MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Orlando, Florida
Thursday, February 20, 2020, 2:45 – 4:45 pm

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Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Co-Chair:	**Betty Hamilton, MD, Cleveland Clinic Foundation, Cleveland, OH; Telephone: 216-445-7580; E-mail: hamiltb2@ccf.org**
Scientific Director:	**Bronwen Shaw, MD, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: beshaw@mcw.edu**
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Statistician:	**Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8515; E-mail: sbosuba2@nmdp.org**

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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 2:45pm on Thursday, February 20, 2020 by Dr. Betty Hamilton. She introduced the current working committee leadership and introduced the incoming chair, Dr. Hélène Schoemans. The leadership thanked Dr. Minoo Battiwalla, the outgoing chair, for his service to the LEWC over the past five years. The CIBMTR COI policy was reviewed and the processes of participating in the working committee, voting guidance, and rules of authorship were outlined.

Dr. Hélène Schoemans was also welcomed as the representative of the EBMT late effects committee for this meeting.

a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)
b. Introduction of incoming Co-Chair:
   Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven; Leuven, Belgium; Telephone: 32 16 34 68 80; Email: helene.schoemans@uzleuven.be

2. Accrual summary

Dr. Shaw reminded the committee that there are PRO data now available for secondary study questions and that the number of PRO surveys available will increased greatly in the next two years.

3. Presentations, published or submitted paper

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

a. **LE13-02** Herr MM, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon EK, Battiwalla M, Buchbinder D, Flowers ME, Brazauskas R, Shaw BE, Morton LM. Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation***. Journal of the American Academy of Dermatology. doi:10.1016/j.jaad.2019.10.034. Epub 2019 Oct 22.***

b. **LE16-02** Kahn JM, Brazauskas R, Tecca HR, Bo-Subait S, Buchbinder D, Battiwalla M, Flowers MED, Savani BN, Phelan R, Broglie L, Abraham AA, Keating AK, Daly A, Wirk B, George B, Alter BP, Ustun C, Freytes CO, Beitinjaneh AM, Duncan C, Copelan E, Hildebrandt GC, Murthy HS, Lazarus HM, Auletta JJ, Myers KC, Williams KM, Page KM, Vrooman LM, Norkin M, Byrne M, Diaz MA, Kamani N, Bhatt NS, Rezvani A, Farhadfar N, Mehta PA, Hematti P, Shaw PJ, Kamble RT, Schears R, Olsson RF, Hayashi RJ, Gale RP, Mayo SJ, Chhabra S, Rotz SJ, Badawy SM, Ganguly S, Pavletic S, Nishihori T, Prestidge T, Agrawal V, Hogan WJ, Inamoto Y, Shaw BE, Satwani P. Subsequent Neoplasms and Late Mortality in Children Undergoing Allogeneic Transplantation for Non-Malignant Diseases. ***Submitted.***

c. **LE17-02** *Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton BK, Battiwalla M, Majhail NS, Lazarus H, Shaw P, Marks D, Litzow MR, Chhabra S, Inamoto Y, DeFilipp Z, Hildebrandt G, Olsson R, Kasow K, Liesveld J, Rotz S, Badawy SM, Bhatt N, Yared J, Page K, Arellano M, Kent MW, Farhadfar N, Seo S, Hematti P, Freytes CM, Rovo A, Ganguly S, Nathan S, Burns L, Shaw BE, Muffly LS.* Late Effects After Ablative Allogeneic Stem Cell Transplantation for Adolescent and Young Adult Acute Myeloid Leukemia. ***Submitted.***

d. **LE17-01** Stenger E, Phelan R, Shaw BE, Battiwalla Minoo, Bo-Subait S, Brazauskas R, Buchbinder DK, Hamilton BK, Shenoy S, Krishnamurti L. Excellent Overall Survival and Low Incidence of Late Effects in Patients Undergoing Allogeneic Hematopoietic Cell Transplant for Sickle Cell Disease: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 61st ASH Annual Meeting and Exposition.***

e. **LE18-02** Bhatt NS, Brazauskas R, Bo-Subait S, Salit RB, Syrjala K, Tecca HR, Battiwalla M, Buchbinder DK, Hamilton BK, Phelan R, Shaw BE. Post-Transplant Work Status of Young Adult Survivors of Allogeneic Hematopoietic Cell Transplant: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 61st ASH Annual Meeting and Exposition.***

f. **LE12-03** Gupta M, Levine MH, Porter D, Bo-Subait S, Shaw BE, Brazauskas R, Phelan R, Battiwalla M, Buchbinder D, Hamilton B, Abt PL. Solid Organ Transplant (SOT) and Hematopoietic Cell Transplantation (HCT). **Poster Presentation at TCT 2020 in Orlando, Fl.**

4. Studies in progress (Attachment 3)

Dr. David Buchbinder briefly listed all studies in progress. He introduced Dr. Lakshmanan Krishnamurti to present an update on LE17-01 and Dr. Neel Bhatt to present on LE18-02.

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) **Analysis**

c. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Analysis**
Dr. Lakshmanan Krishnamurti presented this study which aims to describe late effects of HCT in sickle cell disease patients, describe the relationship of transplant-related factors to organ dysfunction and sickle cell disease related complications, and to compare survival of transplanted cohort to a cohort of non-transplanted sickle cell disease patients. Overall survival, late effects, and comparison of SCD-related symptoms pre and post were reported on within the transplant cohort. The committee had time to ask several questions and for discussion

e. **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**

f. **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) **Manuscript Preparation**
Dr. Neel Bhatt presented this study which aims to assess the post-HCT work status of young adults undergoing alloHCT, and to examine pre-HCT factors associated with work status at 1-year post-HCT. Work status post-transplant was reported and compared with pre-HCT work status. Risk factors associated with work status at 1-year post-HCT were presented.
The committee had time to ask several questions and for discussion

g. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) **Protocol Development**
h. **LE19-02** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) **Protocol Development**

5. Future/proposed studies

a. **PROP 1911-23** Influence of Busulfan based vs melphalan based Chemo regimens On early and late cardiac toxicity post SCT (*Farhan*) (Attachment 4)
Dr. Shatha Farhan presented this proposal aiming to describe the incidence of early and late cardiac complications post-transplant, and to determine the patient and treatment related risk factors including conditioning regimen associated with cardiac complications. There were a few comments on expanding the conditioning to be investigated (beyond melphalan and busulfan, but also taking into account other exposures during conditioning) as well as included the pre-HCT therapies given as this may influence late effects. Specific questions about the availability of data on proteasome inhibitors were raised. It was acknowledged that more granular cardiovascular outcomes were not collected in the registry until recently, except for measures of cardiomyopathy (though the way this was collected has differed over time)
It was also noted that it is important to look at cardiovascular disease by subtype. Concerns were raised about the ability to determine cardiovascular events that happened as a late effect instead of cardiac toxicity related to aging leading to a cardiovascular event and stress the importance of the years of follow up post-transplant. This study was not accepted due to the above stated concerns, particularly regarding the granularity of late effects data and pre-transplant exposures.

b. **PROP 1911-30** Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant (*Taylor/Knight/Baker/Cole*) (Attachment 5)
Dr. Jennifer Knight presented this proposal aiming to examine associates between CTRA gene expression and PROs, and to explore the relationship between CTRA gene expression, PROs and clinical outcomes such as relapse-free survival, engraftment, GHVD and overall survival. The study is powered on a previous analysis done by this group using CIBMTR clinical outcome data, but not PRO's.
One attendee commented that it may be best to homogenize the population by selecting further on disease or age, however because the number of patients with PROs is low this would be limiting. Dr. Knight stressed this is a hypothesis generating study which would be used as preliminary data for grant proposals. The testing of donor samples was raised and Dr. Knight commented that she is currently working on a similar study with donor samples.
The reasoning for selection of the genetic profile was also expanded upon by highlighting that this profile as a whole has been shown to be impacted by periods of stress, such as undergoing HCT, and this is not a discovery gene panel, but a panel that can be summarized in a composite score and used as a continuous variable for analysis.

c. **PROP 1911-59** New Cancers after Autologous Hematopoietic Cell Transplantation for Systemic Light-Chain Amyloidosis *(Chakraborty/Majhail/Lentzsch)* (Attachment 6)
Dr. Rajshekhar Chakraborty presented this proposal aiming to determine the incidence of new cancers after autoHCT for AL amyloidosis, to identify risk factors for subsequent cancer, and to compare the incidence of subsequent cancers in AL survivors with demographically matched healthy controls. It was noted that it may be possible to use standardized mortality ratios to address a comment regarding the potential for increased risk of subsequent cancers within the non-transplant therapies (an ideal control would be patients with amyloid but no transplant). It was suggested clarity be added about whether these are first cancers post-transplant and the history of cancer prior to transplant. This study was not accepted due to the above stated concerns as well as prioritization of other proposed studies due to potential higher/novel impact on the field.

d. **PROP 1911-176** Cardiometabolic Risk after Total Body Irradiation during Childhood (*Friedman/Chow*) (Attachment 7)
Dr. Danielle Friedman presented this proposal aiming to use CCSS and CIBMTR data to determine long-term risk of developing cardiovascular disease comorbidities in survivors treated with TBI versus non-TBI HCT and conventional chemotherapy, as compared to siblings; identify other treatment, primary disease, demographics and specific chronic conditions that modify risk of cardiovascular comorbidities after TBI; and to assess whether lifestyle factors modify risk.
Dr. Christy Duncan had grant funding to collect supplemental data for her study looking at late cardiovascular morbidity and mortality in the pediatric population and is happy to contribute data to this proposed study. Outcomes data would come from CCSS and transplant specific data would come from CIBMTR. These data would be linked by an honest broker using personal identifiers which have been confirmed to be available from both sources (including names) suggesting that this linkage will be feasible. Linked CCSS and CIBMTR data will provide a rich dataset for future studies to be proposed and addressed. The inclusion of healthy siblings in the CCSS dataset would provide an excellent control for CIBMTR studies which is unavailable now.

e. **PROP 1911-203** Pre-transplant body mass index and late effects among children, adolescent, and young adult (CAYA) childhood leukemia survivors following allogeneic hematopoietic cell transplantation (*Joffe/Broglie/Ladas/Kadan-Lottick/Satwani*) (Attachment 8)
Dr. Larisa Broglie presented this proposal aiming to determine the incidence of late effects and secondary malignancies in CAYA patients based on pre-HCT weight (BMI) categories and to determine the incidence of late mortality in patients who are obese or overweight at the time of transplant compared to the general population.
One attendee was concerned about the change in weight over time and the time gap from exposure to outcomes, including our inability to track post-transplant weight and the potential for large changes in that variable. Post-transplant weight was not collected until recently (2017), but this could be added to the study in the future when the data is more robust. Another attendee suggested subdividing the obese category into obese and morbidly obese since treating the morbidly obese patients poses a greater challenge than the patients that technically fall into the obese category.
This study was not accepted due to the above stated concerns, most notably the lack of broader ranges or pre and post-transplant BMI data.

f. **PROP 1912-07** Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) In The Modern Era *(Al-Mansour/Farhadfar/Socie/Wingard)* (Attachment 9)

Dr. Zeina Al-Mansour presented this proposal aiming to determine overall mortality of alloHCT survivors who were disease free at 2 years post-transplant, evaluate factors associated with late mortality, compare survival with matched controls from the general population, compare changes in causes of death over time, and to compare relative late fatality rates and causes of death within subgroups.

It was noted that autopsy reports are collected by CIBMTR but would only be available on a subset of the population since it is up to the site to decide whether to submit an autopsy report. Infection would be collected as cause of death for transplant recipients but generally is not collected beyond 2-years post-transplant. An attendee asked whether to study population really needs to go back to 1980 versus 1990 or 2000; the PIs would like to include cases back to 1980 to increase the number of cases and to allow for the ability to study causes of death and rate of mortality in the modern era compared to the earlier cases. Suggestions were made to stratify the population by age.

This study was not accepted due to the above stated concerns, overlapping themes with an ongoing study (LE18-01) as well as prioritization of other proposed studies due to potential higher/novel impact on the field.

Dropped proposed studies

a. **PROP 1911-27** Recurrence of primary solid cancers after allogeneic hematopoietic cell transplantation. *Dropped due to feasibility.*
b. **PROP 1911-103** Secondary malignancies after reduced intensity or non myeloablative stem cell transplantation in non-malignant disorders. *Dropped for overlap with an existing study.*
c. **PROP 1911-114** Incidence and Outcomes of Kaposi Sarcoma after Hematopoietic Stem Cell Transplantation: A CIBMTR study. *Dropped due to feasibility.*
d. **PROP 1911-188** Tumor Immunogenicity as a Predictor of Second Cancer Relapse after Allogeneic Hematopoietic Cell Transplantation in Patients with History of Solid Organ Cancer. *Dropped due to feasibility.*
e. **PROP 1911-195** Outcomes of long-term survivors of umbilical cord blood allogeneic HSCT. *Dropped for overlap with an existing study.*
f. **PROP 1911-223** Late treatment related mortality vs competing causes of death after all HCT for secondary AML and MDS in pediatric patients. *Dropped due to feasibility.*

6. Other Business

Dr. Minoo Battiwalla reminded the working committee to score each proposal with 1 being the best and 9 being not the best. He introduced Dr. Rachel Phelan to give an update on the annual CIBMTR and EBMT collaborative reviews.

a. CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party Review
   The male-specific late effects review which was accepted last year is currently being written by each subgroup. There was a lot of interest, so the review leadership stressed from the beginning the importance of active participation in order to be included as an author. Additionally, to address the large number of people interesting in participating, the paper was split into an adult and pediatric paper. A methodology subgroup was put together to organize and standardize search strategies within each subgroup and is putting out a white paper on conducting systematic reviews within this field. The next call for proposals will go out around March of 2020; young investigators are encouraged to get involved.

7. Closing Remarks

The role of Scientific Director for the Late Effects and Quality of Life Working Committee will be transitioning from Bronwen Shaw to Rachel Phelan beginning March 1, 2020.

Rachel Phelan has been promoted from the position of Assistant Scientific Director for the Late Effects and Quality of Life Working Committee, to the Scientific Director and will assume all responsibilities.

Oversight Assignments for Working Committee Leadership (March 2020)

David Buchbinder	**LE17-01** Long-term follow up after HSCT for sickle cell disease
	LE18-01 Survival trends amongst two-year survivors of alloHCT
	LE18-02 Return to work or school status in survivors of young adult AlloHCT
	LE20-01 Cardiometabolic Risk after Total Body Irradiation during Childhood
Betty Hamilton	**LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients
	LE19-02 Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies
Helene Schoemans	**LE12-03** Solid organ transplant after HCT
	LE20-02 Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant
Bronwen Shaw	**LE99-01** Quality of life in late HCT survivors

Working Committee Overview Plan for 2020-2021

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

b. **LE12-03** Solid organ transplant after HCT. This study is in analysis and we plan to start manuscript prep by July 2020.

c. **LE17-01** Long-term follow up after HSCT for sickle cell disease. This study is in analysis and we plan to complete the analysis and start manuscript preparation by July 2020.

d. **LE18-01** Survival trends amongst two-year survivors of alloHCT. This study is in data file prep. We aim to be in manuscript preparation by July 2020.

e. **LE18-02** Return to work or school status in survivors of young adult AlloHCT. This study is in manuscript preparation and we aim to have it submitted by July 2020.

f. **LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients. This study is in protocol development and we aim to have it in analysis by July 2020.

g. **LE19-02** Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. This study is in protocol development and we aim to have it in data file preparation by July 2020.

h. **LE20-01** Cardiometabolic Risk after Total Body Irradiation during Childhood. Protocol is pending on this study and hours will begin July 2020.

i. **LE20-02** Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant. Protocol is pending on this study and hours will begin July 2020.

Not for publication or presentation

Working Committee Overview Plan for 2020-2021

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total hours allocated
LE12-03: Solid organ transplantation and hematopoietic cell transplantation	Analysis	Submitted – July 2021	110	110	60	50	110
LE17-01: Long-term follow up after hematopoietic stem cell transplantation for sickle cell disease	Analysis	Submitted – July 2021	110	110	60	50	110
LE19-01: Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Protocol development	Manuscript Preparation – July 2021	230	160	100	60	160
LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.	Protocol development	Manuscript Preparation – July 2021	330	260	100	160	260
LE20-01: Cardiometabolic Risk after Total Body Irradiation during Childhood	Protocol pending	Data file preparation – July 2021	370	100	0	100	100

LE20-02: Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant	Protocol pending	Analysis – July 2021	330	200	0	200	200