factors which may impact auto-HCT outcomes in patients from different socioeconomic groups. If our study confirms similar outcomes based on socioeconomic factors, these results would suggest that there may be a significant number of patients from underserved populations who would benefit from a potentially curative therapy, yet face barriers to referral.

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:
- Patients undergoing autologous stem cell transplant from 1/1/2005 to 10/1/2020
- Age 18 to 75 years old
- Patients with an underlying hematologic malignancy including lymphoma and multiple myeloma

Q21. Does this study include pediatric patients?

- No

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

The focus in on adult patient population

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

Baseline recipient data
● Demographics: age at HCT, race/ethnicity, gender
● Karnofsky performance score/ECOG
● Zip code
● Distance from transplant center
● Socioeconomic information: highest level of education, household income, number of dependents, type of health insurance, employment status, marital status, primary language (non-English vs. English speaking)
● Co-existing diseases
Disease related:
● Time from diagnosis to HCT, months
● Disease sub-classification or histology
● Disease status/stage at transplant
● Disease risk status (including cytogenetics)
● Number and types of prior treatments
Transplant related:
● Conditioning regimen
● Cell dose
Post-HCT data:
● Response: complete, partial, stable disease, progressive disease
● Transplant outcomes
o Overall survival
o Days to count recovery (ANC >500/mm3, platelets>20,000/mm3)
o Relapse (including time to relapse)
● New malignancies
● Cause of death: relapse/progression of disease, transplant related mortality, infection (not identified, bacterial, fungal, viral, protozoal, other), other

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:

Costa, Luciano J., et al. “Disparities in Utilization of Autologous Hematopoietic Cell Transplantation for Treatment of Multiple Myeloma.” Biology of Blood and Marrow Transplantation, vol. 21, no. 4, 2015, pp. 701–706., doi:10.1016/j.bbmt.2014.12.024.

Hong, S & Rybicki, L & Abounader, D & Bolwell, Brian & Dean, Raymond & Gerds, Aaron & Hamilton, B & Hill, Brian & Jagadeesh, D & Kalaycio, Matt & Liu, H & Pohlman, B & Sobecks, R & Majhail, N. (2016). Association of socioeconomic status with autologous hematopoietic cell transplantation outcomes for lymphoma. Bone Marrow Transplantation. 51. 10.1038/bmt.2016.107.

Majhail NS, Omondi NA, Denzen E, Murphy EA, Rizzo JD. Access to hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant. 2010;16:1070– 1075.

Mielcarek M, Gooley T, Martin PJ, Chauncey TR, Young BA, Storb R, et al. Effects of race on survival after stem cell transplantation. Biol Blood Marrow Transplant. 2005;11:231– 239.

Rao K, Darrington DL, Schumacher JJ, Devetten M, Vose JM, Loberiza FR Jr. Disparity in survival outcome after hematopoietic stem cell transplantation for hematologic malignancies according to area of primary residence. Biol Blood Marrow Transplant. 2007 Dec;13(12):1508-14. doi: 10.1016/j.bbmt.2007.09.006. PMID: 18022581.

Schriber, Jeffrey R., et al. “Hispanics Have the Lowest Stem Cell Transplant Utilization Rate for Autologous Hematopoietic Cell Transplantation for Multiple Myeloma in the United States: A CIBMTR Report.” Cancer, vol. 123, no. 16, 2017, pp. 3141–3149., doi:10.1002/cncr.30747.

Verma PS, Howard RS, Weiss BM. The impact of race on outcomes of autologous transplantation in patients with multiple myeloma. Am J Hematol. 2008;83:355– 358.

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

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Baseline characteristics for lymphoma and multiple myeloma patients receiving autoHCT during 2005-10/1/2020 age 18-75

Characteristic	N (%)
No. of patients	111037
No. of centers	344
TED vs. CRF track - no. (%)	
TED	98186 (88)
CRF	12851 (12)
Age at HCT - median (min-max)	59 (18-75)
Age at HCT - no. (%)	
18-29	5474 (5)
30-39	6203 (6)
40-49	13826 (12)
50-59	32917 (30)
60-69	43022 (39)
>=70	9595 (9)
Recipient sex - no. (%)	
Male	65918 (59)
Female	45119 (41)
KPS - no. (%)	
90-100	65964 (59)
< 90	41651 (38)
Missing	3422 (3)
HCT-CI - no. (%)	
0	36266 (33)
1	14913 (13)
2	16590 (15)
3	17362 (16)
4	9770 (9)
5	5473 (5)
6	5848 (5)
TBD, inconsistencies between parent and sub-questions	622 (1)
NA, f2400 (pre-TED) not completed	1 (0)
Missing	4192 (4)
Race - no. (%)	
White	79821 (72)
Black or African American	13003 (12)
Asian	3655 (3)
Native Hawaiian or other Pacific Islander	219 (0)
American Indian or Alaska Native	501 (0)
More than one race	238 (0)

Characteristic	N (%)
Missing	13600 (12)
Ethnicity - no. (%)	
Hispanic or Latino	9879 (9)
Non Hispanic or non-Latino	86152 (78)
Non-resident of the U.S.	13006 (12)
Missing	2000 (2)
Primary disease for HCT - no. (%)	
Non-Hodgkin lymphoma	34163 (31)
Hodgkin lymphoma	10889 (10)
Multiple Myeloma	65985 (59)
Disease status prior to HCT (NHL/HD) - no. (%)	
CR	27373 (25)
PR	14427 (13)
Chemoresistant	2477 (2)
Untreated	134 (0)
Unknown	641 (1)
N/A, other disease	65985 (59)
Disease status prior to HCT (MM) - no. (%)	
SCR / CR	10155 (9)
VGPR	23663 (21)
PR	25375 (23)
SD	3770 (3)
PD / Relapse	1904 (2)
Missing	1118 (1)
N/A, other disease	45052 (41)
Graft type - no. (%)	
BM	181 (0)
PB	110577 (100)
UCB	8 (0)
Missing	271 (0)
Highest educational grade the recipient completed (CRF track)	
No primary education	17 (0)
Less than primary or elementary education	41 (0)
Primary or elementary education	134 (0)
Lower secondary education	341 (0)
Upper secondary education	3230 (3)
Post-secondary, non-tertiary education	1091 (1)
Tertiary education, Type A	2642 (2)
Tertiary education, Type B	781 (1)
Advanced research qualification	482 (0)
Tertiary education, Type A or Type B	56 (0)

Characteristic	**N (%)**
Missing	4036 (4)
Not collected on TED	98186 (88)
Household gross annual income - no. (%)	
Less than $20,000	165 (0)
$20,000–$39,999	165 (0)
$40,000–$59,999	167 (0)
$60,000–$79,999	115 (0)
$80,000–$99,999	76 (0)
$100,000 and over	138 (0)
Recipient declines to provide this information	253 (0)
Missing	11772 (11)
Not collected on TED	98186 (88)
Employment- no. (%)	
Full-time	3578 (3)
Part-time	550 (1)
Unemployed	1081 (1)
Medical disability	1704 (2)
Retired	3567 (3)
Missing	2371 (2)
Not collected on TED	98186 (88)
Year of HCT - no. (%)	
2008	5954 (5)
2009	7199 (6)
2010	7924 (7)
2011	8279 (7)
2012	8853 (8)
2013	8719 (8)
2014	8850 (8)
2015	9121 (8)
2016	9619 (9)
2017	10202 (9)
2018	10265 (9)
2019	10156 (9)
2020	5896 (5)
Follow-up - median (range)	50 (0-160)

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	310	5	293	224	166	21	16	13	9	11
Infusion type - no. (%)										
Transplant	308 (99)	0	289 (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)	55 (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	49 (16)	0 (0)	36 (12)	31 (14)	26 (16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
50-59	86 (28)	1 (20)	87 (30)	74 (33)	48 (29)	2 (10)	0 (0)	0 (0)	3 (33)	5 (45)
60-69	98 (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	180 (58)	5 (100)	172 (59)	130 (58)	88 (53)	17 (81)	11 (69)	8 (62)	6 (67)	6 (55)
Female	130 (42)	0 (0)	121 (41)	94 (42)	78 (47)	4 (19)	5 (31)	5 (38)	3 (33)	5 (45)
Race/Ethnicity - no. (%)										
White	281 (91)	5 (100)	256 (87)	197 (88)	154 (93)	20 (95)	14 (88)	12 (92)	9 (100)	10 (91)
Black or African American	15 (5)	0 (0)	7 (2)	7 (3)	5 (3)	0 (0)	1 (6)	1 (8)	0 (0)	0 (0)
Asian	8 (3)	0 (0)	8 (3)	6 (3)	4 (2)	1 (5)	0 (0)	0 (0)	0 (0)	1 (9)
More than one race	0 (0)	0 (0)	1 (<1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not reported	6 (2)	0 (0)	21 (7)	13 (6)	3 (2)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Ethnicity of US residents - no. (%)										
Hispanic or Latino	12 (4)	0 (0)	19 (7)	10 (4)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not Hispanic or Latino	297 (96)	5 (100)	271 (92)	212 (95)	162 (98)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
Not reported	1 (<1)	0 (0)	3 (1)	2 (1)	1 (<1)	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
Not a US resident	0 (0)	0 (0)	0 (0)	0 (0)	1 (<0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Indication for transplant - no. (%)										
Acute leukemia	139 (45)	0 (0)	108 (37)	87 (39)	63 (38)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CML	20 (6)	0 (0)	14 (5)	14 (6)	11 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MDS/MPS	53 (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	32 (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	26 (8)	3 (60)	64 (22)	36 (16)	10 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nonmalignant diseases	13 (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 (60)	0 (0)	121 (42)	113 (50)	94 (57)	0 (0)	0 (0)	0 (0)	0 (0)	3 (27)
2013	53 (17)	0 (0)	38 (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 (5)	0 (0)	11 (4)	13 (6)	12 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2021	33 (11)	5 (100)	111 (36)	52 (23)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Measures completed - no. (%)										
FACT-BMT and SF-36	256 (83)	0 (0)	168 (58)	155 (70)	129 (78)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FACT-BMT only	7 (2)	0 (0)	1 (<1)	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)

Variable	Baseline	30 day	100 day	6 months	1 year	2 year	3 year	4 year	5 year	≥6 year
PROMIS only	0 (0)	5 (100)	122 (41)	0 (0)	19 (12)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
PROMIS + CoST	47 (15)	0 (0)	0 (0)	65 (28)	13 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median follow-up (range), months	96 (3-107)	N/A	95 (0-107)	95 (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)	70 (6-95)	84 (39-111)