Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR HEALTH SERVICES AND INTERNATIONAL STUDIES
Houston, TX
Thursday, February 21, 2019, 2:45 – 4:45 PM

Co-Chair:	**Shahrukh K. Hashmi, MD, MPH, Mayo Clinic;** **Telephone: 507-284-3417; E-mail: hashmi.shahrukh@mayo.edu**
Co-Chair:	**Nandita Khera, MD, Mayo Clinic Arizona, Phoenix, AZ;** **Telephone: 480-342-0195; Email: khera.nandita@mayo.edu**
Co-Chair:	**William A. Wood, MD, MPH, University of North Carolina, Chapel Hill, NC;** **Telephone: 919-843-6517; E-mail: william_wood@med.unc.edu**
Scientific Director:	**Wael Saber, MD, MS, CIBMTR Statistical Center;** **Telephone: 414-805-0677; Email: wsaber@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center;** **Telephone: 414-955-8687; E-mail: ruta@mcw.edu**
Statistician:	**Naya He, MPH, CIBMTR Statistical Center;** **Telephone: 414-805-0685; E-mail: nhe@mcw.edu**

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1. **Introduction**
   a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
   b. Instructions for sign-in and voting
2. **Accrual summary** (Attachment 2)
3. **Presentations, published or submitted papers**
   a. **HS12-02** K Paulson, R Brazauskas, N Khera, N He, N Majhail, G Akpek, M Aljurf, D Buchbinder, L Burns, S Beattie, C Freytes, A Garcia, J Gajewski, T Hahn, J Knight, C LeMaistre, H Lazarus, D Szwajcer, M Seftel, B Wirk, W Wood, W Saber. Inferior Access to Allogeneic Transplant in Disadvantaged Populations: A CIBMTR Analysis. **Submitted**
   b. **HS15-01** D K. Buchbinder, R Brazauskas, K Bo-Subait, K K. Ballen, T E. Hahn, T D John, S K Parsons, S K. Hashmi, N Khera, W A. Wood, W Saber**.** Lost to Follow-up Rates Are Higher in Pediatric Than Adult Survivors, but Not By Transplant Type: A Report from the Center for International Blood and Marrow Transplant Research. **Poster presentation at ASH in San Diego, CA, December 2018**
   c. **HS15-02** K O Bona, R Brazauskas, N He, L E. Lehmann, J Wolfe, J Dalal, S K. Hashmi, T E. Hahn, N Khera, W A. Wood, C Duncan, W Saber. Area-Based Socioeconomic Status and Pediatric Allogeneic Hematopoietic Stem Cell Transplantation Outcomes: A CIBMTR Analysis. **Oral presentation at ASH in San Diego, CA, December 2018**
   d. **HS16-02** J Tay, R Brazauskas, N He, S Beattie, C Bredeson, J Dalal, S K. Hashmi, T E. Hahn, N Khera, W A. Wood, W Saber. The Impact of Marital Status on Hematopoietic Stem Cell Transplant (HCT) Recipient Outcomes: A Surrogate for Consistent Caregiver. a CIBMTR Registry Study. **Poster presentation at ASH in San Diego, CA, December 2018**
   e. **HS17-01** S Hong, R Brazauskas, K Herbert, T E. Hahn, N S. Majhail, S J. Lee, D Rizzo, S K. Hashmi, N Khera, W A. Wood, W Saber. Community Health Status and Its Association with Patient Outcome Post Allogeneic Hematopoietic Cell Transplantation. **Oral presentation at TCT in Houston, TX, February 2019**

4. **Studies in progress** (Attachment 3)
   a. **HS14-01** Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia (S Arnold/ R Aplenc/M Pulsipher/P Satwani) **Manuscript preparation**
   b. **HS15-01** Who is lost to follow-up in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry? (D Buchbinder/T Hahn/K Ballen/ W Saber/ S Parsons) **Manuscript preparation**
   c. **HS15-02** Impact of socioeconomic status on pediatric stem cell transplant outcomes (K Bona/ J Wolfe/C Duncan/ L Lehmann) **Manuscript preparation**
   d. **HS16-01** Trends in Utilization and Outcomes of Autologous and Allogeneic Hematopoietic cell Transplantation in Racial and Ethnic Minorities (N Khera/ T Hahn/ S Ailawadhi / W Saber) **Protocol Development**
   e. **HS16-02:** The Impact of Marital Status on Hematopoietic Stem Cell Transplant Recipient Outcomes: A surrogate for consistent caregiver (S M Beattie/ J Tay/ C Bredeson) **Manuscript preparation**
   f. **HS16-03** Relationship of Race/Ethnicity and Survival after Single and Double Umbilical Cord Blood Transplantation (K Ballen) **Protocol Development**
   g. **HS17-01** Association of community health status and center survival for allogeneic hematopoietic cell transplantation (S Hong/ N Singh Majhail) **Datafile preparation**
5. **CIBMTR strategic initiative: Fostering international collaboration**
   a. **PROP 1811-31** Haploidentical stem cell transplantation for malignant and non-malignant hematological diseases in patients without sibling donor: a multicenter prospective longitudinal study of the Brazilian bone marrow transplantation study group (Nelson Hamerschlak/ Mariana Kerbauy/Anrezea Riberio) (Attachment 4)
   b. **PROP 1811-116** Outcomes after allogeneic stem cell transplants performed in Brazil from HLA-matched siblings, unrelated and mismatched related donors. Retrospective study on behalf of the Brazilian Bone Marrow Transplantation Society (SBTMO), GEDECo (Brazil-Seattle Transplant-related complications Consortium), Hospital Israelita Albert Einstein (AmigoH), Associação da Medula Óssea do Estado de São Paulo (Ameo), Program Nacional de Apoio à Atenção Oncológica (Pronon), and CIBMTR (Adriana Seber/ Nelson Hamerschlak/ Mary Flowers/ Marcelo Pasquini) (Attachment 5)
   c. **PROP 1811-32** Comparing outcomes of myeloablative T-replete haploidentical transplantation with PT-CY protocol and ATG+G-CSF Protocol in patients with cytogenetic intermediate/high risk acute myeloid leukemia in first complete remission (Xiao-Jun Huang) (Attachment 6)
6. **Future/proposed studies**
   a. **PROP 1811-02** Outcomes of autologous stem cell transplantation for patients with multiple myeloma from rural America (Siddhartha Ganguly) (Attachment 7)
   b. **PROP 1811-10** Relative mortality risk in AYA vs younger and older survivors of allogeneic HCT for acute leukemia (Seth Rotz/ Rabi Hanna/ Navneet Majhail) (Attachment 8)
   c. **PROP 1811-53** Factors associated with clinical trial participation among HSCT patients: a CIBMTR Analysis (Tamryn Gray, Areej El-Jawahri) (Attachment 9)
   d. **PROP 1811-114** Incidence and Predictors of Post-Transplant Emotional Distress in Patients Undergoing Hematopoietic Cell Transplant (Neel Bhatt/ Heather Tecca/ Aksha Sharma/ Bronwen E. Shaw) (Attachment 10)
   e. **PROP 1811-130** Socioeconomic factors and their impact on non-relapse mortality, GVHD and GVHD survival among patients who received an allogeneic transplant for AML (James Martin/ Henry Fung) (Attachment 11)

Dropped proposed studies

a. **PROP 1811-15** Comparison of specific ethnic population (Pakistan) with western population for GVHD outcomes. *Dropped due to feasibility.*
b. **PROP 1811-44** Evaluating the effect of delay in allogeneic stem cell transplantation due to donor unavailability on recipient stem cell transplantation outcomes**.** *Dropped due to feasibility and small sample size*.
c. **PROP 1811-84** Evaluation of Factors that Contribute to Cancellation or Delay of planned Hematopoietic Stem Cell Transplantation (HSCT). *Dropped due to feasibility and small sample size*.
d. **PROP 1811-87** Variations in the use of myeloablative versus reduced intensity conditioning in different countries among patients more than 50 years of age using the CIBMTR database. *Dropped due to low scientific impact.*
e. **PROP 1811-149** Cost Effective Analysis of Allogeneic bone marrow transplantation with cyclophosphamide–total body irradiation versus Bulsulphan–cyclophosphamide conditioning regimens. *Dropped due to feasibility.*
f. **PROP 1811-177** Predictors of Cost of Initial Hospitalization for Pediatric Allogeneic Hematopoietic Cell Transplantation. *Dropped due to overlapped with previous studies.*

7. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR HEALTH SERVICES AND INTERNATIONAL STUDIES
Salt Lake City, UT
Saturday, February 24, 2018, 2:45 – 4:45 PM

Co-Chair:	**Jignesh Dalal, MD; Rainbow Babies and Children's Hospital, Cleveland, OH; Telephone: 216-983-1027; E-mail: jdalal2002@gmail.com**
Co-Chair:	**Theresa Hahn, PhD, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Telephone: 716-845-5819; E-mail: Theresa.hahn@roswellpark.org**
Co-Chair:	**Nandita Khera, MD, Mayo Clinic Arizona, Phoenix, AZ; Telephone: 480-342-0195; Email: khera.nandita@mayo.edu**
Co-Chair:	**William Wood, MD, MPH, University of North Carolina, Chapel Hill, NC; Telephone: 919-843-6517; E-mail: william_wood@med.unc.edu**
Scientific Director:	**Wael Saber, MD, MS, CIBMTR Statistical Center; Telephone: 414-805-0677; Email: wsaber@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center; Telephone: 414-955-8687; E-mail: ruta@mcw.edu**
Statistician:	**Naya He, MPH, CIBMTR Statistical Center; Telephone: 414-805-0685; E-mail: nhe@mcw.edu**

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1. Introduction

a. Minutes and Overview Plan from February 2017 meeting (Attachment 1)
b. Instructions for sign-in and voting

The meeting was called to order at 2:45pm by Dr. Nandita Khera. She described the goals, expectations, and limitations of the committee, and she gave an introduction of the data that are collected in CRF and TED database. She also explained the voting process, role of working committee members, rules of authorship and statistical hour allocation, and importance of the conference evaluations.

Dr. Nandita Khera announced that Dr. Shahrukh Hashmi has been appointed as the co-Chair of the Health Services and International Studies Working Committee starting March 1st. Meanwhile, Dr. Theresa Hahn and Dr. Jignesh Dalal will be completing their 5-year term as co-Chair at the end of this month. On behalf of the committee, Dr. Saber thanked Dr. Theresa Hahn and Dr. Jignesh Dalal for their leadership and service to the committee.

The minutes of the February 2017 meeting were approved without modifications.

2. Accrual summary (Attachment 2)

Due to the full agenda, the accrual summary of registration and research cases between 2008 and 2017 were not presented to the committee but were available as part of the Working Committee attachments.

3. Presentations, published or submitted papers

Due to the full agenda, the 2017 presentations and published papers were mentioned, but not presented. Two papers were published, one submitted.

a. **HS13-01** A El-Jawahri, Y-B Chen, R Brazauskas, N He, S J. Lee, J Knight, N Majhail, D Buchbinder, R M. Schears, B M. Wirk, W A. Wood, I Ahmed, M Aljurf, J Szer, S M. Beattie, M Battiwalla, C Dandoy, M-Angel Diaz, A D'Souza, C O. Freytes, J Gajewski, U Gergis, S K. Hashmi, A Jakubowski, R T. Kamble, T Kindwall-Keller, H M. Lazarus, A K. Malone, D I. Marks, K Meehan, B N. Savani, R F. Olsson, D Rizzieri, A Steinberg, D Speckhart, D Szwajcer, H Schoemans, S Seo, C Ustun, Y Atsuta, J Dalal, C Sales-Bonfim, N Khera, T Hahn, W Saber. The Impact of pre-transplant depression on the outcomes of allogeneic and autologous hematopoietic stem cell transplantation. **Cancer. 2017 Jan 19. doi: 10.1002**

b. **HS13-02** SD. Arnold, R Brazauskas, N He, Y Li, R Aplenc, Z Jin, M Hall, Y Atsuta, J Dalal, T Hahn, N Khera, C Bonfim, N S. Majhail, M Angel Diaz, C O. Freytes, W A. Wood, B M. Savani, R T. Kamble, S Parsons, I Ahmed, K Sullivan, S Beattie, C Dandoy, R Munker, S Marino, M Bitan, H Abdel-Azim, M Aljurf, R F. Olsson, S Joshi, D Buchbinder, M J. Eckrich, S Hashmi, H Lazarus, D I. Marks, A Steinberg, A Saad, U Gergis, L Krishnamurti, A Abraham, H G. Rangarajan, M Walters, J Lipscomb, W Saber, P Satwani. Clinical Risks and Healthcare Utilization of Hematopoietic Cell Transplantation for Sickle Cell Disease in the U.S. Using Merged Databases. **Haematologica. 2017 Nov;102(11):1823-1832. doi: 10.3324**

c. **IS10-01** W Allen Wood, R Brazauskas, Zhen-H Hu, H Abdel-Azim, I A Ahmed, M Aljurf, S Badawy, A Beitinjaneh, G Biju, D Buchbinder, J Cerny, L Dedeken, M Diaz-Perez, C Freytes, S Ganguly, U Gergis, D G. Almaguer, A Gupta, G Hale, S K Hashmi, Y Inamoto, R T Kamble, A Kehinde, T Kindwall-Keller, J Knight, L Kumar, Y Kuwatsuka, J Law, H Lazarus, C LeMaistre, R Olsson, M Pulsipher, B N Savani, K R Schultz, A A Saad, M Seftel, S Seo, T C Shea, A Steinberg, K Sullivan, D Szwajcer, B Wirk, J Yared, A Yong, J Dalal, T Hahn, N Khera, C Sales-Bonfim, Y Atsuta, W Saber. Country-level Macroeconomic Indicators predict Early Post-Allogeneic Hematopoietic Cell Transplantation Survival in Acute Lymphoblastic Leukemia: A CIBMTR Analysis. **Submitted.**

4. Studies in progress (Attachment 3)

The progress of the ongoing studies during the past year was not presented in order to provide reasonable time to the new proposals for presentation and discussion. A summary of the progress was provided as an attachment to the committee members.

a. **HS12-02** Rates of Transplantation in Urban vs Rural Patients: Are Rural Patients Less Likely to Receive an Allogeneic Transplant? (K Paulson/ M Seftel/ D Szwajcer) **Manuscript preparation**

b. **HS14-01** Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia (S Arnold/ R Aplenc/M Pulsipher/P Satwani) **Manuscript preparation**

c. **HS15-01** Who is lost to follow-up in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry? (D Buchbinder/T Hahn/K Ballen/ W Saber/ S Parsons) **Analysis**

d. **HS15-02** Impact of socioeconomic status on pediatric stem cell transplant outcomes (K Bona/ J Wolfe/ C Duncan/ L Lehmann) **Data file preparation**

e. **HS16-01** Trends in Utilization and Outcomes of Autologous and Allogeneic Hematopoietic cell Transplantation in Racial and Ethnic Minorities (N Khera/ T Hahn/ S Ailawadhi / W Saber) **Protocol Development**

f. **HS16-02:** The Impact of Marital Status on Hematopoietic Stem Cell Transplant Recipient Outcomes: A surrogate for consistent caregiver (S M Beattie/ J Tay/ C Bredeson) **Data file preparation**

g. **HS16-03** Relationship of Race/Ethnicity and Survival after Single and Double Umbilical Cord Blood Transplantation (K Ballen) **Protocol Development**

h. **HS17-01** Association of community health status and center survival for allogeneic hematopoietic cell transplantation (S Hong/ N Singh Majhail) **Protocol Development**

5. Future/proposed studies

Dr. Theresa Hahn, Dr. William Wood, and Dr. Jignesh Dalal led this section.

a. **PROP 1707-02** Patient outcomes in the first five years after centers initiate alternative donor hematopoietic cell transplant programs for hematologic malignancy (Mary-Elizabeth Muchmore Percival/William Allen Wood) (Attachment 4)
Dr. Percival presented this study. The specific aims of this study are two-fold: 1. To characterize center-level trends in the use of alternative donor transplantation with umbilical cord blood and/or haploidentical HCT over time. 2. To evaluate the association of center-level alternative donor transplantation experience and volume with center-level treatment-related mortality, disease-free survival, and overall survival following alternative donor transplantation. Comments received about how to get the characteristics of the transplant patients and how centers select patients. Other meeting participants raised concerns about how to deal with centers that changed the transplant type over time and incorporate it into the analysis.

b. **PROP 1711-26** International collaborative study to compare the prognosis for acute leukemia patients transplanted with intensified myeloablative regimens (Yasuyuki Arai/Yoshiko Atsuta/Shingo Yano/Shinichi Kako) (Attachment 5)
Dr. Arai presented this study. The specific aims of this study are three-fold: 1. To determine the precise type and frequency of intensified myeloablative regimens used in the conditionings for acute leukemia. 2. To confirm the prognostic differences between the conventional and intensified myeloablative regimens in each patient's characteristic such as age, comorbidity, disease risk/status, donor source, GVHD prophylaxis and so on. 3.To compare the merit/demerit of intensified regimen between the US and Japan. Comments received about the body shape difference between Japanese people and US people and how to adjust for graft source difference between these two populations. This proposal was accepted by the working committee and leadership.

c. **PROP 1711-27** Fludarabine/busulfan versus fludarabine/melphalan conditioning in patients with acute lymphoblastic leukemia; An international collaborative study of cohorts from the US and Japan (Yasuyuki Arai/Yoshiko Atsuta/Shinichi Kako/Koji Kawamura) (Attachment 6)
Dr. Arai presented this study. The specific aim of this study is to compare the overall survival, relapse, and non-relapse mortality between the two widely used RIC regimens (Flu/ivBu vs. Flu/Mel) in patients with ALL treated either in the US or Japan. Comments received on carefully checking the same conditioning that used in different time period since less toxicity conditioning regimens are using recent years and whether MRD information is collected the same between US and Japan database.

d. **PROP 1711-43** Racial differences in long term survivor outcomes after Allogeneic hematopoietic cell transplantation (Brandon J. Blue/Navneet Majhail) (Attachment 7)
Dr. Blue presented this study. The primary aim of this study is to evaluate long-term outcomes by ethnicity/race after allogeneic HCT in recipients with hematologic malignancies who have survived for

at least 2 years in remission after transplantation. Probability of OS, NRM and relapse at 7 years post-transplant (5 years after cohort inclusion, since patients need to be in remission for 2 years) will be estimated in White, Black, Hispanic, Asian/Pacific Islander, and other race category patients. Comments received about if only analyze transplant patients who survived for 2 years will lose information about patients who developed early post transplant complications in different races; how to deal with center effect. This proposal was accepted by the working committee and leadership.

e. **PROP 1711-109** Racial/ethnic disparities in receipt of hematopoietic cell transplantation and subsequent resource utilization in children with acute leukemia (Lena Winestone/ Richard Aplenc/ Kelly Getz) (Attachment 8)
Dr. Winestone presented this study. The specific aims of this study are three-fold: 1. Among a cohort of pediatric acute leukemia patients, compare the rates of hematopoietic cell transplant by donor source between racial/ethnic minorities compared to the White non-Hispanic populations (accounting for SES). 2. Among those who received stem cell transplants, compare resource utilization by race and ethnicity (accounting for donor source). 3. Among those who received stem cell transplants, evaluate the role of pre-transplant resource utilization in predicting post-transplant resource utilization (and outcomes) by race and ethnicity. Comments received regarding the definition of race or ethnic, if it's center reported or patient reported; if there are discrepancy of race information between two data base will do sensitivity analysis. Dr. Winestone also introduced the insurance information that PHIS database collected. This proposal was accepted by the working committee and leadership.

f. **PROP 1711-113** Do patient outcomes following hematopoietic cell transplantation vary in the time period before and immediately after introduction of an electronic health record? (Mary-Elizabeth Muchmore Percival/ William Allen Wood) (Attachment 9)
Dr. Percival presented this study. The specific aims of this study are two-fold: 1. To compare unadjusted survival outcomes (overall survival, relapse-free survival, and treatment-related mortality) in HCT recipients in the 12-month periods before and after EHR implementation (so-called "go live" dates). 2. To compare adjusted survival outcomes in the same population using a multivariable model to control for relevant factors. Comments received about how to deal with the difference of pattern of adoption on electronic record entry in each individual center; how to measure how much time hospital staffs spend on after hours on EHR and how to compare it to before; the challenge on the survey design.

g. **PROP 1711-130** Race, ethnicity and outcomes of allogeneic stem cell transplantation for acute lymphoblastic leukemia in Hispanic patients (Anne S. Renteria/ Luis Isola/ Nina A. Bickell) (Attachment 10)
Dr. Renteria presented this study. The specific aim of this study is to investigate if the differences in outcomes experienced by Hispanics vs Non-Hispanics with ALL can be explained by disease-related characteristics, less access to HCT, or both. Comments received about why only focus on pediatric ALL patients; concerns on the difference of the self-race identification between first, second and third generations. One meeting participant suggested expanding the study population to worldwide to get more information. Dr Hahn expressed concern regarding why use SPARCS database since there are some limitations in this database.

Dropped proposed studies

a. **PROP 1706-01** Deconstructing the Biological Impact of Race on Outcomes after Myeloablative Conditioning and Hematopoietic Stem Cell Transplantation for Pediatric Patients with Acute Leukemia. *Dropped due to overlapped with previous studies.*

b. **PROP 1711-54** Trends and cost prediction in pediatric allogeneic hematopoietic cell transplant. *Dropped due to overlapped with previous studies.*
c. **PROP 1711-58** Exploring the Transplant Center Volume-Outcomes relationship in acute leukemias. Dropped due to overlapped with previous studies.
d. **PROP 1711-87** Bone Marrow Transplant Utilization and Survival Outcomes among Adults by Appalachian and Non-Appalachian Areas of the United States. Dropped due to overlapped with previous studies.
e. **PROP 1711-110** Effect of race on outcomes following HLA- haploidentical transplant with post-transplant Cytoxan for hematological malignancies. Dropped due to small sample size.

6. Other Business

Working Committee Overview Plan for 2018-2019	
a.	**HS12-02** Rates of Transplantation in Urban vs Rural Patients: Are Rural Patients Less Likely to Receive an Allogeneic Transplant? - We anticipate a submitted manuscript by June 2018. No statistical hours have been allocated to accomplish this goal.
b.	**HS14-01** Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia- We anticipate a submitted manuscript by June 2018. 80 statistical hours have been allocated to accomplish this goal.
c.	**HS15-01** Who is lost to follow-up in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry? - We expect to submit the final manuscript by June 2019. 150 statistical hours have been allocated to accomplish these goals.
d.	**HS15-02** Impact of Socioeconomic Status on Pediatric Stem Cell Transplant Outcomes – We anticipate having a final dataset for analysis by April 2018. After circulating to the Writing Committee for feedback, we expect to submit the final manuscript by June 2019. 250 statistical hours have been allocated to accomplish these goals.
e.	**HS16-01** Trends in Utilization and Outcomes of Autologous and Allogeneic Hematopoietic Cell Transplantation in Racial and Ethnic Minorities – We anticipate preparing the data file by June 2019. 160 statistical hours have been allocated to accomplish these goals.
f.	**HS16-02** The Impact of Marital Status on Hematopoietic Stem Cell Transplant Recipient Outcomes: A surrogate for consistent caregiver - We anticipate preparing the data file by April 2018 and submit the manuscript by June 2019. 220 statistical hours have been allocated to accomplish these goals.
g.	**HS16-03** Relationship of Race/Ethnicity and Survival after Single and Double Umbilical Cord Blood Transplantation - We anticipate having the protocol finalized by June 2018. We further anticipate preparing the data file by June 2019. 240 statistical hours have been allocated to accomplish these goals.
h.	**HS17-01** Association of community health status and center survival for allogeneic hematopoietic cell transplantation-- We anticipate having the protocol finalized by June 2018. We further anticipate preparing the data file by June 2019. 160 statistical hours have been allocated to accomplish these goals.

Oversight Assignments for Working Committee Leadership (March 2018)	
William Wood	**HS14-01:** Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia
	HS15-02 Impact of Socioeconomic Status on Pediatric Stem Cell Transplant Outcomes
	HS16-03 Relationship of race/ethnicity and survival after single and double umbilical cord blood transplantation
	HS17-01 Association of community health status and center survival for allogeneic hematopoietic cell transplantation
Nandita Khera	**HS15-01** Who is lost to follow-up in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry?
	HS16-01 Trends in utilization and outcomes of autologous and allogeneic hematopoietic cell transplantation in racial and ethnic minorities
	HS16-02 The impact of marital status on hematopoietic stem cell transplant recipient outcomes: a surrogate for consistent caregiver
Shahrukh Hashmi	**HS18-01** International collaborative study to compare the prognosis for acute leukemia patients transplanted with intensified myeloablative regimens
	HS18-02 Racial differences in long term survivor outcomes after Allogeneic hematopoietic cell transplantation
	HS18-03 Racial/ethnic disparities in receipt of hematopoietic cell transplantation and subsequent resource utilization in children with acute leukemia

Accrual Summary for the Health Services and International Studies Working Committee

Table 1. Characteristics of recipients who underwent a first allogeneic transplant registered with the CIBMTR

Characteristic	TED N (%)	CRF N (%)
Number of patients	236553	101722
Number of centers	637	563
Age at transplant, years		
Median	37 (0-88)	32 (<1-88)
0-9	33711 (14)	17367 (17)
10-19	30401 (13)	15089 (15)
20-29	31676 (13)	14700 (14)
30-39	35164 (15)	15653 (15)
40-49	39459 (17)	15691 (15)
50-59	37697 (16)	13119 (13)
60-69	24941 (11)	8664 (9)
70+	3496 (1)	1439 (1)
Missing	8 (<1)	0
Recipient gender		
Male	138391 (59)	59716 (59)
Female	97896 (41)	42001 (41)
Missing	266 (<1)	5 (<1)
Recipient race		
Caucasian	159513 (67)	81303 (80)
African-American	10887 (5)	5653 (6)
Asian	17516 (7)	7771 (8)
Pacific islander	448 (<1)	204 (<1)
Native American	718 (<1)	356 (<1)
Other	8374 (4)	3933 (4)
Unknown	39097 (17)	2502 (2)
Disease		
Acute myelogenous leukemia	74495 (31)	28740 (28)
Acute lymphoblastic leukemia	40701 (17)	16935 (17)
Other leukemia	6051 (3)	2253 (2)
Chronic myelogenous leukemia	28960 (12)	14792 (15)
Myelodysplastic/myeloproliferative disorders	27558 (12)	12294 (12)
Other acute leukemia	2604 (1)	973 (<1)
Non-Hodgkin lymphoma	16164 (7)	5873 (6)
Hodgkin lymphoma	1540 (<1)	555 (<1)
Plasma cell disorder/Multiple Myeloma	3275 (1)	1334 (1)

Characteristic	TED N (%)	CRF N (%)
Other Malignancies	1168 (<1)	498 (<1)
Breast Cancer	182 (<1)	93 (<1)
Severe aplastic anemia	13603 (6)	7031 (7)
Inherited abnormalities erythrocyte differentiation or function	9384 (4)	4913 (5)
SCID and other immune system disorders	5937 (3)	2968 (3)
Inherited abnormalities of platelets	205 (<1)	105 (<1)
Inherited disorders of metabolism	2618 (1)	1516 (1)
Histiocytic disorders	1587 (<1)	719 (<1)
Autoimmune Diseases	113 (<1)	43 (<1)
Other diseases	408 (<1)	87 (<1)
Year of transplant		
<1985	4898 (2)	4507 (4)
1985-1989	10635 (4)	9497 (9)
1990-1994	22860 (10)	14686 (14)
1995-1999	35798 (15)	16632 (16)
2000-2004	40500 (17)	16853 (17)
2005-2009	40118 (17)	17778 (17)
2010-2014	47160 (20)	11181 (11)
2015-2018	34584 (15)	10588 (10)
Education		
No primary education	NA	44 (<1)
Less than primary or elementary education		67 (<1)
Primary of elementary education		683 (<1)
Lower secondary education		656 (<1)
Upper secondary education		9949 (10)
Post-secondary, non-tertiary education		3740 (4)
Tertiary education, Type A		7330 (7)
Tertiary education, Type B		1559 (2)
Advance research qualification		1938 (2)
Age<18 years old		29350 (29)
Missing		46406 (46)
Health insurance		
No insurance	NA	3673 (4)
Medicaid		8502 (8)
Medicare		4933 (5)
Disability insurance		661 (<1)
HMO		2446 (2)
Private health insurance		19205 (19)

Characteristic	TED N (%)	CRF N (%)
National health insurance		15145 (15)
VA/Military		721 (<1)
Other		3364 (3)
Missing		43072 (42)
Occupation		
Professional, technical, or related occupation	NA	17867 (18)
Manager, administrator or proprietor		3380 (3)
Clerical or related occupation		2384 (2)
Sales occupation		1803 (2)
Service occupation		2731 (3)
Skilled crafts or related occupation		2840 (3)
Equipment/vehicle operator or related occupation		1293 (1)
Laborer		1808 (2)
Farmer		348 (<1)
Member of military		277 (<1)
Homemaker		1352 (1)
Student		9713 (10)
Under school age		2398 (2)
Not previously employed		1744 (2)
Other, specify		7623 (7)
Missing		44161 (43)

Table 2. Characteristics of recipients who underwent a first autologous transplant registered with the CIBMTR

Characteristic	TED N (%)	CRF N (%)
Number of patients	229666	43468
Number of centers	601	445
Age at transplant, years		
Median	53 (<1-86)	50 (<1-83)
0-9	9990 (4)	2245 (5)
10-19	7458 (3)	1714 (4)
20-29	15794 (7)	3050 (7)
30-39	24253 (11)	5571 (13)
40-49	42794 (19)	9696 (22)
50-59	63239 (28)	11480 (26)
60-69	54999 (24)	8345 (19)
70+	11139 (5)	1367 (3)
Recipient gender		
Male	122998 (54)	21139 (49)
Female	106283 (46)	22322 (51)
Missing	385 (<1)	7 (<1)
Recipient race		
Caucasian	160427 (70)	34712 (80)
African-American	19726 (9)	4799 (11)
Asian	5590 (2)	1181 (3)
Pacific islander	272 (<1)	40 (<1)
Native American	622 (<1)	185 (<1)
Other	5495 (2)	1423 (3)
Unknown	37534 (16)	1128 (3)
Disease		
Acute myelogenous leukemia	8269 (4)	2423 (6)
Acute lymphoblastic leukemia	1608 (<1)	476 (1)
Other leukemia	792 (<1)	253 (<1)
Chronic myelogenous leukemia	713 (<1)	294 (<1)
Myelodysplastic/myeloproliferative disorders	283 (<1)	94 (<1)
Other acute leukemia	148 (<1)	31 (<1)
Non-Hodgkin lymphoma	63766 (28)	10615 (24)
Hodgkin lymphoma	23984 (10)	3725 (9)
Plasma cell disorder/Multiple Myeloma	87889 (38)	13589 (31)
Other Malignancies	18671 (8)	4271 (10)
Breast Cancer	22372 (10)	7502 (17)

Characteristic	TED N (%)	CRF N (%)
Autoimmune Diseases	688 (<1)	130 (<1)
Other diseases	483 (<1)	65 (<1)
Year of transplant		
<1985	31 (<1)	5 (<1)
1985-1989	2085 (<1)	672 (2)
1990-1994	19750 (9)	7335 (17)
1995-1999	41103 (18)	12804 (29)
2000-2004	35815 (16)	6205 (14)
2005-2009	37914 (17)	7674 (18)
2010-2014	51324 (22)	3951 (9)
2015-2018	41644 (18)	4822 (11)
Education		
No primary education	NA	13 (<1)
Less than primary or elementary education		35 (<1)
Primary of elementary education		306 (<1)
Lower secondary education		311 (<1)
Upper secondary education		5969 (14)
Post-secondary, non-tertiary education		2514 (6)
Tertiary education, Type A		4978 (11)
Tertiary education, Type B		1041 (2)
Advance research qualification		1602 (4)
Age<18 years old		3478 (8)
Missing		23221 (53)
Health insurance		
No insurance	NA	767 (2)
Medicaid		3276 (8)
Medicare		3784 (9)
Disability insurance		374 (<1)
HMO		2931 (7)
Private health insurance		9754 (22)
National health insurance		1743 (4)
VA/Military		632 (1)
Other		2062 (5)
Missing		18145 (42)
Occupation		
Professional, technical, or related occupation	NA	16240 (37)
Manager, administrator or proprietor		1497 (3)
Clerical or related occupation		1101 (3)

Characteristic	TED N (%)	CRF N (%)
Sales occupation		733 (2)
Service occupation		1370 (3)
Skilled crafts or related occupation		1316 (3)
Equipment/vehicle operator or related occupation		664 (2)
Laborer		899 (2)
Farmer		185 (<1)
Member of military		134 (<1)
Homemaker		571 (1)
Student		1044 (2)
Under school age		371 (<1)
Not previously employed		897 (2)
Other, specify		3225 (7)
Missing		13221 (30)

Table 3. Characteristics of recipients who received a first transplant from US centers reported to the CIBMTR, 2008 – 2018 (CRF)

Characteristic	Allogeneic N (%)	Autologous N (%)
Number of patients	24273	11231
Number of centers	182	176
Patient age, median	50 (<1-88)	58 (<1-82)
Education		
No primary education	16 (<1)	11 (<1)
Less than primary or elementary education	41 (<1)	16 (<1)
Primary of elementary education	95 (<1)	66 (<1)
Lower secondary education	439 (2)	265 (2)
Upper secondary education	4966 (20)	2821 (25)
Post-secondary, non-tertiary education	1655 (7)	959 (9)
Tertiary education, Type A	4588 (19)	2377 (21)
Tertiary education, Type B	1035 (4)	677 (6)
Advance research qualification	848 (3)	436 (4)
Age<18 years old	4868 (20)	655 (6)
Missing	5722 (24)	2948 (26)
Health insurance		
No insurance	408 (2)	151 (1)
Medicaid	4971 (20)	1523 (14)
Medicare	4064 (17)	2382 (21)
Disability insurance	504 (2)	298 (3)
Private health insurance	12944 (53)	6184 (55)
National health insurance	129 (<1)	9 (<1)
VA/Military	315 (1)	179 (2)
Other	474 (2)	119 (1)
Missing	464 (2)	386 (3)
Occupation		
Professional, technical, or related occupation	4637 (19)	2533 (23)
Manager, administrator or proprietor	2136 (9)	1096 (10)
Clerical or related occupation	1360 (6)	784 (7)
Sales occupation	1094 (5)	516 (5)
Service occupation	1663 (7)	1040 (9)
Skilled crafts or related occupation	1665 (7)	924 (8)
Equipment/vehicle operator or related occupation	800 (3)	476 (4)
Laborer	1062 (4)	625 (6)
Farmer	177 (<1)	110 (<1)

Characteristic	Allogeneic N (%)	Autologous N (%)
Member of military	174 (<1)	102 (<1)
Homemaker	568 (2)	286 (3)
Student	3905 (16)	474 (4)
Under school age	1494 (6)	299 (3)
Not previously employed	471 (2)	259 (2)
Other, specify	1132 (5)	482 (4)
Missing	1935 (8)	1225 (11)
Recipient zip code		
Not Available	1372 (6)	447 (4)
Available	22901 (94)	10784 (96)

Table 4. Characteristics of recipients who received allogeneic transplants registered with the CIBMTR by WHO region, 2008 – 2018(TED)

Characteristic	Africa	Latin Americas	US / Canada	Eastern Mediterranean	Europe	Southeastern Asia	Western Pacific
Number of patients	36	3532	69582	3053	13402	1498	6977
Number of centers	2	33	206	8	107	10	27
Age, in years							
<10	0	685 (19)	7441 (11)	1323 (43)	1103 (8)	482 (32)	845 (12)
10-19	6 (17)	693 (20)	5936 (9)	709 (23)	955 (7)	370 (25)	826 (12)
20-29	6 (17)	552 (16)	5919 (9)	511 (17)	1410 (11)	212 (14)	788 (11)
30-39	2 (6)	547 (15)	6137 (9)	265 (9)	1506 (11)	204 (14)	906 (13)
40-49	7 (19)	485 (14)	9276 (13)	175 (6)	2284 (17)	131 (9)	1250 (18)
50-59	9 (25)	400 (11)	15840 (23)	60 (2)	3055 (23)	92 (6)	1522 (22)
60-69	6 (17)	140 (4)	16212 (23)	10 (<1)	2742 (20)	7 (<1)	812 (12)
≥70	0	30 (<1)	2821 (4)	0	347 (3)	0	28 (<1)
Gender							
Male	26 (72)	2097 (59)	40114 (58)	1795 (59)	7864 (59)	990 (66)	4046 (58)
Female	10 (28)	1435 (41)	29468 (42)	1258 (41)	5538 (41)	508 (34)	2931 (42)
Primary disease							
AML	13 (36)	928 (26)	26862 (39)	580 (19)	5386 (40)	270 (18)	2787 (40)
ALL	2 (6)	922 (26)	10990 (16)	526 (17)	2240 (17)	173 (12)	1460 (21)
CML	3 (8)	235 (7)	2390 (3)	105 (3)	477 (4)	57 (4)	182 (3)
Myelodysplastic disorders	7 (19)	386 (11)	11799 (17)	99 (3)	2431 (18)	101 (7)	1049 (15)
NHL	3 (8)	75 (2)	5489 (8)	19 (<1)	683 (5)	35 (2)	288 (4)
Hodgkin lymphoma	0	21 (<1)	360 (<1)	3 (<1)	70 (<1)	9 (<1)	27 (<1)
Multiple myeloma	0	3 (<1)	282 (<1)	8 (<1)	77 (<1)	1 (<1)	7 (<1)
Other malignancies	1 (3)	91 (3)	3398 (5)	47 (2)	720 (5)	19 (1)	262 (4)
Severe aplastic anemia	4 (11)	486 (14)	2589 (4)	375 (12)	494 (4)	220 (15)	519 (7)
Other non-malignancies	3 (8)	385 (11)	5423 (8)	1291 (42)	824 (6)	613 (41)	396 (6)
Donor type							
HLA-identical sibling	15 (42)	1988 (56)	21706 (31)	2332 (76)	4331 (32)	991 (66)	2673 (38)
Other Related donor	1 (3)	412 (12)	7369 (11)	408 (13)	749 (6)	305 (20)	826 (12)
Unrelated donor	20 (56)	1131 (32)	40497 (58)	313 (10)	7537 (56)	202 (13)	3477 (50)
Missing	0	1 (<1)	10 (<1)	0	785 (6)	0	1 (<1)
Graft type							
Bone Marrow	1 (3)	1911 (54)	15841 (23)	1579 (52)	2869 (21)	219 (15)	1304 (19)
Peripheral Blood	34 (94)	1427 (40)	46759 (67)	1186 (39)	9977 (74)	1278 (85)	5076 (73)
Cord Blood	1 (3)	193 (5)	6980 (10)	287 (9)	552 (4)	1 (<1)	592 (8)

Characteristic	Africa	Latin Americas	US / Canada	Eastern Mediterranean	Europe	Southeastern Asia	Western Pacific
Missing	0	1 (<1)	2 (<1)	1 (<1)	4 (<1)	0	5 (<1)
Year of transplant							
2008	5 (14)	188 (5)	4908 (7)	436 (14)	1612 (12)	56 (4)	491 (7)
2009	11 (31)	313 (9)	5465 (8)	460 (15)	1724 (13)	49 (3)	659 (9)
2010	8 (22)	385 (11)	5703 (8)	451 (15)	1715 (13)	31 (2)	761 (11)
2011	10 (28)	343 (10)	6216 (9)	220 (7)	1567 (12)	122 (8)	860 (12)
2012	1 (3)	409 (12)	6358 (9)	251 (8)	1561 (12)	136 (9)	828 (12)
2013	1 (3)	357 (10)	6828 (10)	209 (7)	1464 (11)	112 (7)	757 (11)
2014	0	325 (9)	6976 (10)	274 (9)	833 (6)	123 (8)	723 (10)
2015	0	315 (9)	7185 (10)	253 (8)	678 (5)	186 (12)	540 (8)
2016	0	312 (9)	7364 (11)	213 (7)	702 (5)	241 (16)	691 (10)
2017	0	311 (9)	7506 (11)	174 (6)	1285 (10)	267 (18)	461 (7)
2018	0	274 (8)	5073 (7)	112 (4)	261 (2)	175 (12)	206 (3)

Table 5. Allogeneic transplant recipients and centers by country registered with the CIBMTR, 2008-2018(TED)

Regions	N	Centers
Africa		
South Africa	36	2
Americas		
USA	65749	192
Argentina	311	6
Brazil	2761	13
Canada	3833	14
Chile	9	2
Venezuela	50	2
Mexico	69	3
Uruguay	44	3
Peru	88	1
Columbia	200	3
Eastern Mediterranean		
Saudi Arabia	1918	3
Egypt	20	2
Iran	671	1
Pakistan	444	2
Europe		
Austria	93	2
Belgium	870	6
Denmark	987	1
UK	1785	15
Finland	404	2
France	1086	10
Germany	2464	17
Ireland	157	1
Israel	880	7

Regions	N	Centers
Italy	546	7
Netherlands	555	8
Norway	69	1
Poland	374	4
Portugal	130	2
Spain	617	8
Sweden	818	4
Switzerland	549	3
Russia	91	1
Turkey	350	3
Greece	3	1
Czech Republic	460	3
Slovak Republic	114	1
Southeastern Asia		
India	1498	10
Thailand	21	1
Western Pacific		
Australia	2901	15
Korea	2659	3
New Zealand	697	4
Taiwan	62	1
Hong Kong	29	1
Singapore	629	3

Table 6. Number of patients who received a first allogeneic transplant registered with the CIBMTR between 2000 and 2018 by country

	CRF		TED	
Country	Malignant disease	Non-malignant disease	Malignant disease	Non-malignant disease
Argentina	100-500	<100	501-999	100-500
Australia	501-999	100-500	≥1000	501-999
Austria	<100	<100	100-500	<100
Belgium	100-500	<100	≥1000	100-500
Brazil	501-999	501-999	≥1000	≥1000
Canada	501-999	100-500	≥1000	501-999
Colombia	<100	<100	100-500	<100
Czech Republic	100-500	<100	501-999	<100
Denmark	100-500	<100	≥1000	100-500
Egypt	<100	NA	501-999	100-500
Finland	<100	<100	501-999	<100
France	100-500	<100	≥1000	100-500
Germany	≥1000	<100	≥1000	100-500
Hong Kong	<100	<100	100-500	<100
India	100-500	100-500	501-999	≥1000
Iran	100-500	100-500	≥1000	501-999
Ireland	100-500	<100	100-500	<100
Israel	100-500	<100	≥1000	100-500
Italy	<100	<100	≥1000	100-500
Japan	501-999	<100	501-999	<100
Korea	501-999	100-500	≥1000	501-999
Mexico	<100	<100	100-500	<100
Netherlands	<100	<100	501-999	<100
New Zealand	100-500	<100	501-999	100-500
Pakistan	<100	100-500	100-500	501-999

Country	CRF		TED	
	Malignant disease	Non-malignant disease	Malignant disease	Non-malignant disease
Peru	<100	<100	100-500	<100
Poland	100-500	<100	501-999	<100
Portugal	<100	<100	100-500	<100
Russia	<100	<100	100-500	<100
Saudi Arabia	501-999	501-999	≥1000	≥1000
Singapore	100-500	<100	501-999	<100
Slovak Republic	<100	<100	100-500	<100
South Africa	100-500	<100	100-500	<100
Spain	100-500	<100	≥1000	100-500
Sweden	100-500	<100	≥1000	100-500
Switzerland	<100	<100	≥1000	<100
Taiwan	<100	NA	100-500	<100
Turkey	<100	<100	501-999	<100
UK	100-500	100-500	≥1000	501-999
USA	≥1000	≥1000	≥1000	≥1000
Uruguay	<100	<100	100-500	<100
Venezuela	<100	<100	100-500	<100

Countries with <100 patients in both CRF and TED dataset are not included in this report.

Table 7. Number of patients who received a first autologous transplant registered to the CIBMTR between 2000 and 2018 by country

	CRF		TED	
Country	Malignant disease	Non-malignant disease	Malignant disease	Non-malignant disease
Argentina	100-500	NA	≥1000	<100
Australia	<100	<100	≥1000	<100
Austria	<100	NA	100-500	<100
Belgium	<100	NA	501-999	<100
Brazil	100-500	<100	≥1000	<100
Canada	501-999	<100	≥1000	<100
Colombia	NA	NA	100-500	<100
Czech Republic	<100	NA	501-999	<100
Finland	<100	NA	100-500	NA
France	<100	NA	501-999	<100
Germany	<100	<100	≥1000	<100
India	<100	NA	100-500	<100
Iran	<100	NA	100-500	<100
Israel	<100	<100	501-999	<100
Italy	<100	NA	≥1000	<100
Korea	<100	NA	501-999	<100
Mexico	<100	NA	100-500	<100
Netherlands	NA	NA	100-500	<100
New Zealand	<100	NA	100-500	<100
Poland	<100	NA	100-500	<100
Portugal	NA	NA	100-500	NA
Russia	<100	<100	100-500	<100
Saudi Arabia	<100	NA	501-999	<100
Singapore	100-500	<100	501-999	<100
South Africa	<100	NA	100-500	<100
Spain	<100	<100	≥1000	<100

	CRF		TED	
Country	Malignant disease	Non-malignant disease	Malignant disease	Non-malignant disease
Sweden	<100	NA	100-500	<100
Switzerland	NA	NA	100-500	<100
Taiwan	NA	NA	<100	NA
Thailand	NA	NA	<100	NA
Turkey	<100	NA	501-999	<100
UK	<100	NA	≥1000	<100
USA	≥1000	100-500	≥1000	501-999
Uruguay	100-500	NA	501-999	<100
Venezuela	<100	NA	100-500	NA

Countries with <100 patients in both CRF and TED dataset are not included in this report.

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TO: Health Services and International Studies Working Committee Members

FROM: Wael Saber, MD, MS; Scientific Director for Health Services and International Studies Working Committee

RE: Studies in Progress Summary

HS14-01 Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia (S Arnold/ R Aplenc/M Pulsipher/P Satwani) This study will describe inpatient health care utilization and adjusted costs of pediatric alloHCT recipients for acute leukemia change over time. The study protocol is under manuscript preparation phase. We expect to submit the manuscript by the end of June 2019.

HS15-01 Who is lost to follow-up in the center for international blood and marrow transplant research registry? (D Buchbinder/ T John/ T Hahn/ K Ballen/ W Saber/ S Parsons) This study will estimate the cumulative incidence of becoming lost to follow-up (LTFU) among hematopoietic cell transplant (HCT) recipients reported to the Center for International Blood and marrow Transplant Research (CIBMTR) registry. The study protocol is under manuscript preparation phase. We expect to submit the manuscript by the end of June 2019.

HS15-02 Impact of socioeconomic status on pediatric stem cell transplant outcomes (K Bona/J Wolfe/ C Duncan/ L Lehmann) First object of this study is to determine the relationship between family socioeconomic status and rates of graft-versus-host-disease in pediatric stem cell transplant. Second object of this study is to determine the relationship between family socioeconomic status and rates of post-transplant infection in pediatric stem cell transplant. The study protocol is under manuscript preparation phase. We expect to submit the manuscript by the end of June 2019.

HS16-01 Trends in Utilization and Outcomes of Autologous and Allogeneic Hematopoietic Cell Transplantation in Racial and Ethnic Minorities (N Khera/ T Hahn/ S Ailawadhi / W Saber) This study will evaluate the trends in utilization and clinical outcomes of autologous and allogeneic HCT in patients of different race/ ethnicity utilizing data collected by the Center for International Blood and Marrow Transplant Research (CIBMTR). This study is in the protocol development phase. The goal is to have the protocol completed by then end of June 2019.

HS16-02 The Impact of Marital Status on Hematopoietic Stem Cell Transplant Recipient Outcomes: A surrogate for consistent caregiver (S M Beattie/ J Tay/ C Bredeson) This study will examine marital status (surrogate for caregiver) on HSCT survival for both autologous and allogeneic transplants, include important HSCT covariates as well as include multi-center data. The study protocol is under manuscript preparation phase. We expect to submit the manuscript by the end of June 2019.

HS16-03 Relationship of Race/Ethnicity and Survival after Single and Double Umbilical Cord Blood Transplantation (K Ballen) This study will compare overall and disease free survivals for White, Hispanic,

Asian, and Black patients after single and double umbilical cord blood transplantation; and determine if survival for White, Hispanic, Asian, and Black patients is comparable if transplanted with units of similar cell dose and HLA match. This study is in the protocol development phase. The goal is to have the datafile ready by then end of June 2019.

HS17-01 Association of community health status and center survival for allogeneic hematopoietic cell transplantation (S Hong/ N Majhail/ T Hahn/ S Lee) This study will evaluate association between social determinants of health for community where patients reside (assessed by *County Health Rankings* based on zip code of patient residence) and patient 1-year overall survival after allogeneic HCT. This study is in datafile preparation phase. The goal is finish the analysis by the end of June 2019.

Proposal: 1811-31

Title:
Haploidentical Stem Cell Transplantation for malignant and non-malignant hematological diseases in patients without sibling donor: A multicenter prospective and longitudinal study of the Brazilian bone marrow transplantation study group (SBTMO)

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Hypothesis:
In Brazil, Overall Survival Haploidentical Stem Cell Transplant with Posttransplant Cyclophosphamide (post-Cy) is not inferior than Matched Related or Unrelated Donor Stem Cell Transplant without Post-Cy.

Specific aims:

- Primary objective: Determine if the 1year Overall Survival after Hematopoietic Stem Cell Transplantation (HCT) plus post-Cy from Haploidentical related donor (Haplo – HCT) for acute myeloid leukemia, Hodgkin Disease (Study Arm 1) and Severe Aplastic Anemia (Arm 2) is not inferior compared to matched related or unrelated allogeneic HCT donor with 10/10 and 9/10 compatibility.
- Secondary objectives: Compare the 1year incidences of Acute GVHD (grades II-IV, and III-IV), Chronic GVHD (NIH moderate to severe), Non-relapse-related Mortality, Disease Relapse (only Arm 1), time to Neutrophil engraftment, time to Platelet Engraftment and Event-free survival between recipients of Haplo plus Post-CY and of matched related and unrelated donors. Events for disease-free survival (DFS) will be defined as death, disease relapse, or disease progression, whichever occurred first. The event for overall survival (OS) will be defined as death from any cause.

Scientific impact:
Determining if the 1 year incidences of acute and chronic GVHD, relapse-free survival (GRFS), and chronic GVHD, relapse-free survival (CRFS) after related haploidentical plus post-Cy prophylaxis are not inferior compared to other donors (10x10 and 9x10 match related and unrelated compatibility reported to the CIBMTR) using other GVHD prophylaxis will be decisive in changing clinical practice in Brazilian patients who need an allogeneic HCT for AML, HD and aplastic anemia.

Scientific justification:
Initiatives of haploidentical transplants initiated in the 1970s and were catastrophic, with graft versus host disease (GVHD) incidence above 70% and 20% of graft failure[(1)]. In the 1980s, with the use of T-cell depletion with sheep erythrocytes, this methodology started to be accepted [(1)]. In 1994, the Italian group showed a decreased risk of rejection using high doses of cells ("mega dose": $13.8x10^6$ CD34 with $1x10^4$ CD3 / kg)[(2)]. The Duke University, led by Nelson Chao, presented a protocol with no selection of CD34 cells "in vitro" but with "in vivo" depletion using Campath® in the conditioning regimen[(3)]. But the major breakthrough came in 2008, when Baltimore's Johns Hopkins Hospital, led by Ephraim Fuchs, consolidated the use of cyclophosphamide on days +3 and +4 post-transplant with in vivo T-cell depletion[(4)].
The scheduled administration of posttransplant cyclophosphamide inhibits both graft rejection and the development of GVHD as it excludes the highly aloreactive T cell clones, which in the absence of any other immunosuppressive therapy, would become activated and proliferate in the first days after transplantation causing severe DECH[(5)(6)]. Studies of the Seattle Group and Johns Hopkins University in recent years have

shown that haploidentical transplantation for treatment of high-risk hematologic malignancies can graft quickly and steadily after non-myeloablative and myeloablative conditioning[7][4].

After that, many studies have compared haplo-HSCT with other types of transplant. In 2013, Bashey A et al compared 53 patients with hematological malignancies submitted to haplo-HCT, 117 patients submitted to matched related donor (MRD) and 101 patients submitted to matched unrelated donor (MUD) and they found similar results in terms of nonrelapse mortality, grades 3 to 4 acute GVHD, adjusted 24-month overall survival and disease free survival, but extensive chronic GVHD occurred in fewer patients of the haploidentical group[8]. In 2015, a review of retrospective studies of haplo-HCT compared to MRD in adults with haematological malignancies showed no differences regarding acute GVHD, relapse-related mortality and overall survival[9]. In the same year, Soloman et al compared 30 patients with malignant diseases submitted to myeloablative haplo-HCT with a contemporaneous cohort of patients receiving myeloablative MUD transplantation and found that for DRI low/intermediate risk disease, 2-yr DFS was superior after haplo compared with MUD transplantations and Grade II to IV acute GVHD and moderate-to-severe chronic GVHD were lower after haplo-HCT compared to MUD transplantation[10].

In patients with acute myeloid leukemia (AML), Ciurea et al have shown that the results of haplo-HCT were compared with MUD transplantation[11]. In patients with adverse karyotype AML, Haplo HCT recipients had comparable overall survival and leukemia free survival when compared to 10/10 and 9/10 MUD[12] and in patients with FLT3-ITD AML, a retrospective analysis of EBMT have demonstrated that relapse and overall survival were comparable between matched sibling, MUD donors or haploidentical donors[13]. In addition, in elderly (≥60 years) AML population, when comparing non-T-cell-depleted Haplo-HSCT to 10/10 MUD, the authors found no significant difference for acute GVHD grade II-IV, relapse, non-relapse mortality, leukemia free survival and overall survival (OS) but extensive chronic GVHD was higher for MUD as compared to Haplo[14].

In patients with Hodgkin's lymphoma (HL), Haplo-HCT with posttransplant cyclophosphamide (Post-CY) had better results in relapse and progression-free survival compared to patients undergoing HLA-compatible stem cell hematopoietic transplantation[9]. In a Brazilian retrospective evaluation of 24 patients who underwent haplo-HCT for relapsed/refractory HL, 2-year-overall survival was 66%[15]. Good results were also found in patients with refractory severe aplastic anemia submitted to haplo-HCT with 1-year overall survival of 67.1% in Brazilian population[16]. In a recent study including 41 patients with aplastic anemia submitted to haplo-HCT versus 48 patients with aplastic anemia submitted to MUD transplant no significant differences were observed between the groups in 3-year overall survival[17].

In conclusion, haplo-HCT with post-Cy has been shown to be safe for both malignant and benign hematologic diseases. Its use has been extended as a therapeutic option for patients who do not have related or unrelated donors, especially in patients belonging to ethnic minorities and, as almost all patients have an potential haploidentical donor and it can be rapidly identified, the transplant process can be easier and faster.

Haploidentical HCT with post-CY have been increasing in Brazilian centers, by mid-2013, 85 transplants had been performed. From this date until the middle of 2015, another 100 transplants occurred, totaling 185 cases. Most were acute leukemias (90 patients), severe aplastic anemia (24 patients) and Hodgkin's lymphoma (20 patients), but until the present moment, there are no prospective comparisons of haplo-HCT, MRD or MUD in the Brazilian population.

Patient eligibility population:

Inclusion criteria

- Age <75 years;
- HLA typing (HLA-A, -B, -Cw, - DRB1 and -DQB1) with adequate resolution to confirm haplotype, with at least 5/10 compatibility;

- High-risk or intermediate risk acute myeloid leukemia in morfologic complete remission with an indication to allogeneic stem cell transplantation (More than a cycle of induction therapy necessary to achieve remission; Preceding myelodysplastic syndrome; Intermediate and adverse risks according to Leukemianet; Acute myeloid leukemia in second remission or more)
- Hodgkin lymphomas: who have failed at least one polychemotherapy regimen and are not eligible for an autologous transplant, due to mobilization failure or relapse after autologous transplantation
- Severe aplastic anemia: in patients aged> 2 years (excluding congenital diseases, DEB test, telomeres, SMD, PNH) and <70 years with documented severe aplastic anemia who have received at least 1 cycle of immunosuppression without success and without related and unrelated donors.
- Allogeneic (haploidentical, MUD or MRD) performed in a Brazilian center

Treatment plan for the related haploidentical HCT study:
Patients may receive bone marrow or peripheral blood as stem cell source. For all protocols, on days +3 and +4, the patient receives Cyclophosphamide 50mg/kg/day with Mesna. Post-transplant immunosuppression is initiated on day +5 with tacrolimus at a target serum level of 5-15ng/mL or Cyclosporin with a target serum level of 200-400ng/mL which may be reduced from D + 90 in cases without DECH and Mycophenolate mofetila 15mg/kg 3x/day which will be maintained until D+35 (non-myeloablative) or +90 (Reduced or myeloablative intensity). Below the conditioning regimen for the study according to diagnosis:

- Acute Myeloid Leukemia: D-6 Melfalan 100 - 140 mg / m 2, D -5 to D-2 Fludarabine 40 mg / m 2; D-1 TBI 200 cGy D -7 or -6 to D-2: Fludarabine 25-30mg / m2 / day; Days -7 to -4: busulfan 110-130mg / m2 / day and Cyclophosphamide 14.5 mg / kg / day on days D -3 and D-2. For patients with comorbidities and at the discretion of the transplant team, non-myeloablative protocol may be used: Fludarabine 30 mg / m2 Day -6, -5 -4, -3 and -2 + Cyclophosphamide 14.5 mg / kg IV Day -6, -5; Day -1 TBI 200-400 cGy.
- Hodgkin's lymphoma: Day -6, -5 fludarabine 30 mg / m2 + Cyclophosphamide 14.5 mg / kg IV; Day -4, -3 and -2 Fludarabine 30 mg / m 2; Day -1 TBI 200-400 cGy;
- Aplastic anemia: The same non-myeloablative protocol used in Hodgkin's lymphoma

Other consecutive patients submitted to HCT in Brazil for AML, HD and SAA from matched related or unrelated donors (10/10 or 9/10 compatible) and reported to the CIBMTR will be used as controls for comparison of 1-year overall survival (defined as death from any cause) and for the following composite *endpoints: acute and chronic GVHD, relapse-free survival (GRFS), and chronic GVHD, relapse-free survival (CRFS).*

Data requirements:
Pre-TED and Post-TED forms

List of variables from the existing CIBMTR data collection forms:

<u>Patient related</u>

- Age at allo-HCT: continuous and categorical by decade
- Gender: male vs. female
- Karnofsky performance status: <90% vs. 90-100%
- Adjusted HCT-CI scores (Renal comorbidity excluded) 0, 1, 2, 3+

Disease related

- Primary disease
- Disease risk index (DRI): low, intermediate, high and very high risk
- Prior autologous stem cell transplant: yes vs. no
- Response to previous therapy

Transplant-related

- Conditioning regimen
- GVHD prophylaxis
- Source of hematopoietic stem cells: bone marrow vs. peripheral stem cell vs. cord blood
- Donor source: HLA-matched related donor, matched-unrelated donor, HLA-mismatched unrelated donor, haploidentical donor (HLA mismatched related)
- Donor-recipient sex match: M/M vs. M/F vs. F/M vs. F/F
- Donor-recipient CMV status: -/- vs. -/+ vs. +/- vs. +/+

Post-transplant

- Status of survival and cause of death
- ANC and platelet recovery
- GVHD (grade II-IV, grade III-IV, extensive chronic GVHD or NIH moderate or severe)
- Liver toxicity and VOD
- New malignancy and lymphoproliferative disease
- Disease assessment
- Post-HCT Therapy
- Relapse or Progression Post-HCT

The present study will require collection of supplemental data regarding infectious complications post-transplant (Annex 1)

Study design:

This is a prospective multicenter and observational study of hematopoeitic stem cell transplant in Brazil between January 2018 to January 2020 for AML, HD and SAA using related haploidentical donors with post-CY (prospective) and observational study (HCT from other matched related and unrelated donors in Brazil for the same population). Data will be collected using pre-TED forms and post-TED forms on days +100, +180 and +365. We will compare the 1 year event free survival and GVHD free survival

Using the data requirement above we will analyzed *the 1-year overall survival* for arm 1 (AML and HD) and for arm 2 (SAA) of the study and compare to HCT recipients of matched related or unrelated donor reported to the CIBMTR for the same diagnosis (control). We will also compare the following composite *endpoints: acute and chronic GVHD, relapse-free survival (GRFS), and chronic GVHD, relapse-free survival (CRFS) between the study patients and the control*

Statistical analyzes will be performed by the FISHER test. Event-free survival will be measured from the date of transplantation. Overall Survival, Progression-free and GVHD-free survival will be estimated by Kaplan-Meier and compared between groups stratified by the COX method. Graft-versus-Host Disease and Relapse Free Survival is defined as absence of relapse, death or presence of GVHD.

The project will only start after appropriate ethical approval of each institution. Before prospective data collection, patients will sign consent form agreeing to participate in the study. Participation of patients in the study is voluntary, and data that can identify patients will be kept confidential. Each patient included in the study will receive an individual identification number.

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Conflicts of Interest:
None

Proposal: 1811-116

Title:
Outcomes after allogeneic stem cell transplants performed in Brazil from HLA-matched siblings, unrelated and mismatched related donors. Retrospective study on behalf of the Brazilian Bone Marrow Transplantation Society (SBTMO), GEDECo (Brazil-Seattle Transplant-related complications Consortium), Hospital Israelita Albert Einstein (AmigoH), Associação da Medula Óssea do Estado de São Paulo (Ameo), Programa Nacional de Apoio à Atenção Oncológica (Pronon), and CIBMTR.

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Hypothesis:
Allogeneic stem cell transplants (HCT) performed in Brazil from unrelated (URD) or mismatched related donors (Haplo) have inferior overall survival than HCT performed with HLA-matched sibling donors (MSD).

Specific aims:
- Primary objective: to compare 1-year overall survival after allogeneic HCT performed in Brazil from URD, Haplo and MSD.
- Secondary objective: to compare the 100-day transplant-related mortality (TRM) and the 1-year event-free survival (EFS) after allogeneic HCT performed in Brazil from URD, Haplo and MSD. Event is defined as relapse of malignant disease, graft rejection or death from any cause.

Scientific impact:
- This will be the first nationwide study evaluating transplant outcomes.
- Understanding transplant-related survival and mortality in the country is essential to include or not HCT in the treatment strategies, especially when other curative alternatives are available.
- Comparing results from MDS, Haplo and URD will guide transplant practices in the country.
- The results of this study will base the first prospective multicentric Brazilian trial comparing survival after transplants from URD, Haplo and MSD for acute myeloid leukemia, Hodgkin disease and severe aplastic anemia.

Scientific justification:
- Brazil has over 200 thousand inhabitants, the 2rd largest URD registry (Redome), performs over 2,000 hematopoietic stem cell transplants per year, most of them paid by the government, and there is virtually no data on patient outcomes.
- Thirty-two of the 80 Brazilian transplant centers perform transplants from unrelated donors. Few of them report to the CIBMTR, and even fewer to the EBMT. The country does not have any active outcomes registry.
- The Brazilian Society of Bone Marrow Transplantation (SBTMO) is working in partnership with the CIBMTR, with Hospital Israelita Albert Einstein (AmigoH) and Brazilian

government support [*Programa Nacional de Apoio à Atenção Oncológica* (Pronon) of the *Associação da Medula Óssea do Estado de Sao Paulo* (Ameo)], to educate data managers in all centers performing transplants from unrelated donors, using the CIBMTR for the national data collection.

- The Brazil-Seattle consortium (GEDECo) is a multidisciplinary team established in 2008 with the objective of establishing a platform to conduct future collaborative studies. Many participants were trained at the Fred Hutchinson Cancer Research Center and the consortium meets monthly by teleconference. GEDECo is the Scientific Investigation branch of the SBTMO.
- This will be the first collaborative trial to train new data managers around the country, to understand HCT results in Brazil and serve as baseline data for all future collaborative studies.

Patient eligibility population

Inclusion criteria:

- All patients undergoing first allogeneic HCT in Brazil between January 1, 2014 and December 31, 2018 will be included in this study, with no restrictions regarding age, disease, disease stage, graft and donor types, prior treatments, specific transplant regimens.

Data requirements:

- Only TED-level variables (2400 Forms) will be included:

Patient: 2400R5.0 Pre-transplant essential data

- Age at allo-HCT: continuous and categorical by decade
- Gender: male vs. female
- Prior autologous stem cell transplant: yes vs. no
- Karnofsky/Lanksy performance status: <90% vs. 90-100%
- Presence of co-morbid conditions: yes vs. no

Disease: 2402R3.0 Disease classification

- Time between diagnosis and transplant
- Primary disease for which the HCT was performed and respective disease status at transplant

AML 85, ALL 147, ambiguous lineage & other myeloid neoplasm 154, CML 163, MDS/MPN 256, other leukemia Atypical CML 265, CLL, PLL, hairy cell 266, Hodgkin disease 283, myeloma/plasma cell disorder 316 *No disease status available, only disease specification: solid tumor, severe aplastic anemia, inherited abnormalities of erythrocyte differentiation or function, disorder of the immune system, inherited abnormalities of platelets, inherited disorders of metabolism, histiocytic disorder, autoimmune disease, other disease

Transplant: 2400R5.0 Pre-transplant essential data

- Donor: allogeneic unrelated cord blood vs. unrelated donor vs. related donor
- Related donor type: syngeneic, HLA-identical, HLA-matched other relative, HLA-mismatched relative
- Donor gender
- Product type (source of HCT): BM vs. PBSC vs. single CB vs. other
- Donor CMV IgG status: reactive vs. non-reactive
- Recipient CMV IgG status: reactive vs. non-reactive
- Conditioning regimen: myeloablative vs. NST vs RIC.
- TBI-based vs Busulfan-based (194)

- ATG given: yes vs. no
- GVHD prophylaxis

Post-transplant: 2450R4.0 Post-transplant essential data

- Status at last follow-up: alive vs. dead
- Cause of death
- Hematopoietic (ANC) recovery date
- Late graft failure: yes vs. no
- Acute GVHD: yes vs. no
- Date of acute GVHD: cumulative incidence
- Maximum grade acute: 0-I vs. II-IV vs. III-IV
- Chronic GVHD: yes vs. no
- Maximum grade chronic: mild vs. moderate vs. severe
- Veno-occlusive disease: yes vs. no
- New malignancy, MDSc, MP, or lymphoproliferative disease: yes vs. no
- Disease status: continued remission/ CR vs. not in CR
- Relapse or Progression Post-HCT: yes vs. no
- Relapse or Progression Post-HCT date

Study design (scientific plan):

- All patients undergoing allogeneic HCT in Brazilian centers between January 1, 2014 and December 31, 2018 and reported to the CIBMTR will be included.
- Overall survival and EFS will be estimated by Kaplan-Meier groups (MSD, MUD, Haplo) and compared with logrank test. Day 100 TRM will be determined by cumulative incidence.
- The information from the CIBMTR will provide the first nationwide analysis of allogeneic transplant outcomes of Brazilian patients. Centers already reporting to the CIBMTR will be asked to kindly update their patient follow-up data.
- Data for this study will be collected until April, 2019. We expect to have the data file ready until July, 2019, statistical analysis until October, 2019 and the first draft of the manuscript circulated among authors until December, 2019.
- A grant from Ameo/Pronon to train new data managers and provide computer access in public HCT services is already approved and funded. The data manager trainers were hired and are already being trained. Hospital Israelita Albert Einstein – AmigoH grant was also approved and funded for specific data management of this project.
- In January, 2019 data managers from all interested Brazilian centers performing HCT will start online training in Portuguese 3 hours/day, 3 days/week for one month. Centers performing unrelated donor HCT were sent a contract to be reimbursed for the participation in this training. Participation and learning will be documented. From February through April, 2019, the trainers will personally visit each center performing unrelated HCT for 2-3 days to establish personal contact, check for difficulties, and help the center to fill in the CIBMTR forms. Once a week the whole group will continue to meet online to exchange experiences and discuss questions throughout the project. In a second and third round of in person visits, the patient forms will be audited to assure completeness and accuracy. The centers performing unrelated donor HCT will be reimbursed for each patient undergoing allogeneic HCT reported to the CIBMTR. We expect all centers to be ultimately trained to fill in the Comprehensive Report Forms. At the end of the second year, Ameo will launch a portal for public access on transplant outcomes with no patient or center identification. A similar portal

is already established in Sao Paulo State, Brazil, to search oncology-related outcomes (RHC-Oncocentro).

- This study will provide baseline data and infra-structure for the first prospective randomized Brazilian clinical trial (2018-2020), and contribute to the development of Brazilian HCT outcomes database in collaboration with the CIBMTR. Reporting to the CIBMTR will continue to be funded by the AmigoH project in all institution participating in the randomized prospective trial up to the end of the study in 2020.

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Conflicts of interest:

None

Appendix 1

Preliminary data file

Variable	Haplo	URD	HLA-id sibling
Number of patients	203	712	1292
Number of centers	8	10	10
Age at HCT, median (range), yrs	18 (<1-77)	18 (<1-75)	33 (<1-75)
Age at HCT			
< 10	58 (29)	180 (25)	161 (12)
10-19	53 (26)	203 (29)	212 (16)
20-29	27 (13)	105 (15)	209 (16)
30-39	22 (11)	100 (14)	222 (17)
40-49	10 (5)	59 (8)	260 (20)
50-59	18 (9)	41 (6)	172 (13)
60-69	9 (4)	19 (3)	50 (4)
>= 70	6 (3)	5 (<1)	6 (<1)
Gender			
Male	126 (62)	421 (59)	747 (58)
Female	77 (38)	291 (41)	545 (42)
KPS at HCT			
90-100	137 (67)	564 (79)	1104 (85)
< 90	66 (33)	141 (20)	180 (14)
Missing	0	7 (<1)	8 (<1)
Disease			
AML	52 (26)	144 (20)	360 (28)
ALL	36 (18)	192 (27)	288 (22)
CML	5 (2)	58 (8)	109 (8)
CLL	0	1 (<1)	20 (2)
MDS	10 (5)	51 (7)	108 (8)
Other LK	2 (<1)	17 (2)	15 (1)
NHL	4 (2)	4 (<1)	32 (2)
HD	4 (2)	0	6 (<1)
Other malig dis	4 (2)	16 (2)	48 (4)
SAA	29 (14)	118 (17)	214 (17)
Hemaglobinopathies	31 (15)	65 (9)	77 (6)
Primary immune deficiencies	18 (9)	34 (5)	10 (<1)
Inherit dis of metabolism	7 (3)	8 (1)	2 (<1)
Other non-malig dis	1 (<1)	4 (<1)	3 (<1)

Graftypecat			
Bone marrow	167 (82)	547 (77)	854 (66)
Peripheral blood	36 (18)	165 (23)	438 (34)
Conditioning regimen intensity			
MAC	106 (52)	612 (86)	1003 (78)
RIC/NMA	96 (47)	94 (13)	276 (21)
Missing	1 (<1)	6 (<1)	13 (1)
Year of HCT			
2008	3 (1)	23 (3)	74 (6)
2009	4 (2)	50 (7)	135 (10)
2010	6 (3)	63 (9)	201 (16)
2011	1 (<1)	69 (10)	173 (13)
2012	24 (12)	89 (13)	163 (13)
2013	32 (16)	82 (12)	134 (10)
2014	22 (11)	82 (12)	113 (9)
2015	38 (19)	97 (14)	126 (10)
2016	43 (21)	105 (15)	101 (8)
2017	30 (15)	52 (7)	72 (6)
Median follow-up of survivors (range), months	13 (3-67)	24 (3-99)	37 (1-100)

Characteristics of patients who underwent first allogeneic transplant between 2014 and 2018 in Brazil registered in the CIBMTR (TED)

Characteristic	N (%)
Number of patients	1279
Number of centers	12
Age at transplant, years	
Median(range)	27 (<1-77)
<10	241 (19)
10 - 19	260 (20)
20 - 29	190 (15)
30 - 39	203 (16)
40 - 49	156 (12)
50 - 59	151 (12)
60 - 69	57 (4)
>=70	21 (2)
Gender	
Male	735 (57)
Female	544 (43)
Karnofsky score prior to transplant	
<90	281 (22)
>=90	995 (78)
Missing	3 (<1)
Disease	
Acute myelogenous leukemia	337 (26)
Acute lymphoblastic leukemia	333 (26)
Other leukemia	14 (1)
Chronic myelogenous leukemia	77 (6)
Myelodysplastic/myeloprolifterative disorders	160 (13)
Other acute leukemia	18 (1)
Non-Hodgkin lymphoma	21 (2)
Hodgkin lymphoma	8 (<1)
Severe aplastic anemia	174 (14)
Inherited abnormalities erythrocyte differention or functuntion	67 (5)
SCID and other immune system disorders	52 (4)
Inherited disorders of metabolism	7 (<1)
Histiocytic disorders	4 (<1)
Autoimmune Diseases	1 (<1)
Other, specify	6 (<1)
Race	

Characteristic	N (%)
Caucasian	1052 (82)
African-American	151 (12)
Asian	6 (<1)
Native American	10 (<1)
More than one race	1 (<1)
Missing	59 (5)
Donor type	
HLA-identical sibling	590 (46)
Other relative	225 (18)
Unrelated	464 (36)
Graft type	
Bone Marrow	835 (65)
Peripheral Blood	419 (33)
Cord Blood	25 (2)
Year of transplant	
2014	240 (19)
2015	283 (22)
2016	271 (21)
2017	250 (20)
2018	235 (18)
Median follow-up of survivors (range), months	13 (1-51)

Proposal: 1811-32

Title:
Comparing outcomes of myeloablative-replete Haploidentical Transplantation with PT-CY protocol and ATG+G-CSF protocol in patients with cytogenetic intermediate/high risk acute Myeloid Leukemia in first complete remission
(PT-CY vs. ATG+G-CSF myeloablative Haplo-HCT for Cyto-int/high risk AML CR1)

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Hypothesis:
We hypothesize that overall survival following myeloablative haploidentical allogeneic hematopoietic cell transplantation (haplo-HCT) with post-transplant cyclophosphamide (PT-CY protocol) is not significantly different from haplo-HCT with pretransplant ATG plus granulocyte colony-stimulating factor (G-CSF) stimulated grafts (ATG+G-CSF protocol) in adult patients with cytogenetic intermediate/high (int/high) risk acute myeloid leukemia (AML) in first complete remission (CR1).

Specific objectives:
To compare post-transplant outcomes in adult patients with int/high risk AML in CR1 undergoing T-replete haplo-HCT with PT-CY versus ATG+G-CSF.
The following outcomes will be evaluated:
Primary outcome:

- Overall Survival (OS)

Secondary outcomes:

- Neutrophil and platelet recovery
- Cumulative incidence of acute and chronic graft-versus-host disease
- Cumulative incidence of non-relapse mortality (NRM)
- Cumulative incidence of disease relapse or progression
- Leukemia-free survival (LFS)
- GVHD-relapse-free Survival(GRFS) /cGVHD-Relapse-free Survival(CRFS)

Scientific justification:
For adult patients with AML needing allo-HCT, a human leukocyte antigen (HLA) matched sibling donor is generally considered the optimal donor source. When such donor is not available, a well matched unrelated donor (MUD) is considered the best alternative[1]. However, for some patients, especially the non-Caucasian, there is limited availability of fully matched unrelated donors[2]. For these patients, alternative donor sources such as haploidentical donors can be the only available donor sources. Understanding the relative risks and benefits associated with each of these alternative donor sources will inform donor selection practices. haploidentical HCT (haplo-HCT) is particularly attractive because it promises nearly universal donor availability. However, historically it was associated with high transplant-related mortality[3].
Recently, T cell replete haplo-HCT was confirmed as an equally good alternative to MSD-HSCT as a post remission therapy for AML patients in the first morphological complete remission (CR1) who lack a matching donor. Specifically, haplo-HCT with a posttransplant cyclophosphamide (PT-CY) protocol (established by a Baltimore group) or pretransplant ATG and granulocyte colony-stimulating factor (G-

CSF) stimulated grafts (ATG+G-CSF) protocol (by the Beijing group) has been described[4-9]. Bashey et al reported that haplo-HCT with PT-CY in hematological malignancies achieves outcomes equivalent to those achieved using MSDs and MUDs[10]. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggested that survival for patients with AML after haplo-HCT with PT-CY is comparable to that after MUD-HSCT, with a 3-year OS of 45% vs 50% (P=0.38) for those receiving myeloablative regimens and 46% vs 44% (P=0.71) after reduced intensity conditioning[11]. Wang et al reported that myeloablative haplo-HCT with ATG+G-CSF and MSD-HSCT exhibited comparable 3-year leukemia-free survival (LFS; 74% vs 78%, P=0.34), OS (79% vs 82%, P=0.36), CIR (15% vs 15%, P=0.98), and nonrelapse mortality (NRM; 13% vs 8%, P=0.13) for int-risk or high-risk AML[12]. Data from the European Society for Blood and Marrow Transplantation (EBMT) registry suggested comparable outcomes for individuals with poor-risk AML in CR1 (2-year LFS for haplo, 52 ± 4%; MSD, 53 ± 1%; and MUD, 53 ± 1%; respectively)[13]. A pair-matched comparative study of MUD-HSCT from the EBMT registry and haplo-HCT with ATG+G-CSF also suggested comparable outcomes for int-risk AML in CR1 (5-year LFS in MUD 60.3% and 73.5% in haplo-HCT, P=0.15) [14]. Due to the worldwide application of haplo-HCT, its incidence among allo-HSCT procedures has grown steadily from 3-5% to more than 15-18% in Europe and the US, and there has been a remarkable leveling off in the replacement of MUD-HSCT by haplo-HCT[15,16]. Meanwhile, the number of haplo-HCT cases increased at the highest rate to approximately 3700 cases per year, making it the largest donor source of allo-HSCT (from 37.6% to 56.3%) in China from 2013 to 2017[17,18].

Both of these two novel approaches for haplo-HSCT have yielded encouraging results with high rates of successful engraftment, effective GVHD control and favourable outcomes[4], yet different haplo-HCT methods have not been prospectively compared. EBMT compared these two approaches with various-risk AML in CR1 orCR2. A total of 308 patients were studied (PTCy, n=193;ATG, n=115), and both groups were well matched in regards to recipient and donor age, AML disease risk, disease status at transplant, and conditioning intensity. At day 100, similar outcomes in grade II-V aGvHD were observed between patients receiving PTCy versus ATG (31% vs. 21%, P=0.07). The incidence of 2-year cGvHD did not differ between the two groups (33.7% vs. 28.3%, P=0.33). LFS and OS were comparable for patients receiving PT-CY versus ATG: 56% versus 47.2% (P=0.26) and 58% versus 54.2% (P=0.37), respectively[19]. Therefore EBMT recommend haplo-HCT regardless of the platform used[5].

We aim to compares outcomes in adult patients with cyto-int/high risk AML in CR1 undergoing T-replete haplo-HCT with PT-CY versus ATG+G-CSF using the CIBMTR and Peking University database. If we can show equivalent outcomes after two platforms, the results will support more widespread use of haploidentical HCT, and support the prospective study with CIBMTR and Chinese Bone Marrow Transplantation Registry (CBMTR).

Study population:

Inclusion criteria:

- Adult patients (age 16-60) with AML, (de novo or secondary) in CR1, cyto-int/high risk (NCCN 2018)[20] undergoing first T-replete haplo-HCT between 2010 and 2016

RISK STATUS	CYTOGENETICS
Favorable-risk	Core binding factor: inv(16)[2,3,4] or t(16;16)[2,3,4] or t(8;21)[2,4] or t(15;17)[4]
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[5]

- Peripheral blood or/and bone marrow as graft source
- For the haploidentical cohort eligibility includes 2 or more antigen-level mismatches among HLA-A, -B, and -DRB1.
- Haploidentical related donor cohort will be limited to those receiving ① post-transplant cyclophosphamide ± other agents ② ATG ± other agents for GVHD prophylaxis.
- Myeloablative regimens, referring to the standard CIBMTR criteria (Bacigalupo et al)

Exclusion criteria:

- Haplo-HCT with in vitro T-cell depletion/ CD34+ selection will be excluded.

Outcomes:

- Hematopoietic recovery: The primary measures for hematopoietic recovery will be
  - ANC recovery: Time to neutrophils (ANC) > 0.5 x10^9/L sustained for three consecutive days within 28 and 100 days post-transplant.
  - Platelet recovery: Time to achieve a platelet count of (a) >20 x 10^9/L independent of platelet transfusions for 7 consecutive days, and (b) >50 x 10^9 /L independent of platelet transfusions for 7 consecutive days within 28 and 100 days post-transplant.

- Incidence of acute GVHD: cumulative incidence of acute GVHD, with death as competing risk. The onset time of TED track haplo cases will be imputed based on the median onset time of CRF track haplo cases separately within each graft type and conditioning intensity category.
- Incidence of limited and extensive chronic GVHD: cumulative incidence of chronic GVHD, with death as competing risk.
- Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse is competing event.
- Relapse/Progression: Cumulative incidence of disease relapse/progression, with NRM as competing event.
- Leukemia-free survival: will be defined as time to relapse or death from any cause. Patients are censored at last follow-up
- Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.

- Primary cause of death: descriptive only.
- GVHD-free, relapse-free survival (GRFS) events were defined as grade III-IV aGVHD, extensive chronic GVHD, relapse, or death
- cGVHD/relapse-free Survival (CRFS) events were defined as Chronic GVHD requiring systemic therapy, relapse, or death

Variables to be described (bolded variables to be considered in MVA):

Main effect:

- **GVHD prophylaxis used for haplo identical transplant: PT-CY vs. ATG+G-CSF**

Patient related:

- **Patient age at HCT (continuous)**
- **Patient gender: male vs. female**
- **Karnofsky performance score: ≥90 vs. <90 and continuous.**
- **HCT-CI: 0 vs. 1-2 vs. ≥3 vs. missing**

Disease related:

- WBC count at diagnosis (<10 vs. 10-50 vs. >50 x10^9/L)
- Time from diagnosis to HCT: 0-6 vs. ≥ 6 months and continuous
- Time to achieve CR1: <4 weeks vs. 4-8 weeks vs. ≥8 weeks vs. missing
- **Courses to achieve CR:1 vs. 2 vs. 3 or above**
- **Consolidation chemo vs NO**
- **Cytogenetic risk: Intermediate (including normal) vs. poor ; MK vs. other poor vs. missing**
- **MRD at the time of HCT: positive vs. negative vs. missing**
- **De novo vs. secondary/therapy-related AML**

Transplant related:

- **TBI vs. No TBI in conditioning**
- Graft type: bone marrow vs. peripheral blood vs. BM+PB
- **Year of HCT: Continuous**
- **Donor/Recipient gender: F/F vs. M/M vs. F/M vs. M/F**
- **HLA disparity: 2 vs. 3 locus mismatch**
- **Donor/Recipient relation: Father vs. Mother vs. Sibling vs. Child vs. others**
- **Donor/Recipient blood type : ABO major mismatch vs. minor mismatch vs. match others**
- **Donor age**
- **Donor/Recipient CMV status: -/+ vs. others**

Other collected data

- **Molecular Marker at diagnosis: FLT3/NPM1/CEBPA/TP53**
- **CD34 Count, MNC of grafts**

Study design:

A retrospective multicenter study will be conducted utilizing CIBMTR dataset vs. Peking University data base. Patients will be eligible if they satisfied the criteria detailed in the "Study population" section. The objective of this analysis is to compare these two approaches and their effects on allo-HCT outcomes. The primary endpoint for this analysis is 3-year OS/LFS/GRFS.

Univariate analysis will be performed using Kaplan-Meier Method and will be compared using log-rank test for OS, LFS, GRFS, while neutrophil / platelet recovery, acute / chronic GVHD, non-relapse mortality (NRM), primary and secondary graft failure, and relapse will be calculated using the cumulative incidence method considering competing risks, with comparisons performed using Gray method.
Multivariate analysis will also be performed using Cox proportional hazard model for OS, LFS, GRFS, NRM and relapse. The variables to be considered in the multivariate models are bolded in Sections 6.0. Main effect of PT_CY vs. ATG+G-CSF will be kept in all models. The assumption of proportional hazards for each factor in the Cox model will be tested by adding time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), models will be constructed breaking the post-transplant time course into two periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions will be further tested. A backward stepwise model selection approach will be used to identify all significant risk factors. Factors which are significant at a 5% level will be kept in the final model. Potential interaction between main effect and significant co-variates will be tested.
Adjusted probabilities of LFS and OS, and adjusted cumulative incidence functions of NRM and relapse will be calculated using the multivariate models, stratified on main effect and weighted by the pooled sample proportion value for each prognostic factor. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors.
All analyses were done using the statistical package SAS version 9.3 (Cary, NC).
Power consideration:
Based on the existing sample size, with 2-sided test at 5% significant level we will have

- 85% power to detect 10% difference in 2 yr OS probability between main effect group
- 86% power to detect 10% difference in 3 yr OS probability between main effect group
- >95% power to detect 15% difference in 2 yr OS probability between main effect group
- >95% power to detect 15% difference in 3 yr OS probability between main effect group

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Table1. Characteristics of patients receiving first haplo (with post-cy) allo-HCT for AML in CR1 between 2010 and 2016 registered in the CIBMTR

Characteristic	N (%)
Number of patients	276
Number of centers	67
Patient age	
18-29	57 (21)
30-39	39 (14)
40-49	68 (25)
50-59	112 (41)
Median (range)	46 (18-60)
Gender	
Male	135 (49)
Female	141 (51)
Race	
Caucasian	175 (63)
African-American	69 (25)
Asian	19 (7)
Pacific islander	1 (<1)
Native American	1 (<1)
Unknown	11 (4)
Karnofsky score	
<90	102 (37)
>=90	159 (58)
Missing	15 (5)
Cytogenetics	
Normal	47 (17)
Favorable	13 (5)
Intermediate	50 (18)
Poor: MK	17 (6)
Poor: other	72 (26)
Not Tested	1 (<1)
Missing	45 (16)
TBD	31 (11)
Type of AML	
De-novo	226 (82)
Transformed from MDS/MPS	32 (12)
Therapy linked	18 (7)
Conditioning intensity	

Characteristic	N (%)
MAC w/ TBI	47 (17)
MAC w/o TBI	94 (34)
RIC/NMA	133 (48)
Missing	2 (<1)
Graft type	
Bone marrow	128 (46)
Peripheral blood	148 (54)
GVHD prophylaxis	
CNI+MTX+-others	3 (1)
CNI+MMF+-others	267 (97)
Others	6 (2)
ATG/Campath	
No ATG or CAMPATH	276
Year of HCT	
2010	13 (5)
2011	17 (6)
2012	17 (6)
2013	42 (15)
2014	41 (15)
2015	64 (23)
2016	82 (30)
Median follow-up of survivors (range), months	36 (3-96)

Table2. Characteristics of patients receiving first haplo (with post-cy) allo-HCT for AML in CR1 between 2010 and 2016 registered in the CIBMTR

Characteristic	CRF	TED only
Number of patients	106	170
Number of centers	40	56
Patient age		
18-29	18 (17)	39 (23)
30-39	18 (17)	21 (12)
40-49	19 (18)	49 (29)
50-59	51 (48)	61 (36)
Median (range)	48 (18-60)	45 (19-60)
Gender		
Male	54 (51)	81 (48)
Female	52 (49)	89 (52)
Race		
Caucasian	68 (64)	107 (63)
African-American	28 (26)	41 (24)
Asian	7 (7)	12 (7)
Pacific islander	0	1 (<1)
Native American	0	1 (<1)
Unknown	3 (3)	8 (5)
Karnofsky score		
<90	48 (45)	54 (32)
>=90	53 (50)	106 (62)
Missing	5 (5)	10 (6)
Cytogenetics		
Normal	37 (35)	10 (6)
Favorable	5 (5)	8 (5)
Intermediate	26 (25)	24 (14)
Poor: MK	8 (8)	9 (5)
Poor: other	27 (25)	45 (26)
Not Tested	1 (<1)	0
Missing	0	45 (26)
TBD	2 (2)	29 (17)
Type of AML		
De-novo	87 (82)	139 (82)
Transformed from MDS/MPS	14 (13)	18 (11)
Therapy linked	5 (5)	13 (8)

Characteristic	CRF	TED only
Conditioning intensity		
MAC w/ TBI	21 (20)	26 (15)
MAC w/o TBI	28 (26)	66 (39)
RIC/NMA	57 (54)	76 (45)
Missing	0	2 (1)
Graft type		
Bone marrow	44 (42)	84 (49)
Peripheral blood	62 (58)	86 (51)
GVHD prophylaxis		
CNI+MTX+-others	0	3 (2)
CNI+MMF+-others	104 (98)	163 (96)
Others	2 (2)	4 (2)
ATG/Campath		
No ATG or CAMPATH	106	170
Year of HCT		
2010	3 (3)	10 (6)
2011	2 (2)	15 (9)
2012	1 (<1)	16 (9)
2013	15 (14)	27 (16)
2014	26 (25)	15 (9)
2015	25 (24)	39 (23)
2016	34 (32)	48 (28)
Median follow-up of survivors (range), months	36 (12-96)	36 (3-83)

Proposal 1811-02

TITLE:
Outcomes of Autologous Stem Cell Transplantation for Patients with Multiple Myeloma From Rural America

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Objectives:

- Determine if there are differences in receiving HCT in Rural patients versus Urban patients with multiple myeloma.
- Determine if there are differences in outcome based on residence.

Scientific justification:
Racial disparities in multiple myeloma (MM) care has previously been reported in literatures (1-2). Access to clinical trials and stem cell transplantation utilization rate (STUR) for newly diagnosed MM (NDMM) patients lag among ethnic minorities (3-5). Compared to race and ethnic disparities in MM, few studies have examined disease characteristics and outcome differences in rural population in United States. Disparities such as lower levels of utilization of cancer screening tests, lower likelihood of receiving guideline-appropriate therapy and access to clinical trials exist in association with rural residence (6). Elsayed et al. showed that rural patients with MM had shorter survival compared to their urban counterpart (7). Most of the studies on rural health had been observational in nature and few studies considered disease characteristics and outcome related to place of residence. Recent studies have confirmed the role of upfront AHCT in patients with newly diagnosed MM (8,9). Despite the proven therapeutic strategy, only 30% of patients in United States are offered and received autologous transplantation for multiple myeloma. Lower STUR is observed in patients with African-American and Hispanic ethnicity (4, 5, 10-12). Not much data exists regarding the STUR for patients from rural areas in USA. In the paper by Elsayed et al, 1/3rd patients from rural New Mexico were offered or educated about ASCT and 18.5% of patients received the therapy. In their paper, there was no difference of transplantation rate between the urban or the rural group, but no outcome analysis was done based on transplantation status (7). Multiple studies have been conducted which address the effect of geographical distance to transplant centers and survival after transplantation. One study found worse survival in rural patients who underwent Auto-HCT. The study reported that rural patients had at least a 5% lower probability of survival at 1 year and 5 years after AHCT (13). This study did not comment on the accessibility of AHCT to rural patients. Lipe et al did not find that distance from the transplant center was associated with worse outcome for patients with MM (14).
To our knowledge, there is no published data for post-transplant outcome for patients with MM from rural areas. Using CIBMTR platform and using Rural-Urban Continuum Codes developed by the US Department of Agriculture, we propose to analyze the STUR and outcome for patients from rural America. Having such information would be of immense help in the development of future health care policy and allocating resources to vital areas for myeloma care.

Study population:
The study population includes all the patients in US < 75 years old who underwent autologous stem cell transplant for Multiple Myeloma and reported to CIBMTR between 2010 and 2016.

Data sources:
HCT data will be obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry database for patients up to age 75 years (generally the maximum transplant age), who received an HCT for any indication in the US in 2010–2016. Because reporting autologous transplants to CIBMTR is voluntary, the database may not include all autologous HCTs performed. Based on data available from Bone Marrow Transplant Information Network (BMT Infonet) which attempts to survey all US transplant centers yearly, we estimate that in the above-mentioned years the CIBMTR collected transplant data on about 80% of autologous performed in the US.
The SEER database will be used to estimate the annual incidence of MM in the US for patients < 75. The annual incidence of autologous transplant will be estimated from the CIBMTR database. This will allow the determination of the likelihood of undergoing stem cell transplant and an odds adjusted ratio will be determined.
Patients will be stratified by Urban versus Rural origin based on Zip Codes and Rural-Urban-Continuum Codes available from the US Department of Agriculture.
We will than compare these patients' outcome using the CIBMTR database to determine if there is any difference in transplant outcome.

Outcomes to be analyzed:

- Treatment-related mortality: Time from transplant to death occurring in continuous complete remission, partial response, minimal response or stable disease. This event is summarized by the cumulative incidence estimate with relapse/progression as the competing risk.
- Progression-free survival: Survival without progressive disease or relapse from CR. Progressive disease, relapse from CR and death in remission are considered events. Patients who are alive and in complete remission, partial response, minimal response or stable disease are censored at time of last follow-up. Clock starts from time of transplant.
- Overall survival: Events are death by any cause. Clock starts from time of transplant. Surviving patients are censored at the time of last contact.

Variables to be described:
Main effect:

- **Rural vs. Urban residence**

Patient-related:

- **Age: Continuous; by decade; <45 vs. 45-60 vs. >60**
- **Gender: Male vs. female**
- **Karnofsky score: ≥90% vs. <90%**
- **HCT-CI score: No comorbidity vs. 1-2 vs. 3+**
- **Clinical trial enrollment: Yes vs. No**
- **Distance from transplant center: <30 miles, 31-100 miles, >100 miles**
- **Race: Caucasian vs African American vs Hispanics non white vs others**

Disease-related:

- Immunochemical subtype at diagnosis: IgG vs. IgA vs. light chain vs. non-secretory vs. others
- Serum Albumin at diagnosis: <3.5 mg/L vs. ≥3.5 mg/L
- **International Staging System/Durie-Salmon Stage at diagnosis: I/II vs. III**
- **Use of Novel Drugs pre transplant yes vs No**

Transplant-related:

- **Status of disease at the time of HCT: CR/sCR vs. VGPR vs. PR vs. SD/Rel/PROG**
- **Melphalan dose, mg/m^2: 140 (including calculated 120-170) vs. 200 (including calculated 170-280)**
- **Time from diagnosis to transplant: <6 months vs. 6-12 months vs. > 12 months**
- **Year of transplant, by years**
- Planned Post-transplant maintenance therapy: Yes vs. No

Study design:

This is a retrospective study to determine the rate of HSCT among patients with Myeloma from rural areas. A secondary objective is to determine if there is a difference in transplant outcomes based on these patient groups.

The Surveillance, Epidemiology, and End Results (SEER) Program database will be used to estimate the annual incidence of MM in the US for patients < 75 between 2010 and 2016. The annual incidence of HSCT will be estimated from the CIBMTR database. This will allow us to determine the probability of undergoing HSCT. A sensitivity analysis will be performed to look at the effect of varied CIBMTR AUTO transplant capture rate.

Descriptive statistics will be used to summarize patient-related, disease-related and transplant-related variables by area of residence. To ensure that both patient groups are similar, we will use the chi-square test and Kruskal-Wallis test for categorical and continuous variables, respectively.

For univariate analyses, the log-rank test will be used to compare the following outcomes; relapse/progression, TRM, PFS and OS by residence (Rural vs Urban). Corresponding Kaplan-Meier and cumulative incidence plots will be produced.

To identify important and statistically significant risk factors for the proportional hazards regression model we will first screen out potentially significant covariates, using univariate Cox PH analyses, for consideration in the multivariate Cox PH regression model. We will use the stepwise variable selection technique to identify risk factors in the multivariate Cox model. No interaction terms will be considered during the variable selection process. However, we will explore interaction between the "main effect" and the variables in the final model. All statistical tests will be two-sided with a significance level of 5%.

The adequacy of the fitted model will be assessed using diagnostic procedures and formal tests. The proportional hazards assumption will be assessed by adding a time-dependent variable to the model and by plotting the scaled Schoenfeld residuals against the observed survival times of everyone. The proportional hazards assumption holds if either test is significant.

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Characteristics of patients (age<75 years old) who underwent the first autologous transplant for Multiple Myeloma between 2010 and 2016 reported to the CIBMTR (CRF)

Characteristic	N (%)
Number of patients	3411
Number of centers	117
Age at transplant, years	
Median(range)	60 (20-75)
18-29	7 (<1)
30-39	101 (3)
40-49	453 (13)
50-59	1149 (34)
>=60	1701 (50)
Gender	
Male	1880 (55)
Female	1531 (45)
Karnofsky score prior to transplant	
<90	1525 (45)
>=90	1836 (54)
Missing	50 (1)
Race	
Caucasian	2078 (61)
African-American	1109 (33)
Asian	108 (3)
Pacific islander	9 (<1)
Native American	28 (<1)
More than one race	16 (<1)
Missing	63 (2)
Graft type	
Bone Marrow	2 (<1)
Peripheral Blood	3409
Highest educational grade completed	
No primary education	3 (<1)
High school or lower	1009 (30)
College	566 (17)
Graduate School	872 (26)
Missing	961 (28)
Zip code availability	
No	94 (3)
Yes	3317 (97)

Characteristic	N (%)
Year of transplant	
2010	245 (7)
2011	327 (10)
2012	336 (10)
2013	611 (18)
2014	515 (15)
2015	663 (19)
2016	714 (21)
Median follow-up of survivors (range), months	39 (<1-100)

Completeness of follow-up

Time	(N = 3411), %
1-year	98
2-year	92
3-year	88
4-year	86

Proposal: 1811-10

Title:
Relative Mortality Risk in AYA vs. Younger and Older Survivors of Allogeneic HCT for Acute Leukemia

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Hypothesis:
We hypothesize that adolescent and young adult (AYA) survivors of allogeneic hematopoietic cell transplantation (HCT) for acute leukemia will have an increased relative risk of mortality compared to the general US population, and this increased relative risk will be greater than children or older adult age groups

Specific aims:
Primary aims:

- Determine if AYA (age 14-29 at transplant) leukemia patients who are alive and in remission one year post allogeneic hematopoietic cell transplantation (HCT) will have increased relative risk of mortality compared to the general US population.
- Determine if the relative risk of mortality compared to the general population for AYA (age 14-29 at transplant) leukemia patients who are alive and in remission one year post HSCT is greater than the relative risk for children age <14 at transplant, or adults age 30-49 at transplant

Exploratory aim:

- Determine if the risk of late death in AYA survivors is associated with measures of socioeconomic status (both from data reported by center and based on Zip Code of residence), insurance status, marital status, and educational attainment at the time of transplant for patients undergoing HCT from 2007 onwards (when these data were collected routinely)

Scientific impact:
Allogeneic HCT is curative for many hematologic diseases in the AYA population, however risks of late complications exists outside of the first year post-HCT. The AYA population has unique challenges and these patients are overall less likely to seek medical care compared to younger children or older adults. AYA patients undergoing HCT for leukemia have worse overall transplant outcomes compared to younger children, but little is known in regards to their risks for late mortality. Younger HCT survivors long-term medical care is significantly governed my parents, and older adults may be more likely to interact with the medical system. This study would provide significant knowledge regarding the risk of late death in AYA HCT patients and explore potential socioeconomic risk factors unique to this age group. Results may also potentially identify a time-period that is particularly high-risk for AYA patients that requires close follow-up.

Scientific justification:
Adolescent and Young adult cancer patients have many unique challenges and represent an underserved population.[1] Overall survival of AYA patients undergoing HCT for leukemia is inferior to pediatric patients.[2,3] The reason for differences in outcomes are multifactorial and have not been clearly elucidated.[4] Survivors of HCT, at least two years post allogeneic-HCT have inferior long-term survival (conditional survival) compared to the general population.[5] The AYA population has a myriad of

psychosocial challenges which may preclude them from getting optimal care after cancer therapy.[6,7] AYA cancer survivors also commonly report adverse behavioral, medical, and health care access characteristics that may lead to poor long-term medical and psychosocial outcomes.[8] Transitions of care are a particularly vulnerable time period for AYA cancer patients;[9] AYA HCT patients typically go through one or more transitions of medical care as they approach adulthood and move into survivorship care. Presumably psychosocial and transition challenges in this age group could lead to suboptimal conditional survival in survivors of allogeneic HCT.

Patient eligibility population:

- Age: <50 years (at the time of HCT)
- Race/Ethnicity: Any
- Disease: Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML)
- Disease stage/status at transplant: Any
- Year of Transplant: 2000-2010
- Graft and Donor Types: Any
- Transplant Type: Allogeneic, MAC only
- Prior Treatments/Specific Regimens: First transplant only, patients requiring subsequent HCT prior to one year will be excluded
- Time post-transplant: Alive and in remission ≥1 year post-HCT

Data requirements:

Outcome variables (to be compared by age group):

- Probability of overall mortality and leukemia-free survival
- Cumulative incidence of non-relapse mortality and relapse
- Relative risk of overall mortality (each individual age groups compared to general population)
- Relative risk of overall mortality (AYA vs. children vs. adults)

Patient Variables:

- Patient age – continuous
- Patient age- by group
- Patient sex: male vs. female
- Performance score: <90% vs. >90%
- Zip code (median household income)
- Socioeconomic/Psychosocial Variables (From form 2000)
    - Marital status: single, never married vs. married or living with a partner vs. separated vs. divorced vs. widowed. Vs unknown
    - Work status prior to illness: full time vs. part time vs unemployed vs. medical disability vs. retired vs. unknown
    - Highest educational grade completed
    - Presently in school: yes/no
    - Covered by health insurance: yes/no
    - Type of health insurance: Medicare vs. Medicaid vs. VA vs. private (individual) vs. employee sponsored
    - Household gross annual income

Disease-related:

- Disease: specific diagnosis

- Relapse number
- Disease status prior to transplant
- Disease Risk Group
- Disease Histology

Transplant-related:

- Conditioning regimen: TBI vs no TBI
- Donor type/HLA matching
- Stem cell source: Bone marrow vs. Peripheral blood vs. Cord blood
- History of acute GVHD
- History of chronic GVHD

Study design:

This proposal will focus on establishing if the risk for late mortality is relatively higher in AYA survivors compared to other age groups. Socioeconomic and psychosocial data will serve as exploratory aims in this proposal as these details have not been obtained for the entire duration of the proposed time period. Additionally, the AYA time period is a time of transition and variables such as marital status at the time of transplant may be less relevant for the long-term AYA survivor. Additionally, as a comparator group we have chosen adults age 30-49. We have omitted older patients who are somewhat less likely to be fit at the time of transplant and may have their own idiosyncratic risks for increased relative risk of late death. Additionally, we will plan to limit the analysis to myeloablative conditioning only, as reduced intensity conditioning for acute leukemia is rare and may represent a somewhat atypical patient population.

The overall statistical plan to complete primary aim one will be to estimate the relative risk of mortality compared to the general population in one year survivors of HCT. Estimates of relative mortality will be performed as described by Andersen and Vaeth, taking into account differences among patients with regard to age, sex, and ethnicity as previously performed by the CIBMTR.[10,11]

For primary aim 2, the relative risk of overall mortality and relapse free mortality at 3, 5, and 10 years post-HCT will be compared between the three age groups (<14 years, 14-29 years, and 30-50 years). Multivariate Cox proportional-hazards regression models will be used to adjust for difference in known risk factors for late death (chronic GVHD, disease, disease risk group). We will also examine the AYA group by dichotomizing this population as <18 years and 19- <30 years old. Aim 1 and 2 can be completed with TED level data only.

For exploratory aim 1, potential risk factors for late death will be analyzed by Cox regression for the AYA age group based on data obtained in form 2000 from patients undergoing HCT from 2007 and onwards. In addition to disease and transplant related variables, we will analyze insurance status, marital status, work status, and educational attainment at the time of transplant. In addition to TED forms, form 2000 (recipient baseline data) will be required. We will also analyze median household income based on zip code at the time of transplant in 2010 US dollars. For this analysis we will include all patients transplanted after 2007, and patients who have zip code data prior to this time.

Patient, disease and HCT related characteristics will be compared by Chi-square statistic for categorical variables and the Kruskal-Wallis test for continuous variables. Probabilities of overall survival will be calculated using the Kaplan-Meier method.

Non-CIBMTR data source:

Estimates of relative mortality for the general US population taking into account differences among patients with regard to age, sex, ethnicity were performed as previously performed by CIBMTR.[10,11] Additionally, we will use median household income based on zip code at the time of transplant.

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Conflicts of interest:

The study team reports no pertinent conflicts of interest.

Characteristics of patients (age<50 years old) who underwent first myeloablative allogeneic transplant for AML and ALL, alive and in remission >=1 year post-HCT, between 2000 and 2010 in US reported to the CIBMTR (CRF)

Characteristic	<14	14-29	30-49
Number of patients	1132	1148	1496
Number of centers	81	136	109
Age at transplant, years, median(range)	7 (<1-14)	22 (14-30)	42 (30-50)
Gender			
Male	662 (58)	690 (60)	707 (47)
Female	470 (42)	458 (40)	789 (53)
Karnofsky score prior to transplant			
<90	114 (10)	246 (21)	377 (25)
>=90	951 (84)	839 (73)	1032 (69)
Missing	67 (6)	63 (5)	87 (6)
Primary disease code			
AML	463 (41)	648 (56)	1075 (72)
ALL	669 (59)	500 (44)	421 (28)
Race			
Caucasian	882 (78)	983 (86)	1316 (88)
African-American	86 (8)	75 (7)	70 (5)
Asian	36 (3)	20 (2)	57 (4)
Pacific islander	2 (<1)	2 (<1)	1 (<1)
Native American	9 (<1)	5 (<1)	5 (<1)
Other	4 (<1)	2 (<1)	2 (<1)
More than one race	26 (2)	17 (1)	7 (<1)
Missing	87 (8)	44 (4)	38 (3)
Donor type			
HLA-identical sibling	161 (14)	224 (20)	431 (29)
Other relative	30 (3)	22 (2)	19 (1)
Unrelated	930 (82)	886 (77)	1033 (69)
Missing	11 (<1)	16 (1)	13 (<1)
Graft type			
Bone Marrow	534 (47)	410 (36)	344 (23)
Peripheral Blood	135 (12)	565 (49)	1055 (71)
Cord Blood	463 (41)	173 (15)	97 (6)
Marital status			
Single, never married	NA	552 (48)	200 (13)
Married	NA	177 (15)	959 (64)

Characteristic	<14	14-29	30-49
Separated/Divorced	NA	19 (2)	156 (10)
Widowed	NA	1 (<1)	7 (<1)
Missing	NA	399 (35)	174 (12)
Highest educational grade completed			
No primary education	118 (10)	0	0
High school or lower	177 (16)	381 (33)	269 (18)
College	1 (<1)	189 (16)	249 (17)
Graduate School	0	76 (7)	207 (14)
Missing	836 (74)	502 (44)	771 (52)
Zip code availability			
No	217 (19)	155 (14)	204 (14)
Yes	915 (81)	993 (86)	1292 (86)
Year of transplant			
2000-2005	560 (49)	514 (45)	574 (38)
2006-2010	572 (51)	634 (55)	922 (62)
Median follow-up of survivors (range), months	118 (12-222)	110 (12-218)	117 (12-218)

Proposal: 1811-53

Study Title:
Factors Associated with Clinical Trial Participation among HSCT Patients: A CIBMTR Analysis

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Specific aims and hypotheses:

- Specific aim 1: To describe rates of clinical trial participation based on HSCT type.
  - Hypothesis 1.1: Patients undergoing allogeneic HSCT are more likely to participate in a clinical trial compared to those who undergo autologous HSCT.
- Specific aim 2: To explore factors that are associated with clinical trial participation in patients with undergoing HSCT.
  - Hypothesis 2.1: Patients who are White, unmarried, younger, and those with private health insurance are more likely to participate in clinical trials.
  - Hypothesis 2:2: Patients with higher education and those with higher income are more likely to participate in clinical trials.
- Specific aim 3: To assess the impact of clinical trial participation on overall survival (OS) and non-relapse mortality (NRM) in autologous and allogeneic HSCT recipients.
  - Hypothesis 3.1: Clinical trial participation will be associated with better OS and lower NRM among autologous and allogeneic HSCT recipients.

Scientific impact:
Our study has the potential to provide unique contributions to the literature. First, to our knowledge, this is the first study to describe rates of clinical trial participation in patients undergoing autologous and allogeneic HSCT. Although some studies have reported on clinical trial participation among patients with solid tumors, the literature examining factors associated with clinical trial participation are lacking. Second, understanding why clinical trial participation may vary based on certain patient- and transplant-related factors has important clinical implications for identifying potential barriers to clinical trial participation as well as developing strategies to enhance participation. Given the critical importance of clinical trial participation to the advancement of the field, understanding potential barriers is crucial. Lastly, this study represents the first to examine the association between clinical trial participation and transplant outcomes, which can only be done using a large database such as the Center for International Blood and Marrow Transplant (CIBMTR). Thus, we propose to utilize data from the CIBMTR to examine whether certain patient factors and health outcomes are associated with clinical trial participation. Study findings may help to better identify, develop, and implement strategies for addressing barriers to enrollment in this population.

Scientific justification:
Participation in clinical trials is critically important to advance the scientific knowledge and enhance the care of patients with cancer.[1–5] While clinical trial participation has been studied in solid oncology, data regarding clinical trial participation in patients undergoing autologous and allogeneic HSCT are lacking. Clinical research has played an important role in advances in the field of hematopoietic stem cell transplantation over the decades.[6,7] The field of blood and marrow transplantation has evolved from

bench to bedside, moving from the original studies in animals in the early 1950s, first human transplants in 1957 to the current state of the science with haploidentical and cord blood transplants and genetically engineered immunotherapy.[8] Clinical trials have contributed to demonstrating the efficacy and safety of these novel therapies[1], and the number of autologous and allogeneic transplants performed continues to rise.[9] However, clinical trial participation among adults with cancer remains as low as 3-5%[2,3], and high-risk groups such as HSCT populations are susceptible to facing additional barriers to trial participation. Thus, we need a more comprehensive understanding of factors that impact clinical trial participation in this population to advance the science and enhance the quality of care delivered to patients undergoing autologous and allogeneic HSCT.

While there are studies examining factors that impact clinical trial participation in solid tumors, there are no data assessing these factors in autologous and allogeneic HSCT. There are likely multiple barriers to clinical trial participation including attitudinal, structural, clinical, and sociocultural barriers.[10,11] Factors such as age, race, income, education, marital status, and health insurance may play an important role in clinical trial participation for patients undergoing autologous and allogeneic HSCT.[4,10,12–17] In addition, to our knowledge, there are no data assessing the impact of clinical trial participation on post-transplant outcomes including OS and NRM. Therefore, assessing barriers to clinical trial participation and the impact of trial participation on transplant outcomes has the potential to identify critical strategies to enhance clinical trial participation in the field of hematopoietic stem cell transplantation.

Given these gaps in the literature, we now propose to conduct a retrospective analysis through the CIBMTR to 1) describe clinical trial participation rates in patients undergoing autologous and allogeneic HSCT; 2) assess factors that are associated with clinical trial participation in this population; and 3) examine the impact of clinical trial participation on post-transplant outcomes. The CIBMTR is ideally suited for addressing the aims of this project given 1) the large sample size and adequate representation of transplant centers across the United States; 2) the ability to assess important patient-factors as potential predictors of clinical trial participation; and 3) the ability to adjust for important patient-, disease-, and transplant-related factors in assessing the impact of clinical trial participation on post-transplant outcomes. Data from this investigation will be critical to enhancing our understanding of barriers to clinical trial participation in HSCT as well as in developing strategies to enhance clinical trial participation in this population.

Patient eligibility population:

We propose to study all adult (≥18 years of age) patients who received an autologous or allogeneic HSCT from 2008-2014 in the United States who have information about clinical trial participation.

Data requirements:

- Data collection forms: (1) Recipient Baseline Data, (2) Pre-Transplant Essential Data-RF, (3) Post-HCT Follow-Up Data, (4) RITN Baseline Form, (5) RITN Follow-Up Form
- No supplemental data collection will be required.
- Data variables: Clinical trial participation (yes vs. no), demographic variables (age, gender, race, ethnicity, marital status, health insurance type, income, education), diagnosis, disease status prior to HSCT, donor age, donor-recipient sex match, donor-recipient CMV status, donor-recipient HLA match, comorbid conditions, conditioning regimen (myeloablative vs. other), year of transplantation, region of transplant center, interval diagnosis to transplant , conditioning chemotherapy, sources of cells, development of acute GVHD, development of chronic GVHD, date of relapse/progression, date of death, HCT type, Recipient or most recent work status prior to illness, Survival status, Engraftment syndrome occurrence, and Karnofsky Scale.

Study design:
The CIBMTR is a prospectively maintained international database that will be used to identify patients who underwent allogeneic or autologous HSCT. Patients will be categorized based on their participation in clinical trials (yes vs. no). Descriptive statistics will be used to describe the proportion of autologous and allogeneic transplant recipients who had participated in a clinical trial. Categorical variables will be presented as frequencies and percentages and continuous variables are presented with mean $\pm$ standard deviation and median when appropriate. In a univariate analysis, patient-, disease-, donor-, and transplant-related variables will be compared by clinical trial participation status using the chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. We will use multivariate logistic regression to examine the association between clinical and demographic factors and clinical trial participation while adjusting for clinically relevant confounders. In a multivariate analysis, we will examine whether clinical trial participation is associated with NRM and OS using Cox proportional hazards models adjusting for potential imbalances in patient-, disease-, and transplant-related characteristics between the two groups (clinical trial participant yes vs. no). A stepwise forward/backward model election approach will be used for model building, with the main effect of clinical trial participation forced into the model at each step. Factors with a p-value less than or equal to 0.05 will be kept in the final model. Final models for NRM and OS will be constructed for autologous and allogeneic HSCT separately. The following variables will be considered in model building: clinical trial participation (yes vs. no), recipient's demographics, pre-transplant performance status, hematologic cancer diagnosis, disease status prior to HSCT, comborbid conditions, years of transplantation, region of transplant center, interval diagnosis to transplant, conditioning regimen, source of stem cells, HLA disparity, donor-recipient gender match, donor recipient CMV status, and donor age.

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Table 1. Characteristics of adult patients (age>18 years old) who underwent first allogeneic transplant between 2008 and 2014 in US reported to the CIBMTR (CRF)

Characteristic	Clinical trial participants	Non-clinical trail participants
Number of patients	2484	9595
Number of centers	91	163
Age at transplant, years, median(range)	54 (18-77)	54 (18-82)
Age at transplant, years		
18-19	46 (2)	222 (2)
20-29	223 (9)	1052 (11)
30-39	249 (10)	1096 (11)
40-49	469 (19)	1592 (17)
50-59	686 (28)	2693 (28)
60-69	714 (29)	2544 (27)
70+	97 (4)	396 (4)
Gender		
Male	1400 (56)	5573 (58)
Female	1084 (44)	4022 (42)
Karnofsky score prior to transplant		
<90	949 (38)	3510 (37)
>=90	1515 (61)	5863 (61)
Missing	20 (<1)	222 (2)
Primary disease code		
AML	1196 (48)	3856 (40)
ALL	339 (14)	1030 (11)
Other leukemia	76 (3)	443 (5)
CML	97 (4)	403 (4)
MDS	473 (19)	2555 (27)
Other acute leukemia	31 (1)	79 (<1)
NHL	170 (7)	772 (8)
HD	12 (<1)	40 (<1)
Plasma cell disorder/Multiple Myeloma	5 (<1)	56 (<1)
Other Malignancies	0	6 (<1)
Severe aplastic anemia	63 (3)	223 (2)
Inherited abnormalities erythrocyte differentiation or function	12 (<1)	80 (<1)
SCID and other immune system disorders	4 (<1)	30 (<1)
Inherited disorders of metabolism	0	5 (<1)
Histiocytic disorders	4 (<1)	10 (<1)
Autoimmune diseases	0	6 (<1)

Characteristic	Clinical trial participants	Non-clinical trail participants
Other, specify	2 (<1)	1 (<1)
Race		
Caucasian	2190 (88)	8122 (85)
African-American	137 (6)	762 (8)
Asian	62 (2)	388 (4)
Pacific islander	8 (<1)	29 (<1)
Native American	8 (<1)	51 (<1)
More than one race	11 (<1)	67 (<1)
Missing	68 (3)	176 (2)
Donor type		
HLA-identical sibling	866 (35)	2460 (26)
Other relative	176 (7)	718 (7)
Unrelated	1441 (58)	6378 (66)
Missing	1 (<1)	39 (<1)
Graft type		
Bone Marrow	419 (17)	1241 (13)
Peripheral Blood	1897 (76)	6603 (69)
Cord Blood	168 (7)	1751 (18)
Marital status		
Single, never married	391 (16)	1667 (17)
Married	1726 (69)	6429 (67)
Separated/Divorced	230 (9)	929 (10)
Widowed	55 (2)	202 (2)
Missing	82 (3)	368 (4)
Highest educational grade completed		
No primary education	1 (<1)	7 (<1)
High school or lower	642 (26)	2804 (29)
College	320 (13)	1354 (14)
Graduate School	697 (28)	2602 (27)
Missing	824 (33)	2828 (29)
Zip code availability		
No	129 (5)	272 (3)
Yes	2355 (95)	9323 (97)
Year of transplant		
2008-2011	903 (36)	5721 (60)
2012-2014	1581 (64)	3874 (40)
Median follow-up of survivors (range), months	49 (3-123)	71 (2-128)

Table 2. Characteristics of adult patients (age>18 years old) who underwent first autologous transplant between 2008 and 2014 in US reported to the CIBMTR (CRF)

Characteristic	Clinical trial participants	Non-clinical trail participants
Number of patients	1232	5037
Number of centers	73	143
Age at transplant, years, median(range)	57 (18-80)	58 (18-82)
Age at transplant, years		
18-19	5 (<1)	31 (<1)
20-29	29 (2)	261 (5)
30-39	76 (6)	349 (7)
40-49	232 (19)	716 (14)
50-59	458 (37)	1515 (30)
60-69	392 (32)	1773 (35)
70+	40 (3)	392 (8)
Gender		
Male	745 (60)	2951 (59)
Female	487 (40)	2086 (41)
Karnofsky score prior to transplant		
<90	425 (34)	2048 (41)
>=90	788 (64)	2811 (56)
Missing	19 (2)	178 (4)
Primary disease code		
AML	9 (<1)	124 (2)
ALL	0	12 (<1)
Other leukemia	0	8 (<1)
MDS	0	1 (<1)
Other acute leukemia	0	2 (<1)
NHL	236 (19)	1471 (29)
HD	51 (4)	461 (9)
Plasma cell disorder/Multiple Myeloma	930 (75)	2769 (55)
Other Malignancies	4 (<1)	166 (3)
Breast cancer	0	2 (<1)
Histiocytic disorders	0	1 (<1)
Autoimmune diseases	2 (<1)	16 (<1)
Other, specify	0	4 (<1)
Race		
Caucasian	984 (80)	3930 (78)
African-American	183 (15)	854 (17)
Asian	31 (3)	123 (2)

Characteristic	Clinical trial participants	Non-clinical trail participants
Pacific islander	1 (<1)	11 (<1)
Native American	7 (<1)	25 (<1)
More than one race	6 (<1)	15 (<1)
Missing	20 (2)	79 (2)
Graft type		
Bone Marrow	3 (<1)	9 (<1)
Peripheral Blood	1229	5028
Marital status		
Single, never married	137 (11)	639 (13)
Married	859 (70)	3475 (69)
Separated/Divorced	127 (10)	545 (11)
Widowed	31 (3)	179 (4)
Missing	78 (6)	199 (4)
Highest educational grade completed		
No primary education	1 (<1)	4 (<1)
High school or lower	334 (27)	1563 (31)
College	184 (15)	799 (16)
Graduate School	321 (26)	1328 (26)
Missing	392 (32)	1343 (27)
Zip code availability		
No	19 (2)	116 (2)
Yes	1213 (98)	4921 (98)
Year of transplant		
2008-2011	666 (54)	2925 (58)
2012-2014	566 (46)	2112 (42)
Median follow-up of survivors (range), months	71 (4-124)	65 (1-128)

Proposal: 1811-114

Title:
Incidence and Predictors of Post-Transplant Emotional Distress in Patients Undergoing Hematopoietic Cell Transplant

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Research hypothesis/ specific aims:

- To study the cumulative incidence and predictors of post-transplant emotional distress (anxiety, depression, post-traumatic stress disorder [PTSD] requiring treatment)
    - Hypothesis: Patient age, sex, pre-HCT marital status, pre-HCT employment status, transplant type will be associated with and predictive of post-HCT emotional distress

- To study the association of post-HCT emotional distress at day 100 with total number of inpatient days in first 100 days post-HCT, chronic graft-vs-host disease (at 6-months, 12-months), infections (6-months, 12-months) and overall survival (1-year) in recipients of allogeneic HCT
    - Hypothesis: Patients who spend fewer days out of the hospital in first 100 days will have significantly higher emotional distress. These patients with emotional distress at day 100 will subsequently have higher chronic graft-vs-host disease (cGVHD) and infections at 6-months and 12-months. Additionally, these patients will have significantly lower 1-year survival compared to those without emotional distress.

Scientific impact:
Hematopoietic cell transplant is an intensive procedure, putting patients at high risk for acute and chronic complications, including emotional distress such as anxiety, depression, and post-traumatic stress disorder (PTSD). Emotional distress could impact patients' global health-related quality of life (HRQOL), several domains such as sleep, sexual, and physical function[1] and lead to unhealthy lifestyle, high risk behaviors such as abnormal dietary habits, excessive smoking, alcohol use and illicit substance use, affect healthcare utilization and adherence to medical management.
In 2017, the CIBMTR added questions in their comprehensive report form (CRF) asking whether patients were diagnosed with anxiety, depression, or PTSD and were receiving therapy for the same. Availability of these data provides a unique opportunity to study the incidence of emotional distress in acute post-transplant period and eventually longitudinal assessment through survivorship phase. It also allows us to study the predictors of these conditions and their association with patients' clinical outcomes such as GVHD, infections, and overall survival.

Scientific justification:
Hematopoietic cell transplant has become the standard of care for several malignant and non-malignant hematological conditions. While the survival rates continue to improve due to improved understanding of transplant physiology and medical management of complications, increased focus has been laid on post-transplant life-altering conditions. Emotional distress such as anxiety, depression, and PTSD could be acute or chronic complications of HCT.

<u>Incidence and predictors of post-HCT emotional distress:</u>

Prior studies have reported 22-43% prevalence of emotional distress in HCT survivors[1]; however it is primarily studied in >1 year survivors of HCT. Additionally, these studies reported self-reported anxiety/ depression through a variety of scales. Very few studies have assessed the incidence of physician diagnosed/ clinically documented emotional distress in immediate post-HCT time-period. Previous studies have reported following as predictors of post-HCT emotional distress: younger age at HCT, female sex, aggressive treatment, lower socio-economic status, and transplant type[1].

Association of emotional distress with overall survival/ post-HCT complications:

A previous CIBMTR study showed that pre-HCT depression was associated with significantly lower overall survival and higher incidence of grade 2-4 acute GVHD[2]. Additionally, this study showed that patients with pre-HCT depression spent significantly lower number of days out of hospital in first 100 days post-HCT. It is important to note that post-HCT depression, anxiety, or PTSD were not captured in the CIBMTR forms then and were not studied. We hypothesize that post-HCT emotional distress will also significantly impact overall survival and be associated with post-HCT complications such as GVHD and infections. Additionally, we hypothesize a significant association between post-HCT emotional distress and inpatient stay based on previous literature[3].

Very few multi-institutional studies have assessed the impact of post-HCT emotional distress on clinical outcomes. A study in adult HCT recipients with self-reported post-HCT depression showed significantly lower 1-year survival compared to those without depression[4]. A recent study from the chronic GVHD consortium showed self-reported depression and anxiety in 19% and 23% of adult patients with cGVHD, respectively[5]. Moreover, depression was associated with worse overall survival. Since this study only included patients with cGVHD, a direct comparison in patients without cGVHD was not possible. Results of these studies underscore the need for a multi-institutional study to assess the impact of post-HCT emotional distress on clinical outcomes in both adults and children undergoing transplant.

Our proposed study using the CIBMTR data will allow us to study the cumulative incidence and predictors of post-HCT emotional distress up to 1-year post-HCT. It will also enable us to study the association of anxiety, depression, and PTSD with patients' overall survival and post-HCT complications such as chronic GVHD development and infections.

Patient eligibility population:

- Patients who underwent HCT for malignant and non-malignant conditions, reported to the CIBMTR
- Transplanted with any donor type
- Peripheral blood, bone marrow, or cord blood as stem cell source
- All conditioning regimens
- Underwent transplant between November 1, 2016 to July 1, 2018

Forms (Following CIBMTR forms will be used):

- 2400 – Pre-Transplant Essentail Data
- 2000 – Recipient Baseline Data
- 2100 – Post-HSCT Data (100 days, 6 months, 2 years)

Patient-related:

- Age at HCT: continuous and 0-9, 10-17, 18-29, 30-39, 40-49, 50-59, ≥60 years
- Sex: male vs female
- Race/ ethnicity: Caucasian vs African American vs Asian/ pacific islander vs Hispanic vs others
- Karnofsky performance score: ≥90 vs <90 vs missing

- HCT-CI: 0 vs 1-2 vs ≥3
- Pre-HCT marital status: single, never married vs married vs separated vs divorced vs widowed vs unknown
- Pre-HCT psychiatric disturbance: no vs yes vs unknown
- History of smoking: no vs yes
- Highest educational grade (for age ≥18): no primary education, less than primary/ elementary, primary or elementary, lower secondary, upper secondary, post-secondary/ non-tertiary, tertiary Type A, tertiary Type B, advanced research
- Pre-HCT annual household income: <$20,000, $20-39,999, $40,000-59,999, $60,000-79,000, ≥$80,000
- Pre-HCT health insurance status: Government vs Private vs None
- Pre-HCT employment status (for age ≥18): working full-time vs working part-time vs unemployed vs retired vs medical disability vs missing/ unknown

Disease-related:

- Disease diagnosis: ALL vs AML vs MDS/MPN vs multiple myeloma vs other hematologic malignancies vs non-malignant disorders
- Disease status prior to HCT (for malignant diseases only)
- Time from diagnosis to transplant
- Disease risk index (for malignant diseases only): low vs intermediate vs high vs very high

Donor-related:

- Donor age
- Donor/ recipient sex
- Donor/ recipient CMV status
- Graft source: bone marrow vs peripheral blood vs cord
- Donor type: HLA-identical vs other related vs matched unrelated vs mismatched unrelated vs autologous

Transplant-related:

- Type of transplant: allogeneic vs autologous
- Conditioning regimen: MAC vs RIC/ NMA as defined by CIBMTR
- TBI use: yes vs no
- TBI dose: MAC vs RIC/ NMA
- GVHD prophylaxis (for allogeneic only): calcineurin inhibitor + MTX vs calcineurin inhibitor + MMF vs others

Post-transplant related:

- Total number of inpatient days in first 100 days post-HCT (continuous)

Outcome:

- Primary: Post-HCT emotional distress (anxiety, depression, or PTSD requiring treatment)
- Secondary: overall survival (1-year), cGVHD (6 months, 1-year), infections (6 months, 1-year)

Study design:

This study will be a retrospective cohort study investigating post-HCT emotional distress (anxiety, depression, PTSD requiring treatment) in patients undergoing HCT for malignant and non-malignant

conditions. The objective of this analysis is to study the cumulative incidence (at 1-year post-HCT) and predictors of these conditions post-HCT. This study intends to use the data currently available from the existing CIBMTR database through CRF forms. Descriptive statistics will be presented for the patient-, disease- and transplant- related variables and will be compared between patients with or without post-HCT anxiety, depression, or PTSD. Frequencies and percentages will be calculated for anxiety, depression, and PTSD at 100 days, 6 months and 1-year time-points.

- Aim 1: Cumulative incidence for each condition will be calculated with death as a competing risk. A Cox proportional hazard model will be created to study the impact of pre-HCT risk factors on development of post-HCT emotional distress. Post-HCT anxiety, depression or PTSD will be considered an event, and patients without any condition will be censored at their last follow-up.
- Aim 2: A Cox proportional hazard model will be created to study the association between post-HCT anxiety, depression, PTSD and overall survival at 1-year time-point. Multivariate models will be created to study the association between emotional distress (at 100 days) and total number of inpatient days in first 100 days post-HCT, and cGVHD and infections (at 6 months, 1 year).

P value < 0.05 will be considered statistically significant. SAS 9.4 (SAS Inc., Cary, NC) will be used for all analyses.

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Conflicts of interest:

None

Table 1. Characteristics of patients who underwent first allogeneic transplant between 2017 and 2018 (before July 1st 2018) in US reported to the CIBMTR (CRF)

Characteristic	N (%)
Number of patients	3009
Number of centers	160
Age at transplant, years, median(range)	56 (<1-88)
Age at transplant, years	
0-9	357 (12)
10-17	175 (6)
18-29	217 (7)
30-39	189 (6)
40-49	307 (10)
50-59	515 (17)
>=60	1249 (42)
Gender	
Male	1756 (58)
Female	1253 (42)
Karnofsky score prior to transplant	
<90	1217 (40)
>=90	1694 (56)
Missing	98 (3)
Primary disease code	
AML	805 (27)
ALL	328 (11)
Other leukemia	70 (2)
CML	38 (1)
MDS	1087 (36)
Other acute leukemia	24 (<1)
NHL	132 (4)
HD	25 (<1)
Plasma cell disorder/ multiple myeloma	7 (<1)
Severe aplastic anemia	184 (6)
Inherited abnormalities erythrocyte differentiation or function	137 (5)
SCID and other immune system disorders	132 (4)
Inherited abnormalities of platelets	3 (<1)
Inherited disorders of metabolism	26 (<1)
Histiocytic disorders	8 (<1)
Other, specify	3 (<1)
Race	

Characteristic	N (%)
Caucasian	2242 (75)
African-American	372 (12)
Asian	169 (6)
Pacific islander	8 (<1)
Native American	30 (<1)
More than one race	38 (1)
Missing	150 (5)
Donor type	
HLA-identical sibling	610 (20)
Other relative	727 (24)
Unrelated	1671 (56)
Missing	1 (<1)
Graft type	
Bone Marrow	818 (27)
Peripheral Blood	1822 (61)
Cord Blood	369 (12)
Highest educational grade completed	
No primary education	266 (9)
High school or lower	973 (32)
College	332 (11)
Graduate School	765 (25)
Missing	673 (22)
Zip code availability	
No	322 (11)
Yes	2687 (89)
Year of transplant	
2017	2464 (82)
2018	545 (18)
Median follow-up of survivors (range), months	6 (1-19)

Completeness of follow-up

Time (set date: 09/30/18)	Overall, %
1-year	74
2-year	62

Table 2. Characteristics of patients who underwent first autologous transplant between 2017 and 2018 (before July 1st 2018) in US reported to the CIBMTR (CRF)

Characteristic	N(%)
Number of patients	1703
Number of centers	129
Age at transplant, years, median(range)	59 (<1-79)
Age at transplant, years	
0-9	57 (3)
10-17	15 (<1)
18-29	67 (4)
30-39	67 (4)
40-49	187 (11)
50-59	494 (29)
>=60	816 (48)
Gender	
Male	977 (57)
Female	726 (43)
Karnofsky score prior to transplant	
<90	814 (48)
>=90	862 (51)
Missing	27 (2)
Primary disease code	
AML	6 (<1)
MDS	1 (<1)
NHL	366 (21)
HD	96 (6)
Plasma cell disorder, multiple myeloma	1146 (67)
Other Malignancies	74 (4)
Inherited abnormalities erythrocyte differentiation or function	1 (<1)
SCID and other immune system disorders	10 (<1)
Inherited disorders of metabolism	1 (<1)
Autoimmune diseases	2 (<1)
Race	
Caucasian	989 (58)
African-American	529 (31)
Asian	98 (6)
Pacific islander	2 (<1)
Native American	24 (1)
More than one race	19 (1)

Characteristic	N(%)
Missing	42 (2)
Graft type	
Bone Marrow	10 (<1)
Peripheral Blood	1692 (99)
Cord Blood	1 (<1)
Highest educational grade completed	
No primary education	52 (3)
High school or lower	513 (30)
College	260 (15)
Graduate School	452 (27)
Missing	426 (25)
Zip code availability	
No	184 (11)
Yes	1519 (89)
Year of transplant	
2017	1261 (74)
2018	442 (26)
Median follow-up of survivors (range), months	6 (1-20)

Completeness of follow-up

Time (set date: 09/30/18)	Overall, %
1-year	74
2-year	62

Proposal: 1811-130

Title:
Socioeconomic factors and their impact on non-relapse mortality, graft-versus-host disease (GVHD), and GVHD-free survival among patients who received an allogeneic transplant for acute myeloid leukemia.

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Hypothesis:
Socioeconomic factors, such as education level and income, have been previously shown to impact various outcomes for recipients of solid organ transplants and hematopoietic stem cell transplants. Prior studies were limited to single institution studies or unrelated donor transplants with heterogeneous diagnosis. We predict that lower income and education levels will have higher rates of non-relapse mortality (NRM) and rates of both acute and chronic graft-versus host disease (GVHD) and inferior GVHD-free survival following transplantation for acute myeloid leukemia (AML).

Specific aims:
The purpose of this study is to determine which socioeconomic variables, if any, impact NRM and acute/chronic GVHD among adult patients with AML who undergo allogeneic hematopoietic stem cell transplant (alloHSCT) while in first or second complete remission (CR1 or CR2). Specifically, we want to explore income level, employment status, marital status, and education level, and their possible effect on NRM (at 100 days, 6 months and 1 year post-transplant), GVHD-free survival, as well as the rates of acute and chronic GVHD within this patient population.

Scientific impact:
Underserved communities have historically had poor outcomes following various medical interventions and are often underrepresented in the medical literature. This study hopes to highlight which socioeconomic factors may predispose a patient to a poor transplant outcomes after related, unelated and haploidentical transplant, with the hope inspiring future interventions in improving the overall care for these communities.

Scientific justification:
AML is an aggressive hematologic malignancy characterized by the accumulation of functionally incompetent myeloid precursors in the bone marrow and peripheral blood. Aggressive induction chemotherapy with cytarabine and an anthracycline can yield CR rates of approximately 70% of adult patients [1, 2]. While some adults may be cured with induction and consolidation chemotherapy, alloHSCT remains an important consolidation strategy for many patients, particularly those with poor-risk disease [3-5]. Currently, AML represents the most common disease for which an alloHSCT is

performed in the United States [6]. The decision to undergo alloHSCT is complex, as the process can be associated with a high degree of morbidity and possible mortality. Acute and chronic GVHD, infectious complications, and even secondary malignancies following alloHSCT are all associated with lower survival rates among transplant recipients [7-9].
Aside from disease-related characteristics, the morbidity and mortality following transplant has been shown to be affected by various socioeconomic factors of the recipient. Hamilton, et al, demonstrated that higher income status was associated with a lower burden of severe chronic GVHD symptoms. Conversely, the inability to return to work following transplantation was associated with higher overall mortality [10]. Lower income has also been shown to poorly impact overall survival in individuals who have undergone allogeneic transplant, regardless of disease type [11, 12]. Moreover, a recipient's race, education level and marital status have also been shown to potentially impact outcomes following stem cell transplantation [13-15].
This proposed study hopes to explore the impact of socioeconomic factors on NRM, rates of acute and chronic GVHD, GVHD-free survival among individuals who received an alloHSCT for AML while in CR1 or CR2. As AML represents the most common reason for alloHSCT in the United States, this information may yield important prognostic value for numerous patients and transplant centers.

Patient eligibility population:
Only adult (>18 years of age) individuals with a diagnosis of AML who underwent an alloHSCT in CR1 or CR2 will be included. Eligible individuals must have available socioeconomic information, including marital status, educational background, occupation and working status, and income level. Transplants performed prior to January 1, 2000 will not be included. If an individual has received more than one allogeneic transplant in their lifetime, only the first transplant should be included in the dataset (provided the circumstances around the transplant meet other eligibility criteria). Both related and unrelated donor transplants will be included. Any conditioning/preparative regimen or GVHD prophylactic regimen will be allowed in the study. Data will be collected at 100 days, 6 months and 1 year after alloHSCT, presuming the individual was alive for ongoing collection of data. Individuals must have 1-year post-transplant data available or have been deceased prior to that time, as would be designated on the preceding collection forms.

Data requirements:
Only previously-collected data will be required.
Socioeconomic data will be obtained from Form 2000.
Survival status, presence of acute or chronic GVHD (with standard disease grading), graft function data, GVHD preventative regimens, infection data, secondary malignancy data, and other clinical follow-up data will be obtained from Form 2100. Data from 60-days, 6-months and 1-year following transplant are required, presuming the individual was alive for collection of data.

Study design:
Marital status, educational background, occupation, working status, and income level will be the key variables assessed for any association with NRM, development of acute/chronic GVHD and GVHD-free survival. We will also explore other variables that may influence transplant outcomes such as transplant center effects, including children transplant programs versus adult transplant program. NRM will be

defined as death from any cause aside from disease relapse/progression. Individuals who are deceased from disease relapse/progression will be noted, but censored from the analysis. Occurrence of acute or chronic GVHD (yes versus no) will be noted. The grade of acute GVHD (I-IV) or chronic GVHD (mild, moderate, severe) will be noted, as recorded on Form 2100. Categorical data will be analyzed using Fisher's exact test, and continuous data will be analyzed using the Mann-Whitney test or the Kruskal-Wallis test, as appropriate. In addition, multivariable logistic regression will be used to determine which key variables are associated with higher rates of NRM or GVHD.

Data source: All data will be derived from the CIBMTR Research Database. No external data is required for this study.

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Conflicts of interest:
None

Characteristics of patients who underwent the first allogeneic transplant in CR1 or CR2 for AML between 2000 and 2016 in US reported to the CIBMTR (CRF)

Characteristic	N (%)
Number of patients	8128
Number of centers	174
Age at transplant, years, median(range)	52 (18-81)
Age at transplant, years	
18-29	1069 (13)
30-39	988 (12)
40-49	1615 (20)
50-59	2322 (29)
>=60	2134 (26)
Gender	
Male	4221 (52)
Female	3907 (48)
Karnofsky score prior to transplant	
<90	2632 (32)
>=90	5162 (64)
Missing	334 (4)
Disease status	
1st Complete remission	5848 (72)
2nd Complete remission	2280 (28)
Race	
Caucasian	7025 (86)
African-American	498 (6)
Asian	312 (4)
Pacific islander	13 (<1)
Native American	29 (<1)
Other	7 (<1)
More than one race	40 (<1)
Missing	204 (3)
Donor type	
HLA-identical sibling	2078 (26)
Other relative	612 (8)
Unrelated	5387 (66)
Missing	51 (<1)
Graft type	
Bone Marrow	1406 (17)
Peripheral Blood	5630 (69)
Cord Blood	1091 (13)
Missing or Other	1 (<1)
Highest educational grade completed	

Characteristic	N (%)
No primary education	5 (<1)
High school or lower	1864 (23)
College	1214 (15)
Graduate School	1507 (19)
Missing	3538 (44)
Zip code availability	
No	1007 (12)
Yes	7121 (88)
Year of transplant	
2000-2004	1344 (17)
2005-2008	2347 (29)
2009-2012	1780 (22)
2013-2016	2657 (33)
Median follow-up of survivors (range), months	73 (1-218)