Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Houston, Texas
Wednesday, February 20, 2019, 2:45 – 4:45 pm

Co-Chair:	**Mary Flowers, MD, Fred Hutchinson Cancer Research Center, Seattle, WA; Telephone: 206-667-5191; E-mail: mflowers@fredhutch.org**
Co-Chair:	**Minoo Battiwalla, MD, MS, Sarah Cannon Research Institute, Nashville, TN; Phone: 301-742-7782; E-mail: minoo.battiwalla@hcahealthcare.com**
Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Scientific Director:	**Bronwen Shaw, MBChB, MRCP, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: beshaw@mcw.edu**
Assistant Scientific Director:	**Rachel Phelan, MD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4153; E-mail: rphelan@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8687; E-mail: ruta@mcw.edu**
Statistician:	**Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0674; E-mail: sbosubait@mcw.edu**

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1. **Introduction**

   a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair: **Betty Hamilton, MD**; Cleveland Clinic Foundation; Email: hamiltb2@ccf.org; Telephone: 216-445-7580

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

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

   a. **LE13-02** Herr MH, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon E, Battiwalla M, Buchbinder D, Flowers M, Brazauskas R, Shaw BE, Morton LM. Risk Factors for the Development of Cutaneous Melanoma after Allogeneic Hematopoietic Cell Transplantation. ***Presented at 60th ASH Annual Meeting and Exposition.***

b. **LE14-01** Radivoyevitch T, Dean RM, Shaw BE, Brazauskas R, Millard HR, Molenaar RJ, Battiwalla M, Savani BN, Flowers MED, Cooke KR, Hamilton BK, Kalaycio M, Maciejewski JP, Ahmed I, Akpek G, Bajel A, Buchbinder D, Cahn JY, D'Souza A, Daly A, DeFilipp Z, Ganguly S, Hamadani M, Hayashi RJ, Hematti P, Inamoto Y, Khera N, Kindwall-Keller T, Landau H, Lazarus H, Majhail NS, Marks DI, Olsson RF,, Seo S, Steinberg A, William BM, Wirk B, Yared JA, Aljurf M, Abidi MH, Allewelt H, Beitinjaneh A, Cook R, Cornell RF, Fay JW, Hale G, Holter Chakrabarty J, Jodele S, Kasow KA, Mahindra A, Malone AK, Popat U, Rizzo JD, Schouten HC, Warwick AB, Wood WA, Sekeres MA, Litzow MR, Gale RP, Hashmi SK. Risk of acute myeloid leukemia and myelodysplastic syndromes after autologous transplant for lymphoma and plasma cell myeloma. ***Leukemia Research.***

c. **LE16-01** Norkin M, Shaw BE, Brazauskas R, Tecca HR, Leather HL, Gea-Banacloche J, Kamble R, DeFilipp Z, Jacobsohn DA, Ringden O, Inamoto Y, Kasow K, Buchbinder D, Shaw P, Hematti P, Schears R, Badawy SM, Lazarus HM, Bhatt N, Horn B, Chhabra S, Page K, Hamilton B, Hildebrandt GC, Yared JA, Agrawal V, Beitinjaneh A, Majhail NS, Kindwall-Keller T, Olsson RF, Schoemans H, Gale RP, Ganguly S, Ahmed I, Schouten HC, Liesveld J, Khera N, Steinberg A, Shah AJ, Solh M, Marks DI, Rybka W, Aljurf M, Dietz AC, Gergis U, George B, Seo S, Flowers MED, Battiwalla M, Savani BN, Riches ML, Wingard JR. Characteristics of late fatal infections after allogeneic hematopoietic cell transplant. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.***

d. **LE16-03** Bhatt NS, Brazauskas R, Tecca HR, Carreras J, Burns LJ, Phelan R, Salit RB, Syrjala KL, Talano JM, Shaw BE. Post-transplantation employment status of adult survivors of childhood allogeneic hematopoietic cell transplant: A report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Cancer.***

e. **LE17-02** Lee CJ, Kim S, Tecca HR, Bo-Subait SL, Brazauskas R, Battiwalla, M, Buchbinder D, Flowers MED, Phelan R, Shaw BE, Muffly LS. Impact of Myeloablative Total Body Irradiation Versus Chemotherapy on Late Effects and Survival Among Adolescent and Young Adult Survivors of Hematopoietic Cell Transplantation for Acute Leukemia: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis. ***Presented at 60th ASH Annual Meeting and Exposition.***

f. **LE17-G1a** Inamoto Y, Valdés-Sanz N, Ogawa Y, Alves M, Berchicci L, Galvin J, Greinix H, Hale GA, Horn B, Kelly D, Liu H, Rowley S, Schoemans H, Shah A, Stanghellini MTL, Argrawal V, Ahmed I, Ali A, Bhatt N, Byrne M, Chhabra S, DeFilipp Z, Fahnehjelm K, Farhadfar N, Horn E, Lee C, Nathan S, Penack O, Prasad P, Rotz S, Rovó A, Yared J, Pavletic S, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers ME, Shaw BE, Petriček I. Ocular graft-versus-host disease after hematopoietic cell transplantation: Expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.**

Inamoto Y, Valdés-Sanz N, Ogawa Y, Alves M, Berchicci L, Galvin J, Greinix H, Hale GA, Horn B, Kelly D, Liu H, Rowley S, Schoemans H, Shah A, Stanghellini MTL, Argrawal V, Ahmed I, Ali A, Bhatt N, Byrne M, Chhabra S, DeFilipp Z, Fahnehjelm K, Farhadfar N, Horn E, Lee C, Nathan S, Penack O, Prasad P, Rotz S, Rovó A, Yared J, Pavletic S, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers ME, Shaw BE, Petriček I. Ocular graft-versus-host disease after hematopoietic cell transplantation: Expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Bone Marrow Transplantation.**

g. **LE17-G1b** Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, Rovó A, Schears R, Shah A, Agrawal V, Ahmed A, Ahmed I, Ali A, Aljurf M, Alkhateeb H, Beitinjaneh A, Bhatt N, Buchbinder D, Byrne M, Callander N, Fahnehjelm K, Farhadfar N, Gale RP, Ganguly S, Hildebrandt GC, Horn E, Jakubowski A, Kamble RT, Law J, Lee C, Nathan S, Penack O, Pingali R, Prasad P, Pulanic D, Rotz S, Shreenivas A, Steinberg A, Tabbara K, Tichelli A, Wirk B, Yared J, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers MED, Shaw BE, Valdés-Sanz N. Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.**

Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, Rovó A, Schears R, Shah A, Agrawal V, Ahmed A, Ahmed I, Ali A, Aljurf M, Alkhateeb H, Beitinjaneh A, Bhatt N, Buchbinder D, Byrne M, Callander N, Fahnehjelm K, Farhadfar N, Gale RP, Ganguly S, Hildebrandt GC, Horn E, Jakubowski A, Kamble RT, Law J, Lee C, Nathan S, Penack O, Pingali R, Prasad P, Pulanic D, Rotz S, Shreenivas A, Steinberg A, Tabbara K, Tichelli A, Wirk B, Yared J, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers MED, Shaw BE, Valdés-Sanz N. Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Bone Marrow Transplantation.**

4. Studies in progress (Attachment 3)

a. **LE99-01** Quality of life in late HCT survivors (J Wingard) **Manuscript Preparation**
b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Data file Preparation**
c. **LE13-02** Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation (M Herr/L Morton) **Manuscript Preparation**
e. **LE16-02** An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases (JM Kahn/P Satwani) **Manuscript Preparation**
f. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Data file Preparation**
g. **LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia (S Lee/L Muffly) **Manuscript Preparation**
h. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Protocol Development**

i. **LE18-02** Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) **Data file Preparation**

5. Future/proposed studies

a. **PROP 1811-73** Late mortality in acute leukemia patients undergoing allogeneic transplantation (*Hashmi/Bar/Lazarus*) (Attachment 4)
b. **PROP 1811-128** Incidence and predictors of long term toxicities and late side effects in elderly patients (≥ 60 years) receiving high dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) for lymphoma *(Dahi/Giralt/Jakubowsky)* (Attachment 5)
c. **PROP 1811-142** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients *(Zinter/Dvorak/Duncan)* (Attachment 6)
d. **PROP 1811-146** Use of data from the CIBMTR dataset of subjects exposed to ionizing radiations to refine and extend estimates of risk of radiation-induced solid cancers currently based on data from the atomic bomb survivors in the Radiation Effects Research Foundation (RERF) dataset, persons with cancer receiving conventional radiation therapy in the US Surveillance and End Results (SEER) dataset and other radiation exposure datasets *(Gale/Zablotska/Hoffman/Hashmi)*(Attachment 7)
e. **PROP 1812-04** Risk of sarcoma after allogeneic hematopoietic stem cell transplantation *(Advani/Morton/Curtis/Schonfeld)* (Attachment 8)
f. **PROP 1812-10** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies *(Veeraputhiran/Pingali/Mukherjee/Muffly)* (Attachment 9)

Dropped proposed studies

a. **PROP 1811-13** Late effects and malignancies among survivors of second hematopoietic cell transplantation for graft failure in non-malignant disorders. *Dropped due to feasibility.*
b. **PROP 1811-179** Late effects and second neoplasms in de novo pediatric acute myeloid leukemia patient treated with TBI vs non-TBI conditioning regimens in the modern era. *Dropped due to feasibility and overlap with an existing study.*

6. Other Business

a. CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party call for review proposals

7. Closing Remarks

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Salt Lake City, Utah
Saturday, February 24, 2018, 12:15 – 2:15 pm

Co-Chair:	**Bipin Savani, MD, Vanderbilt University Medical Center, Nashville, TN; Telephone: 615-936-8422; E-mail: bipin.savani@vanderbilt.edu**
Co-Chair:	**Mary Flowers, MD, Fred Hutchinson Cancer Research Center, Seattle, WA; Telephone: 206-667-5191; E-mail: mflowers@fredhutch.org**
Co-Chair:	**Minoo Battiwalla, MD, MS, National Heart Lung and Blood Institute – NIH Phone: 301-827-0939; E-mail: battiwam@nhlbi.nih.gov**
Scientific Director:	**Bronwen Shaw, MBChB, MRCP, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: beshaw@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8687; E-mail: ruta@mcw.edu**
Statistician:	**Heather Millard, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0703; E-mail: hmillard@mcw.edu**

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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 12:15pm on Saturday, February 24, 2018, by Dr. Mary Flowers. She introduced the current working committee leadership and introduced the incoming chair, Dr. David Buchbinder. The leadership thanked Dr. Bipin Savani, the outgoing chair, for his service to the LEWC over the past five years. Dr. Flowers welcomed Dr. Zinaida Peric of the EBMT Complications and Quality of Life Working Party. The processes of participating in the working committee, voting guidance, and rules of authorship were described.

Dr. Bronwen Shaw presented the available quality of life data collected by the CIBMTR, which includes 263 adult transplant recipients and 77 pediatric transplant recipients. This data has been used for several studies and is open for use for future proposals.

a. Minutes and Overview Plan from February 2017 meeting (Attachment 1)

Minutes from February 2017 were approved by the LEWC.

b. Introduction of incoming Co-Chair: **David Buchbinder, MD**; CHOC Children's Hospital; Email: DBuchbinder@choc.org; Telephone: 714-509-8744

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **SC09-05** Shaw BE, Brazauskas R, Millard HR, Fonstad R, Flynn K, Abernethy A, Vogel J, Petroske C, Mattila D, Drexler R, Lee SJ, Horowitz MM, Rizzo JD. Centralized patient-reported outcome data collection in transplantation is feasible and clinically meaningful. ***Cancer. 2017 Dec 1; 123(23), 4687-4700.***

Bhatt NS, Brazauskas R, Millard HR, Vogel J, Mattila D, Drexler R, Lee SJ, Horowitz MM, Rizzo JD, Shaw BE. Female Gender and Malignancy are Associated with Low PedsQL Scores at 12 Months Post-Hematopoietic Cell Transplantation. ***Presented at Pediatric Blood and Marrow Transplant Consortium 2017.***

Bhatt NS, Brazauskas R, Millard HR, Vogel J, Mattila D, Drexler R, Lee SJ, Horowitz MM, Rizzo JD, Shaw BE. Variations in Self-Reported and Parent Proxy PedsQLTM Scores in Pediatric Patients Undergoing Hematopoietic Cell Transplantation. ***Presented at International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer 2017.***

Bhatt NS, Brazauskas R, Millard HR, Vogel J, Mattila D, Lee SJ, Horowitz MM, Rizzo JD, Shaw BE. Female Gender is Associated with Poor Health-Related Quality of Life in Children at 12-months Post-Hematopoietic Cell Transplantation. ***Submitted.***

D'souza A, Millard HR, Knight J, Brazauskas R, Lee SJ, Flynn KE, Rizzo JD, Shaw BE. Prevalence of self-reported sleep dysfunction before allogeneic hematopoietic cell transplantation. ***Submitted.***

b. **LE11-02** Gabriel M, Brazauskas R, Chen M, Savani B, Flowers M, Battiwalla M, Shaw BE, Shaw P. Risk Factors for Subsequent Central Nervous System Tumors in Pediatric Allogeneic Hematopoietic Cell Transplant: A Study from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Biology of Blood and Marrow Transplantation. 2017 August; 23(8), 1320-1326.***

c. **LE12-02** Vrooman LM, Millard HR, Brazauskas R, Majhail NS, Battiwalla M, Flowers MED, Savani BN, Akpek G, Aljurf M, Bajwa R, Baker KS, Beitinjaneh A, Bitan M, Buchbinder D, Chow E, Dandoy C, Dietz AC, Diller L, Gale RP, Hashmi SK, Hayashi RJ, Hematti P, Kamble RT, Kasow KA, Kletzel M, Lazarus HM, Malone AK, Marks DI, O'Brien TA, Olsson RF, Ringden O, Seo S, Steinberg A, Yu LC, Warwick A, Shaw BE, Duncan C. Survival and Late Effects after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancy at Less than Three Years of Age. ***Biology of Blood and Marrow Transplantation. 2017 August; 23(8), 1327-1334.***

d. **LE15-01** Myers RM, Hill BT, Shaw BE, Kim S, Millard HR, Battiwalla M, Majhail NS, Buchbinder D, Lazarus HM, Savani BN, Flowers MED, D'Souza A, Ehrhardt MJ, Langston A, Yared JA, Hayashi RJ, Daly A, Olsson RF, Inamoto Y, Malone AK, DeFilipp Z, Margossian SP, Warwick AB, Jaglowski S, Beitinjaneh A, Fung H, Kasow KA, Marks DI, Reynolds J, Stockerl-Goldstein K, Wirk B, Wood WA, Hamadani M, Satwani P. Long-term outcomes among 2-year survivors of autologous hematopoietic cell transplantation for Hodgkin and diffuse large b-cell lymphoma. ***Cancer. 2017 Nov 10.***

e. **LE16-G1** Kelly DL, Buchbinder D, Duarte RF, Auletta JJ, Bhatt N, Byrne M, DeFilipp Z, Gabriel M, Mahindra A, Norkin M, Schoemans H, Shah AJ, Ahmed I, Atsuta Y, Basak GW, Beattie S, Bhella S, Bredeson C, Bunin N, Dalal J, Daly A, Gajewski J, Gale RP, Galvin J, Hamadani M, Hayashi RJ, Adekola K, Law J, Lee CJ, Liesveld J, Malone AK, Nagler A, Naik S, Nishihori T, Parsons SK, Scherwath A, Schofield HL, Soiffer R, Szer J, Twist I, Warwick A, Wirk BM, Yi J, Battiwalla M, Flowers ME, Savani B, Shaw BE. Neurocognitive Dysfunction in Hematopoietic Cell Transplant Recipients: Expert Review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Complications and Quality of Life Working Party of the

European Group for Blood and Marrow Transplantation. ***Biology of Blood and Marrow Transplantation. 2017 Sep 20.***

Buchbinder D, Kelly DL, Duarte RF, Auletta JJ, Bhatt N, Byrne M, DeFilipp Z, Gabriel M, Mahindra A, Norkin M, Schoemans H, Shah AJ, Ahmed I, Atsuta Y, Basak GW, Beattie S, Bhella S, Bredeson C, Bunin N, Dalal J, Daly A, Gajewski J, Gale RP, Galvin J, Hamadani M, Hayashi RJ, Adekola K, Law J, Lee CJ, Liesveld J, Malone AK, Nagler A, Naik S, Nishihori T, Parsons SK, Scherwath A, Schofield HL, Soiffer R, Szer J, Twist I, Warwick A, Wirk BM, Yi J, Battiwalla M, Flowers ME, Savani B, Shaw BE. Neurocognitive Dysfunction in Hematopoietic Cell Transplant Recipients: Expert Review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Complications and Quality of Life Working Party of the European Group for Blood and Marrow Transplantation. ***BMT (In Press).***

f. **LE13-01** Duncan CN, Brazauskas R, Huang J, Shaw BE, Majhail NS, Savani BN, Flowers MED, Battiwalla M, Beebe K, Dietz AC, Dvorak CC, Giller R, Jacobson DA, Kletzel M, Martin PL, Nemecek ER, Nuechterlein B, Talano J, Pulsipher MA, Baker KS. Late cardiovascular morbidity and mortality following pediatric allogeneic hematopoietic cell transplantation. ***BMT (In Press).***

g. **LE14-01** Radivoyevitch T, Dean RM, Shaw BE, Brazauskas R, Millard HR, Molenaar RJ, Battiwalla M, Savani BN, Flowers MED, Cooke KR, Hamilton BK, Kalaycio M, Maciejewski JP, Ahmed I, Akpek G, Bajel A, Buchbinder D, Cahn JY, D'Souza A, Daly A, DeFilipp Z, Ganguly S, Hamadani M, Hayashi RJ, Hematti P, Inamoto Y, Khera N, Kindwall-Keller T, Landau H, Lazarus H, Majhail NS, Marks DI, Olsson RF, Seo S, Steinberg A, William BM, Wirk B, Yared JA, Aljurf M, Abidi MH, Allewelt H, Beitinjaneh A, Cook R, Cornell RF, Fay JW, Hale G, Holter Chakrabarty J, Jodele S, Kasow KA, Mahindra A, Malone AK, Popat U, Rizzo JD, Schouten HC, Warwick AB, Wood WA, Sekeres MA, Litzow MR, Gale RP, Hashmi SK. Risk of acute myeloid leukemia and myelodysplastic syndromes after autologous transplant for lymphoma and plasma cell myeloma. ***Submitted.***

4. Studies in progress (Attachment 3)

Dr. Bipin Savani briefly listed all studies in progress. He introduced Dr. Prakash Satwani to present an update on LE16-02 and Dr. Yoshi Inamoto to present LE17-G1.

a. **LE99-01** Quality of life in late HCT survivors (J Wingard) **Manuscript Preparation**
b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Data file Preparation**
c. **LE13-02** Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation (M Herr/L Morton) **Analysis**
e. **LE16-01** Analysis of late mortality from infections in allogeneic hematopoietic transplant recipients with hematologic malignances (M Norkin/JR Wingard/J Gea-Banacloche) **Manuscript Preparation**
f. **LE16-02** An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases (JM Kahn/P Satwani) **Manuscript Preparation**

Dr. Prakash Satwani presented this study, which aims to determine the risk of subsequent neoplasms in children undergoing allogeneic hematopoietic cell transplant (alloHCT) for non-malignant disorders. The population included 6,028 patients under the age of 21. Individual malignancy rates in the US population were compared to the general US population with age and sex matched controls, finding a significant increase of developing malignancies in the alloHCT cohort. The population was then grouped by primary disease into high, intermediate, and low risk groups and compared to the general population, looking at incidence of developing any new malignancy. Committee members suggest confirming that AML/MDS subsequent malignancies were not due to an undetected co-existing

primary disease (or incorrect assignment of the primary disease), and suggested that these diagnoses be analysed separately. Members also felt it would be helpful to know details on which subsequent malignancies developed in each of the primary diseases studied, in particular the hemaglobinopathies (where a high risk is not thought to occur).

g. **LE16-03** PostHCT employment status in adult survivors of childhood HCT (N Bhatt/BE Shaw) **Manuscript Preparation**

h. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Protocol Development**

i. **LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia (S Lee/L Muffly) **Data File Preparation**

j. **LE17-G1a** GVHD ocular complications after HCT (Y Inamoto/I Petricek/N Sanz) **Manuscript Preparation**

k. **LE17-G1b** Non-GVHD ocular complications after HCT (Y Inamoto/I Petricek/N Sanz) **Manuscript Preparation**

Dr. Yoshi Inamoto presented an update on the reviews of ocular complications post-transplant. He explained the methods of searching PubMed and reviewing relevant articles. It became clear to the PIs during the process that the information was too abundant for a single paper and has been split into two companion papers: one for ocular GVHD and one for non-GVHD ocular complications. PIs plan to circulate the draft manuscript in May and submit by July 2018. One committee member suggested to add a supplemental document for additional references if there were too many for the main document. Another member requested that the PIs develop a handout that can be given to ophthalmologists by transplant physicians.

5. ***Future/proposed studies***

a. **PROP 1711-30/131** Incidence and predictors of long term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for advanced hematological malignancies (Veeraputhiran/Pingali /Mukherjee/Patel/Muffly/Iyer) (Attachment 4)

Dr. Muthu Veeraputhiran presented a joint proposal (resulting from the merging of two separate proposals) aiming to study late effects after alloHCT for AML or MDS in patients age 60 years or older. Preliminary population selection identified 1,795 patients eligible for this study. Working committee members were concerned with the amount of data on comorbidities available prior to transplant and suggested using HCT-CI (although this was only collected since 2007) or using an external dataset with this information. Other members suggested only including one-year survivors. While the PIs proposed looking at 2 or more late effects as the event of interest, the committee felt the late effects should be looked at separately, not grouped, and each of the late effects to be studied should have a hypothesis associated with it. The committee felt that the population could be expanded to include other diseases. The importance of matching to non-HCT sex and age matched controls was stressed – these patients could age faster than their peers but it was also mentioned that they may be 'healthier', as they are eligible for transplant.

b. **PROP 1711-36** Survival trends amongst two-year survivors of allogeneic hematopoietic cell transplantation (Satwani/Broglie) (Attachment 5)

Dr. Larisa Broglie presented this proposal aiming to identify trends in long term survival from 1980-2010 in children, adolescent, and young adult (CAYA) patients that underwent myeloablative alloHCT for AML or ALL. Preliminary population selection identified 10,789 patients eligible for this study. Working committee members felt that it may be better to study 5-year intervals from 2000-2015 instead of decades starting in 1980. Members stressed that AYA is an important group and more

studies should be done on them. Members also felt that late effects should be included in this analysis.

c. **PROP 1711-47** Return to Work or School Status in Survivors of Adolescent and Young Adult (AYA) Allogeneic Hematopoietic Cell Transplant (Bhatt/Salit/Shaw/Syrjala) (Attachment 6)

Dr. Neel Bhatt presented this proposal aiming to study post-transplant employment status in patients that underwent alloHCT as young adults (age 18-39) and survived at least one year after HCT. This study has already been completed in patients transplanted before age 18, showing that it is feasible to study. Preliminary population selection identified 1,598 patients eligible for this study. Working committee members asked about how data was collected, availability of insurance data, how to compare age groups, and how to adjust for the recession in 2008. Members also felt it would be interesting to compare to a non-HCT control group and consider excluding patients under age 30, which would mostly exclude the student status, and then be able to account for pre-HCT work status. A suggestion to compare 30-40 to 40-50 was made. For adults, education level and pre-HCT employment status should be considered. One member asked if this is actually assessing the impact of transplant, or just issues in this population in general.

d. **PROP 1711-96** Outcomes of patients undergoing Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) at transplant centers with versus without a Long-Term Follow-Up Program for Hematopoietic Cell Transplant Survivors (Shah/Hashmi) (Attachment 7)

Dr. Minoo Battiwalla announced that this proposal was withdrawn by the PIs prior to the meeting due to a conflicting analysis which had come to light, and it will not be voted on.

Dropped proposed studies

e. **PROP 1711-78** Dementia in Older Adults Following Hematopoietic Stem Cell Transplantation. *Dropped due to feasibility.*

f. **PROP 1711-86** Longitudinal Changes in BMI and Trends in Obesity Prevalence in AlloHCT Survivors. *Dropped due to feasibility.*

g. **PROP 1711-132** Lung Transplantation in Patients with End-Stage Pulmonary Dysfunction after AlloHCT. *Dropped due to overlap with LE12-03.*

6. Other Business

Dr. Shahrukh Hashmi announced that he intends to submit a proposal to compare patients receiving total body irradiation to other datasets of people that have been exposed to other sources of radiation.

Oversight Assignments for Working Committee Leadership (March 2018)

Mary Flowers	**LE14-01** Risks and outcomes of therapy related myeloid neoplasms after autologous HCT
	LE16-01 Late mortality from infections after AlloHCT
	LE17-G1a/b Ocular complications after HCT
	LE18-02 Return to work or school status in survivors of young adult AlloHCT
Minoo Battiwalla	**LE12-03** Solid organ transplant after HCT
	LE17-01 Long-term follow up after HSCT for sickle cell disease
	LE16-02 New malignant neoplasms after AlloHCT for pediatric pts with non-malignant diseases
David Buchbinder	**LE13-02** Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation
	LE17-02 Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia
	LE18-01 Survival trends amongst two-year survivors of alloHCT
Bronwen Shaw	**LE99-01** Quality of life in late HCT survivors
	LE16-03 Post-HCT employment status in adult survivors of childhood HCT

Working Committee Overview Plan for 2018-2019

a. **LE99-01** Quality of life in late HCT survivors. This study is ongoing.

b. **LE12-03** Solid organ transplant after HCT. We are in the process of merging updated UNOS data to the CIBMTR dataset. This study is in data file preparation and will be in manuscript preparation by July 2018. We plan to submit this paper by December 2018.

c. **LE13-02** Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation. This study is in analysis phase and will be submitted by June 2018.

d. **LE14-01** Risks and outcomes of therapy related myeloid neoplasms after autologous HCT. This study has been submitted for peer-review and we plan to have it published by June 2018.

e. **LE16-01** Late mortality from infections after AlloHCT. This study is in manuscript preparation and we plan to have it submitted by May 2018.

f. **LE16-02** New malignant neoplasms after AlloHCT for pediatric pts with non-malignant diseases. This study is in manuscript preparation and we plan to have it submitted by July 2018.

g. **LE16-03** PostHCT employment status in adult survivors of childhood HCT. This study is in manuscript preparation and we plan to submit by June 2018.

h. **LE17-01** Long-term follow up after HSCT for sickle cell disease. This study is in protocol development and aims to be in data file preparation by July 2018. We plan to complete the analysis and start manuscript preparation by February 2019.

i. **LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia. This study is in data file preparation preparation and will be in manuscript preparation by June 2018. We plan to submit this paper by September 2018.

j. **LE17-G1a** GVHD ocular complications after HCT. This study is in manuscript preparation and will be submitted by July 2018.

k. **LE17-G1b** Non-GVHD ocular complications after HCT. This study is in manuscript preparation and will be submitted by July 2018.

l. **LE18-01** Survival trends amongst two-year survivors of alloHCT. Protocol is pending on this study and hours will begin July 2018. We aim to finish data file preparation by February 2019.

m. **LE18-02** Return to work or school status in survivors of young adult AlloHCT. Protocol is pending on this study and hours will begin July 2018. We plan to complete this analysis by June 2019.

Follow-up of **adult** patients (age≥18) after **allogeneic** transplant reported to CIBMTR, 1990-2018

Variable	TED	CRF
All patients	171361	59835
3 year survivors	50472	16964
5 year survivors	34371	11688
10 year survivors	13273	4737
15 year survivors	4954	1427
Acute Myelogenous Leukemia	62024	20058
3 year survivors	16232	5410
5 year survivors	10550	3649
10 year survivors	3493	1245
Acute Lymphoblastic Leukemia	23681	7449
3 year survivors	5956	1843
5 year survivors	3779	1224
10 year survivors	1225	475
Chronic Myelogenous Leukemia	23812	8988
3 year survivors	9621	3071
5 year survivors	7413	2404
10 year survivors	3974	1342
Myelodysplastic/Myeloproliferative Diseases	24112	10416
3 year survivors	6061	2557
5 year survivors	3767	1558
10 year survivors	1250	551
Multiple Myeloma/Plasma Cell Disorders	3186	1094
3 year survivors	1044	320
5 year survivors	721	213
10 year survivors	301	69
Lymphoma	16402	5227
3 year survivors	5414	1627
5 year survivors	3893	1176
10 year survivors	1528	526

Variable	TED	CRF
Other Malignant	8835	3053
3 year survivors	2710	910
5 year survivors	1785	588
10 year survivors	520	198
Severe Aplastic Anemia	6770	2650
3 year survivors	2646	965
5 year survivors	1944	708
10 year survivors	815	268
Immune deficiencies	347	108
3 year survivors	95	29
5 year survivors	43	15
10 year survivors	2	1
Other Non-malignant	2017	792
3 year survivors	659	232
5 year survivors	453	153
10 year survivors	153	62

Follow-up of **pediatric** patients (age<18) after **allogeneic** transplant reported to CIBMTR, 1990-2018

Variable	TED	CRF
All patients	52718	21716
3 year survivors	21113	8500
5 year survivors	15584	6435
10 year survivors	6548	2892
15 year survivors	2296	841
Acute Myelogenous Leukemia	9809	3858
3 year survivors	3432	1337
5 year survivors	2549	989
10 year survivors	1143	433
Acute Lymphoblastic Leukemia	14001	5521
3 year survivors	5004	1902
5 year survivors	3713	1426
10 year survivors	1615	656
Chronic Myelogenous Leukemia	2142	846
3 year survivors	966	389
5 year survivors	762	317
10 year survivors	368	165
Myelodysplastic/Myeloproliferative Diseases	2911	1255
3 year survivors	1196	530
5 year survivors	890	418
10 year survivors	387	212
Multiple Myeloma/Plasma Cell Disorders	14	2
3 year survivors	5	0
5 year survivors	4	0
10 year survivors	4	0
Lymphoma	1150	416
3 year survivors	387	135
5 year survivors	268	98
10 year survivors	105	37

Variable	TED	CRF
Other Malignant	1052	418
3 year survivors	385	164
5 year survivors	273	127
10 year survivors	102	44
Severe Aplastic Anemia	5044	2015
3 year survivors	2438	906
5 year survivors	1835	702
10 year survivors	764	277
Immune deficiencies	4990	2332
3 year survivors	2218	1092
5 year survivors	1587	850
10 year survivors	641	385
Other Non-malignant	11576	5053
3 year survivors	5072	2045
5 year survivors	3697	1508
10 year survivors	1419	683

Follow-up of **adult** patients (age≥18) after **autologous** transplant reported to CIBMTR, 1990-2018

Variable	TED	CRF
All patients	218534	33990
3 year survivors	91654	13720
5 year survivors	57786	8344
10 year survivors	18061	2429
15 year survivors	6343	542
Acute Myelogenous Leukemia	7120	1332
3 year survivors	2475	417
5 year survivors	1776	286
10 year survivors	831	98
Acute Lymphoblastic Leukemia	1120	207
3 year survivors	278	40
5 year survivors	182	24
10 year survivors	91	11
Chronic Myelogenous Leukemia	656	206
3 year survivors	285	96
5 year survivors	189	56
10 year survivors	86	22
Myelodysplastic/Myeloproliferative Diseases	254	48
3 year survivors	111	23
5 year survivors	74	12
10 year survivors	30	3
Multiple Myeloma/Plasma Cell Disorders	91060	13829
3 year survivors	39584	6397
5 year survivors	22807	3815
10 year survivors	4460	1019
Lymphoma	85816	10646
3 year survivors	36293	4329
5 year survivors	24385	2819
10 year survivors	8625	919

Variable	TED	CRF
Other Malignant	31443	7597
3 year survivors	12297	2357
5 year survivors	8127	1279
10 year survivors	3839	333
Severe Aplastic Anemia	14	3
3 year survivors	3	1
5 year survivors	2	1
10 year survivors	0	0
Immune deficiencies	14	2
3 year survivors	0	0
5 year survivors	0	0
10 year survivors	0	0
Other Non-malignant	935	119
3 year survivors	277	59
5 year survivors	203	51
10 year survivors	72	23

Follow-up of **pediatric** patients (age<18) after **autologous** transplant reported to CIBMTR, 1990-2018

Variable	TED	CRF
All patients	15625	2748
3 year survivors	5904	986
5 year survivors	3985	632
10 year survivors	1492	250
15 year survivors	547	69
Acute Myelogenous Leukemia	981	248
3 year survivors	389	50
5 year survivors	302	29
10 year survivors	157	14
Acute Lymphoblastic Leukemia	388	123
3 year survivors	127	19
5 year survivors	87	7
10 year survivors	44	0
Chronic Myelogenous Leukemia	23	3
3 year survivors	12	1
5 year survivors	7	0
10 year survivors	4	0
Myelodysplastic/Myeloproliferative Diseases	22	4
3 year survivors	7	0
5 year survivors	5	0
10 year survivors	3	0
Multiple Myeloma/Plasma Cell Disorders	106	3
3 year survivors	18	2
5 year survivors	13	2
10 year survivors	3	0
Lymphoma	2746	344
3 year survivors	1149	148
5 year survivors	796	90
10 year survivors	282	31

Variable	TED	CRF
Other Malignant	11111	1967
3 year survivors	4131	748
5 year survivors	2725	492
10 year survivors	978	203
Severe Aplastic Anemia	7	3
3 year survivors	4	2
5 year survivors	4	2
10 year survivors	0	0
Immune deficiencies	45	34
3 year survivors	13	9
5 year survivors	5	4
10 year survivors	0	0
Other Non-malignant	169	19
3 year survivors	46	7
5 year survivors	35	6
10 year survivors	18	2

Quality of life data on **adult** patients

Variable	Baseline	100 day	6 months	1 year
Number of adult patients	263	171	159	134
Median age at transplant (range), years	55 (19-75)	55 (19-74)	55 (19-75)	54 (19-74)
18-29	34 (13)	17 (10)	19 (12)	11 (8)
30-39	24 (9)	17 (10)	13 (8)	14 (10)
40-49	40 (15)	23 (13)	23 (14)	22 (16)
50-59	77 (29)	58 (34)	56 (35)	47 (35)
60-69	78 (30)	52 (30)	43 (27)	36 (27)
70+	10 (4)	4 (2)	5 (3)	4 (3)
Gender				
Male	153 (58)	97 (57)	94 (59)	77 (57)
Female	110 (42)	74 (43)	65 (41)	57 (43)
Race/Ethnicity				
Caucasian/White	235 (89)	162 (95)	150 (94)	125 (93)
Black	12 (5)	0	2 (1)	3 (2)
Hispanic	7 (3)	4 (2)	2 (1)	1 (<1)
Asian/Hawaiian/Pacific Islander	7 (3)	3 (2)	3 (2)	3 (2)
Unknown/Declined	2 (<1)	2 (1)	2 (1)	2 (1)
Indication for transplant				
Acute leukemia	129 (49)	85 (50)	74 (47)	62 (46)
CML	19 (7)	11 (6)	12 (8)	10 (7)
MDS/MPS	49 (19)	32 (19)	28 (18)	24 (18)
Other leukemia	20 (8)	15 (9)	14 (9)	10 (7)
NHL	22 (8)	13 (8)	15 (9)	14 (10)
HD	6 (2)	3 (2)	4 (3)	4 (3)
Multiple myeloma/plasma cell leukemia	7 (3)	4 (2)	4 (3)	4 (3)
Nonmalignant diseases	11 (4)	8 (5)	8 (5)	6 (4)
Year of transplant				
2011	25 (10)	12 (7)	12 (8)	12 (9)
2012	185 (70)	121 (71)	113 (71)	94 (70)
2013	53 (20)	38 (22)	34 (21)	28 (21)
Measures completed				
FACT-BMT and SF-36	256 (97)	168 (98)	155 (97)	129 (96)
FACT-BMT only	7 (3)	1 (<1)	0	2 (1)
SF-36 only	0	2 (1)	4 (3)	3 (2)
Median follow-up of survivors (range), months	26 (8-38)	26 (13-38)	27 (13-38)	26 (12-38)

Quality of life data on **pediatric** patients

Variable	Baseline	100 days	6 months	1 year
Number of patients	77	45	46	37
Median age at transplant (range), years	7 (2-18)	7 (2-17)	8 (2-17)	7 (2-17)
2-4	24 (31)	14 (31)	13 (28)	9 (24)
5-7	21 (27)	12 (27)	11 (24)	12 (32)
8-12	18 (23)	9 (20)	10 (22)	7 (19)
13-18	14 (18)	10 (22)	12 (26)	9 (24)
Gender				
Male	42 (55)	28 (62)	28 (61)	21 (57)
Female	35 (45)	17 (38)	18 (39)	16 (43)
Race/Ethnicity				
Caucasian/White	63 (82)	39 (87)	39 (85)	33 (89)
Black	6 (8)	3 (7)	3 (7)	2 (5)
Hispanic	5 (6)	1 (2)	3 (7)	1 (3)
Asian/Hawaiian/Pacific Islander	2 (3)	1 (2)	1 (2)	1 (3)
Unknown/Declined	1 (1)	1 (2)	0	0
Indication for transplant				
AML	11 (14)	7 (16)	7 (15)	4 (11)
ALL	17 (22)	10 (22)	10 (22)	10 (27)
CML	1 (1)	0	1 (2)	1 (3)
MDS/MPD	4 (5)	2 (4)	3 (7)	1 (3)
Severe aplastic anemia	6 (8)	3 (7)	3 (7)	3 (8)
Inherited abnorm. of erythrocytes	17 (22)	12 (27)	12 (26)	10 (27)
SCID & other immune disorders	10 (13)	4 (9)	4 (9)	3 (8)
Inherited disorders of metabolism	1 (1)	0	0	0
Histiocytic disorders	9 (12)	6 (13)	5 (11)	5 (14)
Autoimmune diseases	1 (1)	1 (2)	1 (2)	0
Year of transplant				
2011	9 (12)	4 (9)	6 (13)	5 (14)
2012	50 (65)	29 (64)	29 (63)	22 (59)
2013	18 (23)	12 (27)	11 (24)	10 (27)
PedsQL measures completed				
Proxy only patients (age<5)	24 (31)	14 (31)	13 (28)	9 (24)
PedsQL and proxy completed	49 (64)	31 (69)	33 (72)	26 (70)
Only PedsQL completed	3 (4)	0	0	1 (3)
Only proxy completed	1 (1)	0	0	1 (3)
Median follow-up of survivors (range), months	25 (6-46)	24 (6-46)	25 (6-46)	25 (11-46)

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TO: Late Effects and Quality of Life Working Committee Members

FROM: Bronwen Shaw, MBChB, MRCP, PhD, Scientific Director for the Late Effects and Quality of Life Working Committee; Rachel Phelan, MD, Assistant Scientific Director for the Late Effects and Quality of Life Working Committee

RE: Studies in Progress Summary

LE99-01: Quality of life in late HCT survivors (J Wingard) This is an ongoing project examining quality of life and social relationships of hematopoietic transplant survivors. Several manuscripts have already been produced. One final manuscript including a methodological analysis is in preparation.

LE12-03: Solid organ transplant after HCT (M Gupta/PL Abt/M Levine) This study aims to report outcomes of solid organ transplantation in HCT recipients and compare survival. The data derives from both CIBMTR and OPTN (UNOS) databases. After presentation at the stats meeting a decision was made to update the data with contemporary cases. New data was requested from UNOS in 2017. We have completed updating the data merge between the two databases. The study is in data file preparation. This study will be submitted by July 2019.

LE13-02: Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation (M Herr/L Morton) This study will identify risk factors of developing melanoma and assess the clinical burden of melanoma in patients who received allogeneic HCT. The analysis was completed externally at the NCI. This study is in manuscript preparation, was presented at ASH in December 2018, and will be submitted by March 2019.

LE16-02: An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases (JM Kahn/P Satwani) This study is analyzing new cancers and late effects in children, adolescents, and young adults undergoing allogeneic hematopoietic cell transplantation for non-malignant diseases. The study is in manuscript preparation, an abstract was submitted to EBMT 2018 meeting, and manuscript will be submitted by March 2019.

LE17-01: Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) This study aims to describe incidence of late effects after HCT for sickle cell disease (SCD) and compare survival to a non-HCT cohort of SCD patients. The study is in data file preparation. This study will be in analysis by April 2019 and manuscript prep by July 2019.

LE17-02: Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia (S Lee/L Muffly) This study will compare subsequent malignancies and late effects after HCT in patients that received a TBI-containing regimen versus a non-TBI regimen. This study scored highly at the Tandem meeting in 2017, but could not be accepted due to available statistical hours. Due to excellent study progress in 2017, the co-chairs agreed

to accept this study off-cycle in July 2017. The study is in manuscript preparation. This study will be submitted by March 2019.

LE18-01: Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) This study aims to evaluate trends in late mortality rates in children and young adults with hematologic malignancies. The study is in protocol development. This study will be in data file preparation by July 2019.

LE18-02: Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) This study aims to describe the return to school or work status of the survivors of hematopoietic cell transplant performed in young adult age group (18-39). The study is in data file preparation. This study will be submitted by July 2019.

Proposal: 1811-73

Title:
Late mortality in acute leukemia patients undergoing allogeneic transplantation

Investigators:
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Primary aim:

- To compare the long term mortality of adult allogeneic transplant recipients with that of general population utilizing standardized mortality ratios.

Secondary aims:

- To evaluate the causes of late mortality in long term survivors of allogeneic transplantation
- To analyze the differences in mortality over time in long term cohorts (age-based) of allogeneic transplant recipients

Hypothesis:

- H_{a1}: The 15 and 20-year mortality in allogeneic HCT survivors who were transplanted for acute leukemias at age of ≥50 years will be very high in the range of 65-80%.
- H_{a2}: The standardized mortality ratios of allogeneic HCT survivors will be significantly higher when comparisons to general population are made.

Scientific justification:
Significant advances in HCT field, particularly due to less toxic conditioning regimens, wider donor availability, newer antifungals and antivirals, have yielded better clinical outcomes and improved survival. We are now transplanting patients in older age groups (i.e. in their 50's, 60's and 70's) more frequently utilizing reduced intensity and non-myeloablative regimens. Recent data clearly indicates improved short term survival in the current era, however, very long term survival in those transplanted in these latter age cohorts is largely unknown. Studies referenced below have indicated that the survival curves in allogeneic HCT survivors, after the first 2-3 years post-HCT plateau, however, very long term data i.e. a 15-year or 20-year survival data is unavailable from *adult* cohorts.
The actuarial life expectancy in the general population of the United States (US) at birth is 81 and 76 years for females and males respectively. At age 50 for the same population, the actuarial life expectancy is 33 and 30 for females and males respectively. None of the previous studies published form large databases have looked into the life expectancy periods based on age of transplant for 15 or 20-year survival using actuarial analysis. Now that the early mortality post-HCT has been reduced and we portray a good risk of survival (non-relapse populations), in the current era of transplant survivorship it is essential to delineate exact survival statistics to our patients. I.e. we don't necessarily tell our patients the 10-year survival at the time of transplant but at 2-year mark post-HCT, we do indicate excellent outcomes in the absence of GVHD and relapse! However, this risk portrayal should be dependent on the timing of HCT with respect to age e.g. what estimates should I provide a leukemia patient undergoing allogeneic HCT when I see him at 2 years post-HCT? Answer would be very different in a patient who received HCT at 10 years of age, compared to someone who received HCT at 30 years of age, and certainly very different for those who received HCT at the age of 50 since in all 3 of these patients, the actuarial life expectancy is very different to begin with; and additionally, this is complicated

by what we know about the epidemiology of late effects (e.g. premature aging phenotypes e.g. cardiovascular disease, new cancers etc.) which significantly affect the survival.
Gooley *et al.* evaluated the trends in mortality of allogeneic HCT by looking into 2 cohorts (1990s and early 2000s) and found better outcomes in the latter cohort; however, the median age at HCT in these groups was only 37 and 47 years respectively. There was no 15 or 20-year mortality depicted due to a shorter follow-up (*and to evaluate very long term survival was not the goal of the study anyways!)*
An analysis by **Bhatia *et al.*** from 2 center cohort (BMTSS), evaluated late mortality in those who survived 2 years post-HCT. Median age at HCT was 25.9 years and median length of follow-up was 9.5 years. The conditional survival probability at 15 years from HCT was 80.2% (SE - 1.9%) for those who were disease-free at entry into the cohort, and the relative mortality was 9.9 (95% CI, 8.7-11.2). At 15-year mark post-HCT, the standardized mortality ratio was still high at 2.2.
A recent study from Japan society for HCT (Atsuta *et al*.) analyzed outcomes in relapse-free survivors at 2 years, and found that the overall survival percentages at 10 and 15 years were 87% and 83%, respectively but the overall risk of mortality was significantly higher compared with that of the general population. Notably the median age at HCT in this study was 29 years.
Based on age at HCT, one needs to evaluate the exact risks and outcomes of death with respect to late mortality, and one size fits all theory for very long term outcomes does not apply to our cohorts that we are taking to HCT.

Patient eligibility population (ALLOGENEIC ONLY):
Selection criteria (both TED level and *available CRF* in CIBTMR database):

- All patients who underwent first cord blood, peripheral stem cell, or bone marrow transplantation between 01/01/1995 and 12/31/2010
- Haploidentical HCT will be included
- Patients who survived 2 years post-HCT
- Both single and double cord CBT will be included
- Both adult and pediatric patients
- All conditioning types (reduced intensity [RIC], myeloablative [MA], non-myeloablative [NMA]).
- HSCT performed specifically for acute leukemias i.e. AML, ALL, biphenotypic leukemia and BPDCN (Blastic plasmacytoid dendritic cell neoplasm)

Data requirements (variables):
Patient-related:

- Age: person years at risk: continuous variable
- Age: age at HCT: continuous variable
- Age cohorts: categorical variable: 0-<2, 2-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70
- Gender: male or female
- Smoking status prior to HSCT
- Marital status
- Karnovsky performance score at the time of transplant
- Race of the patient: nominal variable
- Geographic location of residence of patient pre-transplant
- Geographic location of transplant center at the time of transplant

Disease-related:

- Primary disease for transplant indication
- Cytogenetics or FISH information of primary disease: normal or abnormal

- Prior treatment with anthracycline: yes/no
- Prior treatment with alkylating agents
- Number of lines of prior therapy pre-HCT
- Radiation prior to transplant: yes/no
- Genetic or familial disease: yes/no

Transplant-related:

- Graft sources: PBSC vs CBU vs BM
- Graft sources: Haplo PBSC vs haplo marrow
- HCT-CI: continuous
- Recipient CMV status: positive/negative
- Donor CMV status: positive/negative
- Acute GVHD: yes/no
- Acute GVHD grade: continuos
- Chronic GVHD: yes/no
- Chronic GVHD grade (NIH grade, or extensive/limited classification): continuos
- Preparative Regimen: NMA vs RIC vs MA
- Preparative regimen: Busulfan yes/no
- T cell depleted graft: yes/no
- Matching: degree of HLA match: Donor/Recipient
- Matching: degree of HLA match: Donor/Donor CBU (if double cord transplant)
- Donor sex: male vs. female (for both units in double CBT)
- Transplant related mortality at 1 year, 2 years, and 5 years
- TBI conditioning: yes/no
- TBI dose ≤800 cGy: yes/no
- Cardiovascular disease (post-2 years after HCT)
- New cancers (post-2 years after HCT)
- Infections (post-2 years after HCT)

Study design:

Definitions

- Transplant Related Mortality (TRM): Time from day 0 of stem cell infusion to death from any cause except relapse of primary disease.
- Person years at risk: will be calculated from day 0 of HCT until date of last contact, death
- Standardized mortality ratio (SMR): Ratio of observed to expected deaths.

Methods:

- Data extraction: It will be done from the CIBMTR database for all groups (graft sources) to produce descriptive tables of patient, disease, and transplant related factors. The specific mortality rates for the US population will be obtained from the CDC's National Center for Health Statistics (NCHS) datasets.
- Analysis: Chi-square tests for categorical and Kruskal-Wallis tests for continuous variables will be utilized. Kaplan Meier estimates will be used for generating OS and TRM probabilities. Variance will be estimated by Greenwood's formula as a guide or as felt appropriate by the CIBMTR statistician. Type I error of 0.05 significance will be set. The log rank test will be used to compare survival curves.

Subgroup analysis for the primary outcome (15-year mortality) will be done based on conditioning regimen, stem cell source, donor, GVHD prophylaxis, presence/absence of acute or chronic GVHD, severity of chronic GVHD, and late effects (new cancers, CVS outcomes, pulmonary outcomes and infections).
SMR will be calculated as ratios of observed (O) to expected (E) numbers of deaths, calculated based on age-, sex-, and calendar time cohorts of allogeneic HCT survivors versus those from the NCHS cohort.

Characteristics of patients age ≥ 18 that underwent a first alloHCT for AML, ALL or biphenotypic leukemia, between 1995 and 2010, and survived at least 2 years post-transplant, reported to the CIBMTR

Characteristic	N (%)
Number of patients	7200
Median age at transplant (range), years	41 (18-78)
Age at transplant	
18-30	2082 (29)
31-50	3176 (44)
51-64	1697 (24)
≥ 65	245 (3)
Sex	
Male	3839 (53)
Female	3360 (47)
Missing	1 (<1)
Karnofsky score	
90-100	5020 (70)
< 90	1747 (24)
Missing	433 (6)
Disease	
AML	5279 (73)
ALL	1790 (25)
Biphenotypic, bilineage or hybrid leukemia	131 (2)
Intended conditioning intensity	
MAC	4319 (60)
RIC/NST	1135 (16)
Form 2400 not filled out	362 (5)
NA, question not asked prior to 2002	1383 (19)
Missing	1 (<1)
Graft type	
Bone marrow	2425 (34)
Peripheral blood	4398 (61)
Umbilical cord blood	372 (5)
Missing	5 (<1)
Donor type	
HLA-identical sibling	2991 (42)
Other related	270 (4)
Unrelated	3538 (49)
Multi-donor	27 (<1)
Cord blood	372 (5)
Missing	2 (<1)
Year of transplant	
1995-1999	1542 (21)
2000-2004	2048 (28)
2005-2010	3610 (50)
Median follow-up of survivors (range), months	110 (24-271)

Proposal: 1811-128

Title:
Incidence and predictors of long term toxicities and late side effects in elderly patients (≥ 60 years) receiving high dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) for lymphoma

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Hypothesis:
HDT-AHCT in elderly patients (≥ 60 years) is associated with significant long-term toxicities and late side effects that can be predicted by pre and post- transplant variables.

Specific aims:
Primary aim:

- To identify and evaluate the incidence of long-term organ toxicities and late side effects of HDT-AHCT in older patients (age ≥ 60) who have survived > 2 years without disease.

Secondary aims:

- To evaluate pre-transplant comorbidities as predictors of late effects in older adults.
- To identify deficiencies in preventive care of older transplant survivors.

Scientific impact:
High-dose therapy and autologous stem cell transplantation (HDT-AHCT) is a curative treatment for a variety of lymphomas. With the advances in transplantation methodology, and reductions in non-relapse mortality (NRM), this procedure has been extended to older patients. However, transplant survivors may suffer from significant late effects that adversely affect their quality of life. Those include diseases of the heart, lung, nervous system, liver and kidneys, and second malignancies. With increasing number of older patients undergoing AHCT, understanding the biology of late effects is critical, and will allow potential preventive strategies that could result in improved quality of life after transplant. Prevention and pre-emptive knowledge could help plan prevent or minimize those late events and also would be useful in educating older adults about the potential for late effects following HDT-AHCT. We aim to evaluate the association of pre-transplant comorbidities with late effects in older adults.

Scientific justification:
Survival after HDT-AHCT is limited by either recurrence of underlying disease or non-relapse mortality. In lymphomas, disease recurrence most commonly occurs within the first two years after transplant[1]. Patients who are disease-free at two or five years after transplant remain at increased risk of late effects that adversely affect their morbidity and mortality[2-5]. Late effects of HDT-AHCT reported by Bhatia, *et al*. studied patients who underwent predominantly TBI-based conditioning regimens between 1981 and 1998 (4). With a median follow-up of 7.6 year, 2-year survivors of HDT-AHCT were at a 13-fold increased risk for late death when compared with the general population. Relapse of primary disease (56%) and subsequent malignancies (25%) were leading causes of late death. A prospective observational study of 1022 survivors who underwent transplant between 1974 and 1998 showed that 66% of the survivors had at least one chronic condition and 18% had severe or life-threatening conditions[6]. Ashton et al. reported the overall and cause-specific mortality and risk factors for late mortality in > 4,000 Australian cancer patients who survived > 2 years after transplant between 1992 and 2005[7]. Mortality rates

approached the age- and sex-matched Australian general population over time but remained significantly increased > 11 years. Relapse remained the most frequent cause of death for all diagnoses even 10 years after transplant. A retrospective study of 1087 survivors also showed that the cumulative incidence of any non-malignant late effect at five years after transplant was 45% among autologous and 79% among allogeneic recipients, and 2.5% of autologous and 26% of allogeneic recipients had three or more late effects[8]. Martin et al. have shown that life expectancy among 5-year transplant survivors remained 30% lower compared with the general population, regardless of their ages and years since transplant[2]. The leading causes of excess deaths in 5-year survivors included secondary malignancies (27%) and recurrent disease (14%), followed by infections (12%), chronic graft-*versus*-host disease (11%), cardiovascular diseases (11%), and respiratory diseases (7%)[2]. Herein, we seek to identify late effects of HDT-AHCT in older lymphoma patients (age $\geq$ 60) who have survived free of disease $\geq$ 2 years. Identification of late effects could guide interventions to prevent or minimize those late events and is important in survivorship care of older patients.

Patient eligibility:
Lymphoma patients that are alive and disease-free at 2-year mark post-HDT-AHCT. This is to identify long-term impact of HDT-ASCT on patient's physical health (heart, lung, liver and kidney).

- Older adults age $\geq$ 60 at the time of HDT-AHCT
- Diagnosis of lymphoma
- Patients must be alive and disease free 2 years after HDT-AHCT
- HDT-AHCT during years 2008 and 2017

Data requirements:
We will utilize Transplant Essential Data (TED) and Comprehensive Report Form (CRF) level data which are collected by the CIBMR prior to HCT, 100 days, 6 months following AHCT, and annually thereafter or until death. TED level data will be utilized and will include variables such as diagnosis, age, sex, date of diagnosis, conditioning regimen, disease survival, transplant-related complication including late effects, secondary malignancies, and cause of death. Specific questions focusing on the following late effects are available from CRF level data: neurological (stroke/seizures), cardiovascular (myocardial infarction), gastrointestinal/hepatic (cirrhosis), renal failure severe enough to warrant dialysis), and pulmonary (COPD, pulmonary fibrosis or other restrictive airway disease)

- Age at transplant
- Patient gender
- Disease: Lymphoma
- Karnofsky score ≥ 90 vs < 90 vs unknown or missing
- Sorror Co-morbidity index: 0 vs 1-2 vs ≥ 3
- Follow-up of survivors, months, median (range)
- Subsequent cancers
- Causes of death

Study design:
A retrospective multicenter study will be performed using the CIBMTR dataset. Patient will be eligible if they satisfied the criteria detailed in study eligibility section. The objective of this analysis is to describe the cumulative incidence of late effects in older adults with lymphoma undergoing HDT-AHCT. Overall survival probabilities will be estimated by the Kaplan-Meier method. Survival probabilities will be calculated from the date of AHCT to the date of death. Outcomes will be calculated from the date of transplant to the date of event or final follow-up. Relapse, NRM, and all-cause mortality will be estimated using the cumulative incidence method. Cox proportional hazards analysis will be used to

identify univariate and multivariate risk factors for NRM and all-cause mortality. Descriptive statistics, including Chi-square, Student T-test or Wilcoxon statistic will be used to compare the distribution of demographic and other patient- and transplant-related characteristics. The incidence and rate of late effects will be analyzed with the cumulative incidence method, accounting for death and relapse as competing risks. Predictors for late effects (including individual pre-transplant comorbidities) will be evaluated in multivariate logistic regression modeling.

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Characteristics of patients that underwent a first autoHCT for NHL or HL, at age 60 or greater, between 2008 and 2016, and survived at least 24 months post-transplant, reported to the CIBMTR [a]

Characteristic	N (%)
Number of patients	745
Median age at transplant (range), years	65 (60-80)
Age at transplant	
60-64	345 (46)
65-69	278 (37)
70-74	108 (14)
75-79	14 (2)
Sex	
Male	455 (61)
Female	290 (39)
Karnofsky score	
90-100	435 (58)
< 90	285 (38)
Missing	25 (3)
HCT-CI	
0	232 (31)
1	119 (16)
2	105 (14)
3+	283 (38)
Missing	6 (<1)
Disease	
Non-Hodgkin lymphoma	691 (93)
Hodgkin lymphoma	54 (7)
Year of transplant	
2008-2011	375 (50)
2012-2016	370 (50)
Median follow-up of survivors (range), months	61 (24-124)

[a] Still need to exclude patients that were not disease-free at 2 years (approximately 14%)

Proposal: 1811-142

Title:
Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients

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Hypothesis:
The objective of this CIBMTR Late Effects Proposal is to test the hypothesis that pediatric HCT patients who survive critical illness are at continued risk for mortality and long-term organ dysfunction. The direct implication of this hypothesis is that subgroups of patients may benefit from targeted screening protocols and tailored therapies aimed at preventing or mitigating the development of complications that threaten long-term survival. In order to test this hypothesis, we will use a unique dataset created by merging two large prospective databases: the Virtual Pediatric Systems (VPS) and Center for International Blood and Marrow Transplant (CIBMTR) databases. The product of this database merge is a cohort of 1,071 pediatric allogeneic HCT patients transplanted at 65 North American HCT centers who account for a combined 1,805 PICU admissions across 77 North American PICU's between January 1, 2009 and December 31, 2014. Given the significant potential to utilize this dataset to improve HCT survivability, we propose the following specific aims.

Specific aims:

- **Specific aim 1: To analyze long-term mortality of critically ill pediatric allogeneic HCT patients.** We will assess 1-, 3-, and 5- year overall survival estimates from the time of critical illness *onset* (PICU admission), from the time of intensification of critical care support (including the initiation of mechanical ventilation), and from the time of critical illness *resolution* (PICU discharge). We will also analyze mortality according to etiology, including relapse- and transplant-related mortality**. Hypothesis 1:** Long-term overall survival of pediatric HCT patients requiring PICU admission will fall below 50% at 1 year for those requiring mechanical ventilation, and PICU survivors will have continued risk for short- and long-term overall and transplant-related mortality.
- **Specific Aim 2: To analyze long-term morbidity of critically ill pediatric allogeneic HCT patients.** We will assess 1-, 3-, and 5- year cumulative incidence estimates of long-term complications from the time of PICU admission, time of intensification of critical care support (ie: mechanical ventilation), and the time of PICU discharge in the presence of death as a competing risk. We will analyze the development of chronic toxicities, organ dysfunction, and impaired functional status as they develop over time. **Hypothesis 2:** Pediatric HCT patients who survive critical illness will develop long-term complications after PICU discharge that affect cardiovascular, pulmonary, renal, hepatic, and neurologic organ systems.
- **Specific Aim 3: To build a parsimonious risk prognostication model that accurately stratifies mortality risk according to physiologic, laboratory, demographic, and transplant-specific characteristics.** We will test for associations between a comprehensive set of patient-level characteristics and post-ICU mortality as well as the development of late toxicities such as pulmonary and cardiovascular disease. **Hypothesis 3:** High-risk patient characteristics including myeloablative conditioning, HCT for acute myelogenous leukemia (AML), HLA-mismatched allografts, viral reactivation, graft-versus-host disease, and the use of mechanical ventilation will

be associated with increased risk for downstream complications. Identified risk-factors associated with poor long-term clinical outcomes may be modifiable and therefore selected for further investigation.

Scientific impact:
This study will leverage a novel contemporary database created by merging two complimentary and partially overlapping independent databases. The result is a unique dataset containing granular oncology and HCT data, intensive care unit details (including critical illness severity scores and use of invasive interventions), and long-term follow-up data to an estimated 5 years post- critical care admission. No current single dataset contains adequate long-term follow-up to study critically ill pediatric HCT patients and hence this is a unique and exciting opportunity to improve our knowledge of the epidemiology, risk-factors, and outcomes of this particularly vulnerable set of patients. As the number of pediatric HCT survivors is anticipated to quadruple between 2009 and 2030, these analyses are of paramount priority for clinical researchers and represent a necessary step in focusing efforts aimed at improving long-term event-free survival. In addition, a further expected benefit of this model is the ability to benchmark future patient outcomes against the current cohort in order to trend improvements in the field. Importantly, the primary results of this work will be disseminated through an interactive web platform that hosts a user-friendly survival and late-toxicity risk calculator and will be made freely available for communities around the world.

Scientific justification:
Hematopoietic cell transplantation (HCT) offers the potential for cure to over 2,500 children globally each year including those with high-risk leukemia (1). In children with refractory or relapsed hematologic malignancies, allogeneic HCT may be the only therapy available with the chance to produce a durable remission. Recent advances in the areas of donor selection, graft manipulation, preparative conditioning, and infection prophylaxis have allowed for increasing complexity of patients eligible for HCT and increasing medical complexity of post-HCT care (2,3).
Unfortunately, complications from HCT frequently lead to critical illness and necessitate pediatric intensive care unit (PICU) admission in 17-35% of children (4). The majority of post-HCT PICU admissions are due to pulmonary, cardiovascular, hepatic, renal, and neurologic dysfunction arising from complex interactions between infection, endothelial and epithelial injury, treatment-related toxicity, fluid overload, immune dysregulation, and alloreactivity (2,5). Potentially modifiable factors contributing to the development of these complications include intensity of pre-HCT conditioning chemotherapy, allograft HLA-mismatch, and prolonged periods of immune reconstitution. As the use of critical care therapies has increased significantly in the pediatric HCT population, the rates of pediatric HCT patients dying in any given PICU admission have decreased from over 85% in the 1990's to below 20% in recent years (2,6-8). However, mortality for patients requiring mechanical ventilation or renal replacement therapies still exceed 40% and 60%, respectively (6,7).
While the probability of surviving to PICU discharge has increased significantly and is the subject of ongoing investigation, many patients have multiple PICU admissions over their first year post-HCT, thus representing an increased cumulative risk for succumbing to post-HCT toxicity. We recently demonstrated that among pediatric HCT patients who required PICU admission but survived to PICU discharge, survival at 1 year was 40% relative to 1-year survival of 65% in patients who never required PICU admission; this suggests an ongoing burden of chronic organ toxicity in these vulnerable patients (2). In addition, we also demonstrated that among pediatric HCT patients who require PICU admission, survival with significant new functional disability is as prevalent an outcome as dying in the PICU (9). Taken together, these data suggest that both short- and long-term outcomes for critically ill pediatric HCT patients remain

suboptimal, and that the survivability of HCT remains a major barrier to long-term morbidity-free childhood for many patients.

As transplant-related mortality (TRM) now accounts for more post-transplant deaths than primary disease relapse (10), the field of post-HCT Late Effects has garnered an increasing level of importance in the oncology and transplant survivorship community (11-14). Currently, the Center for International Blood & Marrow Transplant Research (CIBMTR), the National Institutes of Health (NIH), the Pediatric Blood & Marrow Transplant Consortium (PBMTC), and the European Society for Blood & Marrow Transplantation (EBMT) have recommended following all pediatric HCT patients for long-term cardiopulmonary, renal, and multiorgan toxicity, as well as for neurodevelopmental outcomes and health-related quality of life (13-15). These recommendations are even more crucial in light of estimates that the number of pediatric survivors of HCT will double between 2009 and 2020, and will likely double again between 2020 and 2030 to reach an estimated 64,000 patients (16). While each of these survivors may be at high-risk for long-term complications, the subset who survived critical illness is likely to be at particularly high-risk for downstream organ dysfunction.

To date, investigators have identified that among patients *without* acute cardiovascular toxicities in the first 2 years post-HCT, the rates of obesity, dyslipidemia, and cardiomyopathy were 63%, 18%, and 3% when followed to 7 years post-HCT and were strongly associated with prior anthracycline exposure and thoracic irradiation (17). However, the rates of these complications in patients with early cardiovascular toxicities, particularly among those requiring critical care for cardiopulmonary dysfunction, remain unknown. With respect to post-HCT pulmonary dysfunction, *Kaya et al* demonstrated that FVC, FEV1, TLC, and DLCO abnormalities were detected in 36%, 46%, 30%, and 77% of post-HCT pediatric patients at 3 months and 42%, 49%, 27%, 75%, of patients at 6 months (18). While pulmonary function improved in many patients by 12 months, many patients did not reach pre-HCT baseline and the recoverability of pulmonary function for the subgroup with early post-HCT pulmonary toxicities remains unknown (19,20). Post-HCT kidney disease is also a common problem in long-term survivors and is estimated to occur in 11-41% of patients. Some data suggest that chronic kidney disease (CKD) may decrease over time as patients survive further from HCT, but whether baseline rates are higher in PICU patients and whether this recovery is arrested in patients who have been critically ill are unclear (21). In the broader pediatric critical care literature, a growing number of studies report significant long-term morbidity in survivors of critical illnesses such as acute respiratory distress syndrome and sepsis (22,23). However, the results of investigations of the long-term health of HCT PICU survivors are inconsistent and have been limited by small numbers of survivors and inconsistent long-term screening practices, and therefore a significant knowledge gap exists.

Patient eligibility population:

This study will leverage a novel, recently created, and largest-of-its kind longitudinal dataset of critically ill pediatric allogeneic HCT patients. This dataset was created by merging records from CIBMTR with records form The Virtual Pediatric Systems (VPS) database, which documents consecutive PICU admissions across over 140 sites predominantly in the United States and Canada. Admission characteristics, severity of illness scores, critical care interventions, and critical care-related diagnosis codes are documented by trained analysts at each site, with >95% inter-rater reliability.

To identify critically ill pediatric HCT patients for this study, VPS was queried for patients ≤21 years of age who were admitted to a PICU between 1/1/2009 and 12/31/2014 with a diagnosis code indicating prior HCT. To avoid analyzing low-risk patients, we excluded patients with short-term semi-elective PICU admissions, which we defined as any scheduled (>12 hours' notice) or perioperative admission lasting <2 days. To obtain further descriptive HCT-related characteristics for these critically ill patients, CIBMTR was queried for patients ≤21 years of age at the time of receiving a first allogeneic HCT between 1/1/2008 and

12/31/2014. While the VPS query included 1/1/2009, the CIBMTR query included the preceding year to capture post-HCT patients with PICU admissions in early 2009 who underwent HCT in 2008. Patients were excluded if they underwent HCT outside of the USA/Canada, had an identical twin, or lacked 100-day follow-up.

2,319 pediatric HCT patients were identified in VPS (0.5% of all PICU patients) and were cross-referenced to 9,183 pediatric allogeneic HCT patients in CIBMTR (12.4% of all CIBMTR patients). 1,248 pediatric HCT patients in VPS were excluded due to lack of 1:1 match in CIBMTR; the majority of exclusions were due to patients having no matching record in CIBMTR, and therefore these VPS records were assumed to represent patients having undergone autologous HCT or allogeneic HCT outside of the US/Canada and/or outside of the study interval. This yielded a final cohort of 1,071 allogeneic HCT patients accounting for 1,805 PICU admissions. These patients were transplanted at 65 HCT centers and were admitted to 77 different PICU's. When last assessed on May 9, 2016, the CIBMTR Completeness Index for 1-, 3-, and 5-year follow-up in this cohort was 99%, 93%, and 85%; 3- and 5-year data completeness will likely be significantly higher when reassessed in 2019. Preliminary work from this cohort was presented in abstract form at the 2018 Annual Tandem Meeting of the American Society of Blood and Marrow Transplantation (ASBMT) and the Center for International Blood and Marrow Transplantation Research (CIBMTR) in Salt Lake City, UT, February 22, 2018 and a manuscript is currently under review as an invited submission in the *American Journal of Respiratory and Critical Care Medicine*.

Data requirements:

In addition to assessing survival status at last follow-up in CIBMTR and reason for death (relapse-mortality, TRM, other causes as listed in CIBMTR), we will analyze the following variables:

Table 1) Variables Potentially Associated with Long-term Survival	
Demographics	Race (polychotomized as Caucasian/non-Hispanic, Caucasian/Hispanic, African-American, Asian/Pacific Islander, Other/unknown)
Pre-HCT Morbidity	HCT-Comorbidity Index (trichotomized as 0, 1-2, ≥3) Pre-HCT Lansky/Karnofsky performance score (dichotomized as <90% vs. 90-100%) History of mechanical ventilation (dichotomized as yes/no)
Underlying Disease	Disease (polychotomized as AML, ALL, other leukemia, Hodgkin and non-Hodgkin lymphoma, MDS/MPD, and other malignancy) Disease status prior to HCT (trichotomized as early, intermediate or late stage malignancy)
HCT Type	Graft source (trichotomized as bone marrow, peripheral blood, umbilical cord blood) Donor type/match (polychotomized as HLA-matched sibling, HLA-matched unrelated, HLA-matched cord blood, HLA-mismatched related [haploidentical], HLA-mismatched unrelated, HLA-mismatched cord blood) Donor/recipient CMV status (polychotomized as negative/negative, negative/positive, positive/negative, positive/positive) Donor/recipient sex match (polychotomized as M-M, M-F, F-M, F-F) Conditioning regimen (polychotomized as myeloablative, non-myeloablative, reduced intensity, none) Serotherapy (dichotomized as yes [ATG or alemtuzumab] vs no)
Post-HCT Course	Acute GVHD (dichotomized as present on PICU admission yes/no) Chronic GVHD (dichotomized as present on PICU admission yes/no) Relapse of underlying malignancy prior to PICU admission (dichotomized as yes/no)
PICU Course *(available through VPS)*	Post-HCT Day at PICU Admission (polychotomized as day 0-30, day 31-99, day 100-364, day 365+) PRISM-3 score (trichotomized by upper/middle/lower tertile) Use of invasive mechanical ventilation (dichotomized as yes/no, survival clock will begin at the start of therapy rather than at PICU admission, will also analyze survival clock beginning at PICU discharge)

	Use of non-invasive ventilation without need for invasive ventilation (dichotomized as yes/no, survival clock will begin at the start of therapy rather than at PICU admission, will also analyze survival clock beginning at PICU discharge) Use of renal replacement therapy (dichotomized as yes/no, survival clock will begin at the start of therapy rather than at PICU admission, will also analyze survival clock beginning at PICU discharge) Documented Gram+ bacterial infection (dichotomized as yes/no) Documented Gram- bacterial infection (dichotomized as yes/no) Documented fungal infection (dichotomized as yes/no) Documented respiratory viral infection (dichotomized as yes/no) Documented herpesvirus infection (including CMV, EBV, HHV-6, dichotomized as yes/no)

Table 2) Long Term Morbidity Assessment: Evaluable Organ Toxicities *(CIBMTR Form 2100)*

Heart	Cardiac arrhythmia Congestive heart failure Coronary artery disease Myocardial infarction Hypertension requiring therapy Hyperlipidemia requiring therapy Obesity: as assessed by body mass index
Lung	Pulmonary dysfunction: non-infectious interstitial pneumonitis and other non-infectious pulmonary abnormalities including bronchiolitis obliterans, COP/BOOP, and diffuse alveolar hemorrhage
Kidney	Acute renal failure requiring dialysis Chronic kidney disease
Liver	Non-infectious liver toxicity: including sinusoidal obstruction syndrome, cirrhosis, and other
Neurologic	Cerebrovascular accident Seizures
Hematologic	Immune Reconstitution: total white blood cell count including percentage of neutrophils and lymphocytes, immunoglobulin levels and need for IVIG repletion, lymphocyte subsets, chimerism Infection: including organism, site, and date of diagnosis Iron Overload requiring therapy New malignancy: including myelodysplasia and myelo/lymphoproliferative disease
Endocrine	Diabetes requiring chronic treatment Growth hormone deficiency Hypothyroidism Pancreatitis
Genitourinary	Gonadal dysfunction requiring hormone replacement Hemorrhagic cystitis
Musculoskeletal	Avascular necrosis Osteoporosis
Multi-organ	Thrombotic microangiopathy: including diagnostic criteria and therapies required Acute GVHD: including organs involved, grade and stage, and therapies required Chronic GVHD: including organs involved, grade and stage, and therapies required
Psychiatric	Depression requiring therapy Anxiety requiring therapy Post-traumatic stress disorder (PTSD) requiring therapy
Quality of Life	Functional status: Lansky/Karnofsky score

Study Design:

Approach to Specific Aim 1:

To analyze long-term mortality of critically ill pediatric allogeneic HCT patients.

Statistical Design, Endpoints, and Statistical Considerations: **Patients:** The analysis population will consist of all 1,071 patients, as described earlier in the Preliminary Results section. Each of these were admitted to a PICU during the study interval and some patients experienced multiple PICU admission. **Outcomes:** The primary outcome is all-cause mortality. The secondary outcome is cause-specific mortality, including relapse-mortality and treatment-related mortality (TRM), and will be characterized according to primary and contributing etiologies of death as documented in CIBMTR. **Time points:** We will analyze all-cause mortality and cause-specific mortality from three starting points. First, in order to provide patients and families with survival estimates at the time of critical care transfer, survival estimates will be generated starting at the time of PICU admission (PICU day 0). Second, in order to provide updated survival estimates at the time of intensification of critical care support, estimates will be generated starting at the time of endotracheal intubation and/or initiation of hemodialysis. Third, in order to document the long-term survival for PICU survivors, survival estimates will separately be generated starting at the time of PICU discharge. Patient dropout will occur when there is loss to follow-up in the CIBMTR records (however CIBMTR completeness index suggests >99% follow-up at 1 year). **Factors:** Survival estimates will be presented for the overall cohort and for each of the polychotomized clinical factors shown in Table 1 below. **Statistical Analyses:** Kaplan Meier survival estimates will be generated and comparisons will be made using the log-rank test stratified by each factor. We will estimate cause-specific mortality using cumulative incidence estimates that can account for competing risks and then will assess for differences in cause-specific mortality among the factors listed in Table 1 using Gray's test (24). We will then explore whether the incidence of multiple PICU admissions during the study interval influences all-cause mortality and/or cause-specific mortality by using a Cox proportional hazards model and a Fine and Gray's subdistribution hazard ratio model, respectively, with each accounting for repeat PICU admissions as a time-varying covariate (24,25). We will also evaluate time-varying covariates to assess the three different time-periods (starting points) in a single model for each outcome.

Expected Results and Significance: For the first time ever, detailed long-term survival data up to 5 years will be generated for >1,000 critically ill pediatric allogeneic HCT patients with malignancies. In concordance with smaller earlier studies, we expect to see <50% survival at 1-year post PICU admission. Further, we will provide ample comparative data analyzing well-known risk factors for long-term mortality, including underlying disease, allograft HLA match, and organ dysfunction at the time of PICU admission. These data will be useful in providing univariate comparisons of important transplant variables. We will also analyze long-term survival for the subset of patients who require invasive mechanical ventilation, non-invasive mechanical ventilation (without bridge to intubation), and renal replacement therapies including hemodialysis and peritoneal dialysis. These data will be particularly useful to counsel families on the long-term outcomes as predicted ***at the time of intensification of critical care support (ie: at the time of intubation)***, which is a particularly challenging time for families and caregivers***.*** Further, we will develop infection-related survival estimates, which we expect to be <30% for patients with fungal infections and patients with CMV infection.

Limitations and Alternative Approaches: First, the Kaplan Meier survival analysis censoring approach assumes that long-term mortality is independent of loss to follow-up. In other words, patients who are lost to follow-up have the same overall risk of long-term mortality as do patients with complete follow-up. This assumption may not be true, as patients who move away from their transplant center may have difficulty re-establishing long-term care in a new location, which may predispose to greater long-term mortality risk due to suboptimal screening for post-HCT complications. On the other hand, patients with chronic morbidities may maintain a closer relationship with transplant physicians, whereas the healthier

patients may stop coming back for follow-up. Second, admission criteria at the 77 different PICU's were not standardized, and therefore centers with liberal PICU transfer strategies may include some patients with low likelihood of mortality whereas other centers may only transfer patients with high likelihood of mortality. To control for this possible confounding, we will stratify by center and will perform Cox regression analysis to control for the admission illness severity, as estimated by the PRISM-3 score. Third, there is not currently a comparison cohort of pediatric allogeneic HCT patients who did not require critical care. To address this, in collaboration with CIBMTR, we will explore the development of a comparison cohort of pediatric allogeneic HCT *at the centers involved in this study* who did not require PICU admission *at the centers involved in this study* and compare long term outcomes using propensity-score matching to account for patient-level heterogeneity.

Approach to Aim 2:

To analyze long-term morbidity of critically ill pediatric allogeneic HCT patients.

Statistical Design, Endpoints, and Statistical Considerations: **Patients:** This aim will include only patients in the CIBMTR Comprehensive Research Form track, which is approximately 43% of the total cohort (460 patients). We will analyze the first PICU admission during the study interval, as this will allow the longest duration of follow-up in CIBMTR and therefore the longest window during which to assess for the development of morbidities. **Outcomes:** We will analyze the following organ toxicities as documented in CIBMTR form 2100 and listed in Table 2 below. **Time points:** As in Aim 1, we will analyze cumulative incidence from three starting time points: PICU admission, intensification of critical care support (ie: initiation of mechanical ventilation), and PICU discharge. **Statistical Analyses:** Cumulative incidence estimates will be generated with non-parametric 95% confidence intervals provided for 1, 3, and 5 year time-points. We will assess differences in the cumulative incidence of the morbidities listed in Table 2 according to the patient factors listed in Table 1 using Gray's test. Fine and Gray's cumulative incidence models will be used to account for time-varying covariates in the presence of competing risks. This model will also be used to account for center effects by stratifying by center.

Expected Results and Significance: We expect to identify a significant burden of long-term organ toxicity in pediatric patients who had post-HCT critical illness. We expect rates to exceed those documented in the general pediatric allogeneic HCT population, which will provide indirect evidence for a cumulative toxicity related to critical illness. While this study will not be able to discern the reason for these toxicities, we speculate these additional toxicities may be long-lasting effects from the underlying critical illness and may also be due to toxicities related to treating critical illness, including nephrotoxic medications, ventilator induced lung injury (VILI), and prolonged immobility. These findings would be highly significant as they would support future research aimed at minimizing toxicities in the peri-critical illness period and would also support aggressive surveillance and early intervention in survivors.

Limitations and Alternative Approaches: First, as fewer than half of all patients were in the Comprehensive Research Form track, our statistical power to detect these long-term complications will be less than the statistical power available for Aim 1. However, we do expect that survivors of critical illness will have increased rates of common toxicities such as pulmonary dysfunction and chronic kidney disease, which may offset the reduced statistical power. Second, it is possible that findings may be confounded by differences among patients with vs. without CRF documentation, and therefore we will compare a comprehensive set of baseline characteristics to determine if the composition of the CRF cohort is different than that of the non-CRF cohort. Third, there is a possibility of a classification error in the assignment of complications, as criteria used to diagnose each complication might vary somewhat by center, despite attempted standardization by CIBMTR.

Approach to Specific Aim 3:

To build a parsimonious risk prognostication model that accurately stratifies mortality risk according to physiologic, laboratory, demographic, and transplant-specific characteristics.

Statistical Design, Endpoints, and Statistical Considerations: **Patients:** All 1,071 patients in the cohort will be used for this analysis. **Outcomes:** As in Aim 1, we will analyze all-cause mortality and cause-specific mortality. **Time points:** As in Aims 1 and 2, we will assess mortality from three starting time points: PICU admission, intensification of PICU support (initiation of mechanical ventilation and/or hemodialysis), and PICU discharge. **Covariates:** Variables considered for the models will be the same as listed in Table 1, with the exception that continuous variables will not be polychotomized as listed in Table 1 (ie: PRISM-3 score will remain continuous for this Aim). We will assess the form of the continuous variables in-terms of linear, quadratic, cubic, and other descriptors. **Statistical Analyses:** In order to assess variables associated with all-cause mortality, we will generate multivariate Cox regression analyses. In order to assess prognostic factors associated with cause-specific mortality (ie: the competing outcomes of relapse-related mortality and treatment-related mortality), we will use Fine and Gray's competing risks regression analyses (25). All models will be stratified by center. A stepwise selection procedure will be used to identify covariates associated with outcomes and will be compared to alternative variable-selection procedures such as Gradient Boosting machine learning and Lasso (27,28). Repeat PICU admissions of the same patient will be addressed using time-varying covariates. We will also assess the different time-periods (starting points) in a single model to evaluate simultaneously whether the results are influenced by subsequent changes in clinical status (ie: intensification of critical care support, PICU discharge). Covariate effects will be summarized using hazard ratios with 95% confidence intervals. Two-sided p-values less than 0.05 will be considered statistically significant, and covariates that meet this criteria will be included in the final models. Any potential interactions between variables in the final model will be evaluated. For each patient, the individual composite risk value will be calculated by summing the model parameter estimates for that patient's observed factor values. Therefore, the composite risk for a specific set of factor values (ie: those which a clinician may enter for her/his patient) can be plotted over time to generate individualized survival estimates with 95% confidence intervals. In addition, the distribution of composite risks for the cohort will be polychotomized into quartiles and then all-cause mortality and cause-specific mortality will be plotted over time for each quartile and compared using the log-rank test and Gray's test, respectively. To determine cutoffs of composite risk associated with specific survival estimates, the nonparametric sliding-window methodology (STEPP) will be used to plot the distributions of 1-, 3-, and 5-year all-cause mortality and TRM across the continuum of composite risks (29). **Power Calculation:** We expect approximately 500 mortality events at 5-year follow-up. We expect sufficient statistical power to build a model incorporating up to 30 continuous or dichotomized covariates. This relies upon work by *Peduzzi et al*, which has recently been shown by *Vittinghoff et al* to be a conservative estimate of the sample size requirement for multivariate regression analyses based on relaxing the rule of 10 (30).

Expected Results and Significance: This aim will incorporate all available clinical, physiologic, and laboratory risk-factors available at the time of PICU admission into a robust model for predicting factors associated with long-term survival. These results will provide crucial insight for oncologists, transplanters, and critical care physicians and will allow the research community to target specific risk-factors in an effort to improve long-term event-free survival. For example, future clinical trials may wish to enroll patients who are at high-risk for poor long-term outcomes (ie: patients with ≤50% survival at 3 years); the use of the STEPP procedure will allow a multivariate approach to selecting such patients according to the composite risk, as estimated by the multivariate Cox regressions described above. Further, by making these models freely and publically available on a graphical web-based platform, the global community will be able to calculate point estimates with confidence intervals for survival at specific time-points such as

1-year post intensive care discharge. Individual patient survival estimates for multiple long-term time points can be estimated by solving the regression models with patient-specific data. Accurate prognostication of long-term outcomes for critically ill pediatric HCT patients is a paramount priority for clinical researchers and is a necessary step in focusing efforts aimed at improving long-term event-free survival. An additional expected benefit of this model is the ability to benchmark future patient outcomes against the current cohort in order to trend improvements in the field.

Limitations and Alternative Approaches: First, no independent cohort of patients exists against which to validate this model. Therefore, each model will be derived on a randomly selected 70% of the cohort and validated on the remaining 30%. We will repeat this process 20 times and average the results (20-fold internal cross-validation) and perform a sensitivity analysis comparing the internally cross-validated model to the original model. We anticipate that having patients from 77 different PICU's will allow adequate external validity and will negate any strong center-specific effects. In addition, data from this first-of-its-kind model can be used to benchmark future cohorts via standardized mortality ratios. Second, time varying confounders could influence the results. While using time-varying survival analysis methods as proposed will protect against this, we will also perform a sensitivity analysis such as inverse probability weighting.

Non-CIBMTR data source:

Virtual Pediatric Systems (VPS) database, as described above.

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Characteristics of patients aged ≤ 21 that underwent a first alloHCT in the US or Canada between 2008 and 2014 that survived 1year post-transplant, reported to the CIBMTR

Characteristic	Control	Case
Number of patients	1856	255
Median age at transplant (range), years	8 (<1-21)	6 (<1-20)
Age at transplant		
0-9	1132 (61)	170 (67)
10-21	724 (39)	85 (33)
Sex		
Male	1094 (59)	158 (62)
Female	762 (41)	97 (38)
Karnofsky score		
90-100	1565 (84)	220 (86)
< 90	255 (14)	33 (13)
Missing	36 (2)	2 (<1)
Disease		
AML	377 (20)	40 (16)
ALL	352 (19)	43 (17)
Other leukemia	32 (2)	2 (<1)
CML	29 (2)	7 (3)
MDS/MPN	114 (6)	19 (7)
NHL	35 (2)	2 (<1)
HD	3 (<1)	1 (<1)
SAA	187 (10)	13 (5)
Inherited abnormalities of erythrocyte differentiation or function	236 (13)	44 (17)
SCID and other immune system disorders	275 (15)	49 (19)
Inherited abnormalities of platelets	15 (<1)	0
Inherited disorders of metabolism	113 (6)	24 (9)
Histiocytic disorders	81 (4)	11 (4)
Autoimmune diseases	2 (<1)	0
Other	5 (<1)	0
Intended conditioning intensity		
MAC	1411 (76)	190 (75)
RIC/NST	425 (23)	59 (23)
NA, regimen not prescribed	20 (1)	6 (2)
Graft type		
Bone marrow	807 (43)	93 (36)
Peripheral blood	209 (11)	24 (9)
Umbilical cord blood	840 (45)	138 (54)
Year of transplant		
2008-2011	1136 (61)	147 (58)
2012-2014	720 (39)	108 (42)
Median follow-up of survivors (range), months	65 (12-127)	69 (12-121)

Proposal: 1811-146

Title:
Use of data from the CIBMTR dataset of subjects exposed to ionizing radiations to refine and extend estimates of risk of radiation-induced solid cancers currently based on data from the atomic bomb survivors in the Radiation Effects Research Foundation (RERF) dataset, persons with cancer receiving conventional radiation therapy in the US Surveillance and End Results (SEER) dataset and other radiation exposure datasets.

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Aim:
Refine risk estimates of risk of new solid cancers from ionizing radiations.

Hypothesis and scientific justification:
Estimates of risk of solid cancers from exposures to ionizing radiations are important in radiation biology and radiation protection. Current risk estimates are based on data from several datasets including the atomic bomb survivors, persons with cancer and other disorders receiving radiation therapy, persons occupationally-exposed to ionizing radiations (uranium miners, nuclear workers, radiologists) and other datasets. These data and estimates are reviewed in many publications from the US National Academy of Sciences (NAS), US National Council on Radiation Protection and Measurements (NCRP), International Council of Radiation Protection (ICRP), United Nations Special Committee on Effects of Atomic Radiations (UNSCEAR) and others. Cancer risk estimates from these databases are the bases for national and international guidelines for radiation protection such as permissible workplace exposures and guidelines for evacuation after nuclear accidents or incidents such as Chernobyl and Fukushima. These estimates are also used for estimating *causality* in scientific, medical and legislative setting and in defining risk: benefit ratios for medical interventions.
Risk estimates of solid cancers from exposures to ionizing radiations are unavoidably imperfect for many reasons. We cannot intentionally expose humans to high doses of ionizing radiations, especially not whole-body exposures. Consequently, risk estimates are extrapolated from lower radiation doses and from partial rather than whole body exposures. Another unavoidable limitation is inaccuracy and imprecision in estimation radiation dose in many of the datasets we cite such as the A-bomb survivors. Lastly, there is substantial controversy regarding the impacts of radiation type (such as photons, neutrons, alpha particle, protons), dose-rate and fractionation on subsequent solid cancer risk.
Radiation-related risk of new cancers *per* Gy has been relatively consistent across several datasets and exposure setting such as acute high-dose and long-term, low-dose. However, the CIBMTR radiation dataset is unique in that it contains data on persons exposed over a wide range of ages to a wide range of doses and dose-rates, fractionation, especially whole-body doses >4 Gy. (There are too few A-bomb survivors or Chernobyl exposed persons to accurately estimate solid cancer risk.) Analyses of the CIBMTR dataset will help answer several fundamental questions in radiation biology not addressable with other datasets such as the A-bomb survivors, occupational exposures radiation therapy recipients.
We emphasize the project objective is to address fundamental questions in radiation biology, not the question of radiation-induced solid cancers in past, present or future transplant recipients. Knowledge gained from executing this project is an important public service. It could also have important implications for present and future transplant recipients such as estimating risks and benefits of using

ionizing radiation containing pretransplant conditioning regimens and appropriate posttransplant surveillance of transplant recipients exposed to ionizing radiations. We think it would be scientifically and ethically wrong not to give radiation biologists and epidemiologists access to the relevant CIBMTR dataset.

Project:
2 of the co-investigators are expert in radiation biology and epidemiology (LZ and FOH). Our team has reviewed the CIBMTR data forms over the past year to determine whether they collect appropriate data for the proposed analyses. Fortunately, the answer seems yes. Subjects from the CIBMTR dataset relevant to the proposed analyses are specified below. Briefly, these are persons exposed to ionizing radiations for pretransplant conditioning and who have survived sufficiently long posttransplant to be at-risk to develop a solid cancer. Other radiation exposures are also captured as are details of the **Our intent is not to compare risks of solid cancers in transplant recipients exposed or not exposed to radiation. It is to compare transplant recipients exposed to ionizing radiations who develop or do not develop a solid cancer with persons in other datasets exposed to ionizing radiations but under different circumstances such as the A-bomb survivors and persons with cancer who received radiation therapy in the SEER dataset.**

We are aware that in analyzing the CIBMTR dataset we need to adjust cancer risk for several variables including:

- increased new cancer risk in persons with a prior cancer diagnosis
- increased cancer risk conferred by conventional anti-cancer therapies
- increased cancer risk conferred by pretransplant drugs
- prior radiation therapy.

Data from different populations can inform our study:

- Normal or reference from SEER database
- persons with cancer not receiving a transplant (from SEER)
- transplant recipients exposed to ionizing radiations at diverse ages, diverse doses, diverse dose-rates, diverse radiation sources and other variables
- A-bomb survivors.

Data requirements (variables):

- Subjects of all ages exposed to ionizing radiation as part of their pretransplant conditioning regimen.
- Subjects receiving a transplant for a solid cancer are excluded when the posttransplant cancer is identical to the pretransplant cancer.
- There must be adequate data on radiation-related variables such as dose, dose-rate, fractionation, shielding *etc*.
- We will limit or analysis to subjects with >5-year cancer-free survival.

Methods
CIBMTR statistician time required for this project is small compared to typical projects. We need to define and clean the dataset within CIBMTR but with input from the radiation biologists and epidemiologists on our project. Thereafter the dataset will be transferred to our team who will perform the statistical analyses. (There is insufficient radiobiological expertise in CIBMTR to conduct the proposed study internally.) All necessary safeguards for subject confidentially etc. will be enforced.

Funding:
We will apply for funding once we have approval from CIBMTR to conduct the study. These funds will be directed to LZ and FOH.

Importance:
The proposed study is unique in the context of typical CIBMTR studies. It proposes to use data in the CIBMTR dataset to address important questions in cancer causation, radiation biology and radiation protection. There is limited use of CIBMTR resources. The team consists of transplant experts and radiation biologists and epidemiologists. If successfully executed knowledge gained with have an important impact on our understanding of the cancer risks of ionizing radiations.

Characteristics of patients that underwent a first alloHCT and received TBI (including a small portion of patients receiving TLI), between 1995 and 2014, and survived at least 5 years post-transplant, reported to the CIBMTR [a]

Characteristic	N (%)
Number of patients	8748
Median age at transplant (range), years	29 (<1-79)
Age at transplant	
0-17	2927 (33)
18-30	1678 (19)
31-50	2869 (33)
51-64	1124 (13)
65+	150 (2)
Sex	
Male	5149 (59)
Female	3598 (41)
Not Answer	1 (<1)
Karnofsky score	
90-100	6619 (76)
< 90	1797 (21)
Missing	332 (4)
Disease	
AML	2175 (25)
ALL	2549 (29)
Other leukemia	426 (5)
CML	1285 (15)
MDS/MPN	634 (7)
NHL	702 (8)
HD	24 (<1)
PCD/MM	92 (1)
Other Malignancies	9 (<1)
SAA	439 (5)
Inherited abnormalities of erythrocyte differentiation or function	245 (3)
SCID and other immune system disorders	54 (<1)
Inherited abnormalities of platelets	6 (<1)
Inherited disorders of metabolism	73 (<1)
Histiocytic disorders	21 (<1)
Autoimmune diseases	4 (<1)
Other	10 (<1)
Intended conditioning intensity	
MAC	4837 (55)
RIC/NST	1009 (12)
Form 2400 not filled out	363 (4)
NA, question not asked prior to 2002	2539 (29)
Graft type	
Bone marrow	4444 (51)
Peripheral blood	3100 (35)
Umbilical cord blood	1204 (14)

Characteristic	N (%)
Donor type	
HLA-identical sibling	2756 (32)
Other related	336 (4)
Unrelated	4425 (51)
Multi-donor	25 (<1)
Cord blood	1204 (14)
Missing	2 (<1)
Year of transplant	
1995-1999	2808 (32)
2000-2004	2342 (27)
2005-2009	2751 (31)
2010-2014	847 (10)
New malignancy	1388 (16)
Median follow-up of survivors (range), months	121 (60-272)

[a] Still need to exclude cases that are not disease-free at 5 years post-transplant

Proposal: 1812-04

Title:
Risk of sarcoma after allogeneic hematopoietic stem cell transplantation

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Specific aims and hypothesis:

- Examine the association between patient-related factors, transplant-related factors (e.g., graft source), pre-HSCT therapies, and conditioning regimens with development of sarcoma after allogeneic HSCT.
  Hypothesis: Patients with more frequent exposure to cytotoxic therapy will have increased risk of developing sarcoma after allogeneic HSCT.
- Examine the role of factors associated with immunosuppression (such as viral infections or GvHD) with development of sarcoma after allogeneic HSCT.
  Hypothesis: Patients with immune alterations (e.g., viral infections, development of acute or chronic GvHD) will have increased risk of developing sarcoma after allogeneic HSCT.
- Examine whether any associations identified above vary by age at transplantation or time since transplantation.
  Hypothesis: Effects of cytotoxic therapies will be strongest among in transplanted at younger ages.

Scientific justification:
Allogeneic (matched sibling/unrelated donor-derived) hematopoietic stem cell transplant (HSCT) offers curative therapy for many malignant as well as non-malignant conditions that were previously incurable. With the introduction of safer transplant regimens, newer indications for HSCT, and alternative graft sources for hematopoietic stem cells, the number of patients undergoing allogeneic HSCT has increased steadily over the past few decades.[1,2] Corresponding with improvements in clinical approaches over time, survival following HSCT has also improved dramatically. The current population of >100,000 long-term HSCT survivors in the US is expected to grow 5-fold by 2030.[2,3] These changes have led to increased focus on the long-term health of HSCT survivors and risks for post-transplant complications, including subsequent neoplasms.
HSCT recipients have higher risk of developing subsequent malignancies compared to the general population.[3] These subsequent neoplasms contribute towards the higher burden of long-term non-relapse mortality and morbidity experienced by HSCT survivors.[4] Among a spectrum of second malignancies that has been observed following allogeneic HSCT,[5] several studies reported statistically significantly elevated risks of bone and soft-tissue sarcoma. A large study conducted among an international cohort of 28,874 recipients of allogeneic HSCT between 1964-1994 reported 6 cases of bone and 7 of soft-tissue sarcoma, corresponding to 8.5- and 6.5-fold increased risks compared with the general population, respectively.[5] In subgroup analyses, sarcoma risk increased with longer time since transplant, as long-term survivors had a 15- to 20-fold increased risk.[5] Similar findings were observed in an Australian cohort of 3,273 adult allogeneic HSCT recipients during 1999-2014 (3 cases of soft-tissue sarcoma, 9.9-fold increased risk).[6] These studies, however, lacked sufficient sample size to investigate patient- or transplant-related risk factors that may increase risk for sarcoma. Consequently, the underlying etiology for sarcoma after allogeneic HSCT remains unexplored.

Although risk factors for sarcoma after allogeneic HSCT have never been specifically investigated, treatments used for HSCT, including radiotherapy, chemotherapy and immunosuppressive therapy, have been associated with increased risk of sarcoma in other settings. Data from childhood cancer survivors demonstrate increased risk of sarcoma associated with increased dose of radiotherapy and chemotherapy.[7-9] Although there are limited studies that examined the risk of sarcoma after these cytotoxic therapies in adults, data from cancer registries and studies of treatment for benign conditions suggest that the risk of sarcoma, particularly after radiation, is also increased in this age group.[10-14] The Life Span Study of the Japanese atomic bomb survivors demonstrate an association between acute exposure to low-to-moderate doses of radiation and risk of developing sarcoma for all age groups.[12,15] Besides the established relation between immunosuppression and Kaposi's sarcoma, studies have also reported an excess of other soft-tissue sarcomas in patients receiving immunosuppression for solid organ transplantation.[16] Allogeneic HSCT recipients typically receive prophylactic systemic immunosuppressive therapy or a graft that is manipulated (example, T-cell depleted) to prevent graft-versus-host disease (GvHD). The role of these exposures along with other patient-, transplant- and disease-related factors have been investigated with respect to the risk of various subsequent neoplasms including basal cell- or squamous cell-carcinoma,[17,18] lymphoproliferative disorders,[19] and breast cancer.[20] However, the role of these factors in development of subsequent sarcoma among allogeneic HSCT recipients is largely unknown.

Sarcomas are a heterogeneous group of rare malignant cancers that warrant further investigation because of their poor prognosis. Although sarcoma constitute a little over 1% of all tumors in the general population,[21] they account for nearly 20% solid malignancies among children,[22] and may therefore represent one of the more common subsequent neoplasms among the pediatric population, which comprises nearly a third of all allogeneic HSCT recipients.[5] Clinical approaches to allogeneic HSCT have also changed over time. In more recent years, reduced-intensity conditioning regimens have been introduced as an alternative to traditional pre-transplant cytotoxic therapies.[23] Additionally, allogeneic HSCT in recent years has expanded to include peripheral blood or umbilical cord blood as a graft source (instead of the traditional bone marrow).[24,25] Risk of sarcoma associated with these changes as well as other specific allogeneic HSCT practices is poorly understood. Understanding the role of various risk factors for development of sarcoma among recipients of allogeneic HSCT is critical for future efforts to reduce these risks as well as identify patients at highest risk who would benefit most from additional surveillance methods.

To address gaps in our understanding of the risk factors for sarcoma among recipients of allogeneic HSCT, we propose to utilize clinical and long-term follow-up data of allogeneic HSCT recipients as registered in the Center for International Blood and Marrow Transplant Research (CIBMTR).

Research design and study population:

We propose to conduct a nested case-control study among patients who received a first allogeneic HSCT between 1985 and 2014 and survived for ≥100 days, as reported to CIBMTR. We will exclude patients who received an allogeneic HSCT for a non-malignant condition, as the treatment for non-malignant conditions may differ significantly from malignant diseases. We will also exclude patients from CIBMTR centers with a completeness index that was below 80% at 5-years post-HCT. Calendar years of reported sarcoma diagnoses will be reviewed carefully, and consideration will be given to excluding transplants in the earliest years of available data when sarcomas may not have been reported as a separate category on the follow-up forms.

Data source and list of variables:

- CIBMTR transplantation data files will be used to obtain information on following variables:
- patient demographics (i.e., age at transplantation, gender, year of transplant)

- indication for transplant (i.e., type of primary disease)
- receipt of prior auto-HSCT: yes vs. no
- Karnofsky performance score prior to preparative regimen
- type and duration of pre-HSCT therapies received (if any)
- type, duration and intensity (myeloablative versus reduced intensity) of conditioning regimens received including information on dosages of total body irradiation and chemotherapy agents
- donor-recipient relationship and histocompatibility (HLA-matched siblings, HLA mismatched related donor, HLA other relative, HLA-matched unrelated donor, HLA mismatched unrelated donor
- stem cell source (bone marrow, peripheral blood or umbilical cord blood)
- type of preventive GvHD prophylaxis therapy received (if any)
- incidence and time since transplantation of acute and/or chronic GvHD and treatment received for GvHD (dose, agent and duration)
- diagnosis of other co-morbidities including infections
- diagnosis of subsequent malignancies
- relapse: yes vs. no
- second transplant: yes vs. no; if yes, year and conditioning regimens
- patient's best response post initial transplant (complete remission, partial remission, stable disease, or progressive disease
- patient's vital status (date of last vital status / date of last follow-up)
- cause of death, when applicable (underlying / primary cause of death and all secondary causes of death (if available)

Ascertainment of cases and controls:

- Cases will include any patient with a reported sarcoma following first allogeneic HSCT (yes/no, site, histology). We will review available pathology reports to confirm diagnosis of sarcoma. Preliminary data suggest that we will have ~100 cases in this analysis.
- Four controls will be identified for each case. Eligible controls will be restricted to allogeneic HSCT recipients from CIBMTR selected from centers that reported at least one subsequent sarcoma. Matching factors will include: age at HSCT (+/- 2 years), sex, primary disease, and survival time since allogeneic HSCT without developing sarcoma

Statistical analyses plan:

To be completed at NCI

For each aim, we will use multivariable conditional logistic regression models to compute the odds ratios and 95% confidence intervals to evaluate the association between the exposures of interest (including type and duration of pre-HSCT therapies and conditioning regimens, occurrence of viral infections or acute/chronic GvHD, type and duration of therapy used towards prophylaxis or treatment of GvHD, and other such risk factors) and development of sarcoma. Covariates (patient-, disease- and transplant-related variables) with a p value of <0.10 in univariable analyses will be considered for inclusion in multivariable models. The final multivariable model will include all factors with $p<0.05$.

Expected clinical impact of the study:

Findings from this study may shed light on whether the use of reduced-intensity conditioning regimens, introduced in recent years, have corresponded to reduced risk for developing therapy-related subsequent neoplasms after allogeneic HSCT. The results of this study also have the potential to provide

insights into the etiology of sarcomas and inform screening and surveillance priorities among recipients of allogeneic HSCT.

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Characteristics of patients that underwent a first alloHCT for malignant diseases, between 1985 and 2014, and survived at least 100 days post-transplant, reported to the CIBMTR[a]

Characteristic	N (%)
Number of patients	57298
Age at transplant	
0-17	12034 (21)
18-30	11182 (20)
31-50	20756 (36)
51-64	10851 (19)
≥65	2469 (4)
Missing	6 (<1)
Sex	
Male	33652 (59)
Female	23643 (41)
Missing	3 (<1)
Karnofsky score	
90-100	40913 (71)
< 90	14093 (25)
Missing	2292 (4)
Disease	
AML	19535 (34)
ALL	11361 (20)
Other leukemia	2386 (4)
CML	10862 (19)
MDS/MPN	7446 (13)
NHL	4007 (7)
HD	338 (<1)
PCD/MM	963 (2)
Other Malignancies	322 (<1)
Breast cancer	77 (<1)
Missing	1 (<1)
Intended conditioning intensity	
MAC	21567 (38)
RIC/NST	7660 (13)
Form 2400 not filled out	1565 (3)
NA, question not asked prior to 2002	23295 (41)
Missing	3211 (6)
Graft type	
Bone marrow	30972 (54)
Peripheral blood	21952 (38)
Umbilical cord blood	4312 (8)
Missing	62 (<1)
Year of transplant	
1985-1994	14775 (26)
1995-2004	21329 (37)
2005-2014	21194 (37)
New malignancy	4990 (9)
Sarcoma	102 (<1)
Median follow-up of survivors (range), months	111 (3-394)

[a] Still need to exclude patients from centers that have less than 80% completeness at 5 years post-transplant

Proposal: 1812-10

Title:
Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.

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Hypothesis:
Allogeneic hematopoietic cell transplantation (allo-HCT) in elderly patients (>=60 years) is associated with significant long term toxicities and late side effects and can be predicted by pre and post-transplant variables

Primary aim:

- To evaluate incidence of late effects (1, 2 , 5 and 10 years post-transplant) such as
  - neurological (strokes, seizures)
  - cardiovascular (CHF with EF < 40%, MI)
  - endocrine (diabetes, hypothyroidism, growth hormone deficiency, adrenal insufficiency, gonadal dysfunction/infertility requiring hormone replacement)
  - genito-urinary (renal failure warranting hemodialysis, hemorrhagic cystitis)
  - gastrointestinal/hepatic (pancreatitis/cirrhosis)
  - musculoskeletal (avascular necrosis)
  - special sensory (cataracts)
  - subsequent cancers (lymphoid, including PTLD, vs MDS/AML vs solid tumors)
  - Pulmonary (COPD, pulmonary fibrosis or other restrictive airway disease)

- Compare survival outcomes with age matched general patient population matched for comorbidities (database to be determined)

Secondary aims:

- To evaluate predictors such as pre-transplant comorbidities and chronic GVHD with incidence of late effects

Scientific impact and justification:
Reduced-intensity conditioning (RIC) has been widely introduced over the past 15 years to allow HCT in elderly and medically infirm patients not eligible for standard myeloablative conditioning (MAC) [1]. Several studies have shown similar survival of older AML/MDS patients after HCT with RIC or MAC [2–7]. Most of these studies have shown that RIC is associated with reduced non-relapse mortality (NRM) but increased relapse rate, resulting in a similar leukemia free survival (LFS) as MAC. However, due to the more recent introduction of RIC, there is paucity of data on the long-term outcome and late effects after RIC while increasing number of older patients are getting transplanted. A recent study from EBMT registry compared the late effects of MAC and RIC in AML patients and did not find any significant difference [8]. A retrospective study of 1087 contemporary survivors also showed that the cumulative incidence of any non-malignant late effect at five years after HCT was 45% among autologous and 79% among allogeneic recipients, and 2.5% of autologous and 26% of allogeneic recipients had three or more

late effects [9]. Although screening for late effects post-transplant has been emphasized there is no clear improvement in the prevalence and incidence likely due to lack of identification and survivorship programs [10]. Prevention and pre-emptive knowledge earlier in the course of transplant could help plan prevent or minimize those late events and also would be useful in educating older adults about the potential for late effects following allo-HCT. The Sorror HCT-CI was routinely collected by the CIBMTR beginning in 2008. Prior to 2008 individual comorbidity data was collected. We aim to evaluate the association of pre-HCT comorbidities with late effects in older adults (using Sorror data for patients transplanted from 2008 on, and available comorbidity data from patients transplanted prior to 2008) and compare with non-HCT age matched controls that will be obtained from population database (to be determined)

Patient eligibility population:

Inclusion criteria:

- Patients age ≥60 yo at the time of first allo-HCT for hematological malignancies
- Patients undergoing first allo-HCT between the years of 2000-2014, with or without donor cell infusions at any time
- Transplant from a matched related or matched (8/8) unrelated donor
- Diagnosis of hematologic malignancies

Exclusion criteria:

- Patients who have received prior autologous or second HCT
- Exclude cord blood

Data requirements:

- Age at transplant
- Patient gender
- Donor/Recipient gender: F/F vs M/M vs F/M vs M/F
- Obesity (BMI > 35 kg/m2) at transplant
- Reduced intensity conditioning according to CIBTMR definitions
- Disease: AML/MDS/ MPN/ ALL/ NHL/ CML and other hematological malignancies
- Disease risk index
- Karnofsky score ≥ 90 vs < 90 vs unknown or missing
- Sorror Co-morbidity index: 0 vs 1-2 vs ≥ 3 (2008 onwards)
- Individual comorbidities (2000-2007)
- Race: White vs African American vs Hispanics vs others
- Disease Risk Index (DRI):
- Time from diagnosis to HCT:
- Donor Type: MRD vs MUD
- Graft Type: BM vs PBSC
- GVHD Prophylaxis: CNI+MTX vs CNI+MMF vs CNI+sirolimus vs TCD vs other vs unknown or missing
- ATG used: no vs yes vs unknown or missing
- Acute GVHD: no vs Grade I-II vs Grade III-IV vs unknown or missing (Grade)
- Chronic GHVD: no vs yes vs unknown or missing
- Maximum grade of cGVHD: Limited vs Extensive vs unknown or missing
- Maximum overall severity of cGVHD: mild/moderate/severe/unknown or missing
- Specific Therapy for cGVHD: steroid alone vs steroid + CNI vs CNI alone a Sirolimus +/- other agent vs other vs unknown or missing

- DLI: no vs yes vs unknown or missing
- Donor/Recipient CMV status: -/+ vs +/- vs +/+ vs -/-
- Follow-up of survivors, months, median (range)

Study design:

A retrospective multicenter study will be performed using the CIBMTR dataset. The objective of this analysis is to describe the cumulative incidence of late effects in older adults with advanced hematologic malignancies undergoing allo-HCT. Late effects will be analyzed in malignant versus non-malignant categories, and then individually.

Cumulative incidence of late effects and survival outcomes will be estimated at 1, 2, 5 and 10 years after HCT, and estimates will be provided with 95% confidence intervals. Survival outcomes will be compared with non-HCT age matched controls obtained from NHANES or similar database.

Descriptive statistics, including Chi-square, Student T-test or Wilcoxon statistic will be used to compare the distribution of demographic and other patient and transplant related characteristics. The incidence and rate of late effects will be analyzed with the cumulative incidence method, accounting for death and relapse as competing risks. Predictors for 2+ late effects (including individual pre-transplant comorbidities and overall scores and presence of chronic GVHD) will be evaluated in multivariate logistic regression modeling.

- neurological (strokes, seizures)
- cardiovascular (CHF with EF < 40%, MI)
- endocrine (diabetes, hypothyroidism, growth hormone deficiency, gonadal dysfunction/infertility requiring hormone replacement)
- genito-urinary (renal failure warranting hemodialysis, hemorrhagic cystitis)
- gastrointestinal/hepatic (pancreatitis/cirrhosis)
- musculoskeletal (avascular necrosis)
- special sensory (cataracts)
- subsequent cancers (lymphoid, including PTLD, vs MDS/AML vs solid tumors)
- other (COPD, pulmonary fibrosis or other restrictive airway disease)

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1812-10: Characteristics of patients aged 60 or older that underwent a first HLA-identical sibling or unrelated donor alloHCT for a hematologic malignancy, between 2000 and 2014, reported to the CIBMTR[a]

Characteristic	N (%)
Number of patients	5144
Median age at transplant (range), years	64 (60-82)
Age at transplant	
60-64	2856 (56)
65-69	1802 (35)
70-74	448 (9)
75-79	37 (<1)
80+	1 (<1)
Sex	
Male	3328 (65)
Female	1816 (35)
Karnofsky score	
90-100	2902 (56)
< 90	1996 (39)
Missing	246 (5)
HCT-CI	
0	732 (14)
1	398 (8)
2	403 (8)
3+	1452 (28)
NA, not collected prior to 2008	2100 (41)
Missing	59 (1)
Disease	
AML	2030 (39)
ALL	163 (3)
Other leukemia	381 (7)
CML	122 (2)
MDS	1887 (37)
Other acute leukemia	23 (<1)
NHL	454 (9)
HD	4 (<1)
MYE	40 (<1)
Other Malignancies	40 (<1)
Intended conditioning intensity	
MAC	1566 (30)
RIC/NST	3335 (65)
Form 2400 not filled out	203 (4)
Missing	40 (<1)
Graft type	
Bone marrow	532 (10)
Peripheral blood	4611 (90)
Missing	1 (<1)

Characteristic	N (%)
Donor	
HLA-identical sibling	1712 (33)
Unrelated donor	3432 (67)
Year of transplant	
2000-2004	933 (18)
2005-2009	2127 (41)
2010-2014	2084 (41)

[a] Still need to exclude mismatched unrelated donors and patients who have received a second HCT