1. Introduction

Dr. Marcie Riches moderated the introduction of the working committee followed by which all the attending co-chairs and the statisticians were introduced.

Dr. Riches reviewed the goal of the working committee to publish high impact studies in a timely manner. The expectations of the meeting are review of the current status of ongoing studies and timelines and for members to assess and select proposals that will have a high impact on the field. The working committee is limited by the complicated nature of infection data (Best before day 100) including data regarding infection prophylaxis which will be the focus of the “other business” section of the meeting.

The working committee Members were asked to vote on a level of scientific impact score, 1 is the highest impact and 9 is the lowest impact score for the new proposals based on the feasibility and impact on the transplant community.

Dr. Riches mentioned the working committee’s membership is open to any individual willing to take an active role in study development and completion. Badge scanning will automatically add you to the Working Committee membership. She also emphasized the rules of the Authorship: 1. substantial and timely contributions to conception and design, acquisition of data, or analysis...
and interpretation of data; 2. drafting the article or revising it critically for important intellectual content; 3. final approval of the version to be published. All three conditions must be met.

The minutes and overview plan from the 2015 Tandem meeting held in San Diego, CA were reviewed and approved by committee members.

2. Published or submitted papers

Dr. Marcie Riches mentioned, the infection working committee submitted six papers in the past year. Four of them have been published or accepted and two are undergoing revisions.


c. **IN10-01** Karen Ballen, Kwang Ahn, Min Chen, Dr. Hisham Abdel-Azim, Ibrahim Ahmed, Dr. Mahmoud Aljurf, Dr. Joseph Antin, Ami Bhatt, Michael Boeckh, George Chen, Dr. Christopher Dandoy, Dr. Biju George, Mary Laughlin, Dr. Hillard Lazarus, Dr. Margaret MacMillan, David Margolis, Prof. David Marks, Dr. Maxim Norkin, Dr. Joseph Rosenthal, Ayman Saad, Prof. Bipin Savani, Dr. Harry Schouten, Jan STOREK, Paul Szabolcs, Dr. Celalettin Ustun, Dr. Michael Verneris, Dr. Edmund K Waller, Dr. Daniel Weisdorf, Dr. Kirsten Williams, John Wingard, Baldeep Wirk, Tom Wolfs, Jo-Anne Young, Jeffery Auletta, Dr. Krishna Komanduri, Dr. Caroline Lindemans, Dr. Marcie Riches: Infection Rates among Acute Leukemia Patients receiving Alternative Donor Hematopoietic Cell Transplantation. *Submitted.*

d. **IN09-01** Richard Maziarz, Dr. Ruta Brazauskas, Min Chen, Dr. Aleksandra McLeod, Dr. Rodrigo Martino, John Wingard, Dr. Mahmoud D Aljurf, Minnoo Battiwalla, Dr. Christopher Dvorak, Prof. Biju George, Dr. Eva Guinan, Dr. Gregory Hale, Dr. Hillard Lazarus, Prof. Jong Wook Lee, Dr. Jane Liesveld, Dr. Muthalagu Ramanathan, Dr. Vijay Reddy, Prof. Bipin Savani, Dr. Franklin Smith, Dr. Lynne Strasfeld, Dr. Randy Taplitz, Dr. Celalettin Ustun, Dr. Michael Boeckh, Dr. Juan Gea-Banacloche, Dr. Caroline Lindemans, Jeffery Auletta, Dr. Marcie Riches: Outcomes of allogeneic HSCT for patients with hematologic malignancies (AML, ALL, MDS, CML) with and without pre-existing fungal infections- pre-existing invasive fungal infection is not a contraindication for subsequent HSCT: a CIBMTR® study. *Submitted.*

e. **IN12-01a** Pierre Teira, Minoo Battiwalla, Muthalagu Ramanathan, Kwang Woo Ahn, Min Chen, Jaime Green, Ayman Saad, Joseph H. Antin, Bipin N. Savani, Hillard M. Lazarus, Matthew Seftel, Wael Saber, Carolyn Behrendt, David Marks, Mahmoud Aljurf, Maxim

f. **IN12-01b** Muthalagu Ramanathan, Pierre Teira, Minnoo Battiwalla, Dr. A. Barrett, Kwang Ahn, Min Chen, Carolyn Behrendt, Jaime Green, Mary Laughlin, Dr. Hillard Lazarus, Prof. David Marks, Ayman Saad, Dr. Matthew Seftel, Dr. Wael Saber, Prof. Bipin Savani, Dr. Edmund K Waller, John Wingard, Jeffery Auletta, Dr. Caroline Lindemans, Michael Boeckh, Dr. Marcie Riches: Impact of Early Cytomegalovirus Reactivation in Cord blood Stem Cell Recipients in the Current Era. Accepted by BMT.

3. **Studies in progress**
Dr. Caroline Lindemans introduced the status of four ongoing studies.

a. **IN07-01/IN11-01** Early Bacterial infection in patients undergoing allogeneic HCT (M Robien/G Papanicolaou/Celalettin Ustun/ JA Young).
The study is on data file preparation stage, are expecting to finish final analysis by June 30, 2016.

b. **IN13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following non- myeloablative and myeloablative regimens (C Usten).
The protocol has been sent to the working committee for comments, we are expecting to finish final analysis by June 30, 2016.

c. **IN14-01** Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphoproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab (S Naik, C Bachier, P Shaughnessy, P Hari, R Kamble)
The study is on protocol development stage, we are expecting to have dataset ready for analysis by June 30, 2016

d. **IN15-01** Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies (Pierre Teira)
This study is on protocol development stage.

4. **Future/proposed studies**
Dr. Caroline Lindemans mentioned there are total 9 proposals received this year and 5 will be presented.

a. **PROP 1510-16** Viral encephalitis in hematopoietic stem cell transplant recipients, 2007-2013 (Maheen Abidi/ Parameswaran Hari)
Dr. Maheen Abidi presented the proposal.
The objective of this proposal are: 1. determine frequency and significance of viral DNA detection in CSF in patients screened for viral encephalitis; 2. Determine risk factors (recipient and transplant related); 3. Determine survival outcomes, encephalitis related mortality rate for different viruses, and for encephalitis due to ≥1 virus. The Hypothesis of this study is: Viral Encephalitis can have significant impact on mortality of Hematopoietic stem cell (HCT) transplant recipients, with significant variation amongst viruses on encephalitis related mortality rates. Mortality tends to be high for viral encephalitis due to more than one virus.
Comments from the audience: It is an important study. There is a concern that there were no Haploidentical cases identified. Dr. Krishna Komanduri pointed out there are more than half of the recipient are cord blood.

b. PROP 1511-27 Impact of early gram-negative bloodstream infections on transplant outcomes in autologous and allogeneic transplant patients (Pearlie Chong/ Marcie Riches/ Krishna Komanduri)
Dr. Pearlie Chong introduced the background of this study: 1. GNBSI occur in 22 – 56% of HCT recipients with high mortality, despite antimicrobial prophylaxis 2. Most data from single centers limited by local practices and resistance patterns. She also introduce the hypothesis of this study: GNBSI occurring between day 0 – day 14 after HCT negatively impacts transplant outcomes
The objective of this study is to compare outcomes in HCT recipients with and without early (d0 – d14) GNBSI, overall, disease-free survival, transplant related mortality, infection related mortality from time of GNBSI and Subsequent (day+15 – day 100) BSI, viral, and fungal infections by day 100
The patient population of the study is: ≥ 18 yrs receiving 1st allo/auto HCT 2008 – 2014 for any disease and using any stem cell source, exclude patients not in CR at time of transplant and patients who die prior to day +14.

The comments from committee are: 1. This should not be limited to adults only. 2. Exclude the patients not in CR.

Dr. Juan Gea-Banacloche comments that the study design is not good; the center effect should be taken into consideration. He proposed a case control study.

Another question from the audience is why excluded the patients who died before day14. Dr. Marcie Riches explained that we have been struggling with statistical analysis, whether or not we can account for multiple infections and early mortality, we were wanting to looking something happened early effect the outcome later. We may try to use the statistical methodology which we are using for IN0701/IN1101 and not exclude the patients who die before day 14. Also make definition, cases are had gram-negative BSI before engraftment.

c. PROP 1511-85 Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections in the first 100 days after stem cell transplant (Christopher Dandoy/ Paulina Daniels)
Dr. Christopher Dandoy presented the proposal. He introduced the background of this proposal:
Central line-associated bloodstream infections (CLABSIs) are a major public health issue; CLABSIs are a determinant of healthcare quality (Major focus of quality improvement efforts, hospital rankings, and reimbursement); Central venous catheter (CVC) maintenance care has been shown to be effective in reducing CLABSIs; The CDC recently modified the CLABSI definition to identify a subset of CLABSIs likely related to mucosal barrier injury termed mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI); Unlike CLABSIs, MBI-LCBIs are not prevented by improved CVC maintenance care. He
mentioned, a blood stream infection is defined as an MBI-LCBI if: 1. Resulted from 1 or more of a group of organisms known to be commensals of the oral cavity or gastrointestinal tract; and 2. Occurred in a patient with signs/symptoms compatible with mucosal barrier injury such as GI-GVHD and/or neutropenia. Importance. There are no reported data on the incidence, risk factors, and outcome of patients that develop MBI-LCBI after HSCT. High rates of MBI-LCBIs are penalizing centers that perform HSCT and care for high acuity patients. This study will lead to the identification of variables to target in future interventional studies.

Dr. Christopher Dandoy mentioned the hypothesis of the proposal are: patients in the first 100 days after stem cell transplant (SCT) who develop mucosal barrier injury laboratory confirmed bloodstream infections (MBI-LCBI) have increased transplant related mortality (TRM) and decreased overall survival (OS) compared to those with no infection or an infection not classified as an MBI-LCBI. The specific aims of the study are: 1) Determine the incidence and timing of MBI-LCBIs in the first 100 days post SCT; 2) Determine the risk factors for development of a MBI-LCBI in the first 100 days; and 3) Compare TRM and OS between patients in the first 100 days post-SCT who develop a MBI-LCBI versus those with no infection or a non-MBI-LCBI. He pointed out the study strengths are: large sample size, contemporary, reflects the global reality of HSCT by including all centers. Since MBI-LCBI are identified as a burden for public health reporting with public health implications, this proposal will target major public health journal such as JAMA.

One concern from the committee is quantifying variability of mucosal damage, Dr. Dandoy mentioned we are going to use CDC criteria based on the organisms identified. Another concern is reporting change during time.

d. PROP 1511-103 Impact of resolved Hepatitis B infection on outcome of allogeneic hematopoietic stem cell transplant for hematologic malignancies (Carrie Yuen/ Jennifer Holter-Chakrabarty)

Dr. Jennifer Holter-Chakrabarty presented the proposal. She introduced the Hypothesis of the proposal: patients with resolved hepatitis B infection have different outcomes after HSCT depending on stem cell sources. She also introduce the objective of the proposal: the primary objective: outcome (GVHD, NRM, duration of survival) in patients with resolved hepatitis B infection after allogeneic HSCT for acute leukemia as compared with control group; the secondary objective: outcome (GVHD, NRM, OS) in patients with resolved hepatitis B infection after cord blood transplant as compared with matched related and matched unrelated donor HSCT.

Dr. Celalettin Ustun suggested adding variable hepatitis B serology for donor and recipient.

e. PROP 1512-02 Evaluation of post-engraftment bacterial blood stream infections occurring within the first 100 days post-transplant (Celalettin Ustun/ Jo-Anne Young/ Genovefa A Papanicolaou)

Dr. Celalettin Ustun presented the proposal. He introduced hypothesis of the proposal is that later post-engraftment BSI are associated with lower overall survival and higher transplant related mortality compared to patients never developing bacterial BSI in the first 3 months after transplant.
The study objective is: To evaluate the incidence of BSI after engraftment through 100 days post-transplant (post-engraftment defined as 15 days from date of neutrophil recovery); To evaluate the effects of these infections on alloHCT outcomes (TRM, OS, DFS, secondary graft failure); To compare transplant outcomes for patients developing a first BSI after engraftment to patients never developing a post-engraftment BSI; To evaluate risk factors resulting in post-engraftment BSI. He mentioned the rationales are: the ongoing study (IN0701/1101) is already evaluating early BSI, and its effects on outcome (Early BSI defined as occurring from day 0 until 14 days beyond ANC recovery); with this study, we will focus on BSI occurring later after engraftment. We can share dataset of IN0701/1101, so this proposed study is an extension of IN0701/1101 and can be done rather quickly. He also explained why we want to focus on Post-engraftment Infections: 1. In the current era of improved diagnostics and HCT supportive care, more patients survive the neutropenic initial phase; 2. We will include all graft sources. Therefore, we can particularly evaluate if BSI after UCB is solely related to engraftment; 3. We will evaluate particular risk factors (GvHD etc) for this period.

One of the suggestions from the committee is to combine Prop 1512-02 and ongoing study IN0701/IN1101. Dr. Marcie Riches mentioned we can share the dataset; it will save the statistical hours and help the new study move quickly, so the committee can accept and finish more studies.

5. Dropped proposed studies
Dr. Krishna Komanduri explained the reasons for the dropped proposed studies.


b. PROP 1508-04 Cytomegalovirus and Effect on Early Chimerism in Patients with Myeloid Disorders Undergoing Stem Cell Transplantation using Anti-thymocyte globulin versus Alemtuzumab. Dropped due to feasibility-low number of patients

c. PROP 1511-77 The efficacy and safety of high-dose valacyclovir for CMV prevention in umbilical cord blood transplant recipients. Dropped due to feasibility -the CIBMTR does not capture the data required to answer the hypothesis.

d. PROP 1511-133 Translating pharmacogenetics of antifungals into clinical outcomes. Dropped due to feasibility -the CIBMTR does not capture the data required to answer the hypothesis.

6. Other Business

Dr. Marcie Riches pointed out based on the statistical hour, the advisory working committee strongly recommended we only accept two proposals this year to proceed forward, if your proposal is not accepted, it does not mean it is not a quality proposal, it is just did not get high priority and it may be presented next year.

At the end, Dr. Riches reported the activities the infection working committee has been doing to improve the data capture. We received 9 proposals and 4 of them were dropped due to the low number of patients or lack of capture of certain data. It has been ongoing for many years. A committee of 17 persons including Dr. Riches, the WC chairs, ID specialists, and data managers are
revising the forms to facilitate the collection of data for studies that require a registry (i.e. cannot be done in a single institution).

One of the changes includes revision of the antimicrobial prophylaxis data on the 2100 form. Specifically, data captured will include the first drug the patient received (up though day 45), by antibacterial, antiviral, antifungal and PCP prophylaxis. Although, it is not going to give us the detail of changing a prophylaxis, it is better than the current data. The group is also working on trying to create additional supplemental data form including modify the fungal forms to capture data about diagnostic methods. The group proposed to add supplemental data form of CMV, EBV and HHV6, also will ask for drugs received for treatment, not duration of the therapy, use start date of the drug, what drugs the patient was receiving at 30 days from time of the diagnosis of the infection. It will help to capture the better information and publish the papers on high impact journals. Any comments and suggestions are welcome.

**Working Committee Overview Plan for 2016-2017**

a. **IN07-01/IN11-01** Early bacterial infection in patients undergoing allogeneic HCT (C Ustun/J-A Young/M Robien/G Papanicolaou). We anticipate finishing final analysis by June 30, 2016 and submitted the paper by June 30, 2017.

b. **IN 13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following nonmyeloablative and myeloablative regimens (C Usten). We anticipate finishing final analysis by June 30, 2016 and submitted the paper by June 30, 2017.

c. **IN 14-01** (PROP 1303-03/PROP1311-19): Post allogeneic hematopoietic transplant Ebstein Barr Virus related lymphproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab (R Kamble/ P Hari/ S Naik /C Bachier/P Shaughnessy). We anticipate having a dataset ready for analysis by June 30, 2016 and submitted the paper by June 30, 2017.

d. **IN 15-01** Incidence of early C. difficile infections after allogeneic hematopoietic cell transplantation over the last 12 years (C Usten). Due to the low scientific impact, the study will be dropped.

e. **IN16-01** Viral encephalitis in hematopoietic stem cell transplant recipients, 2007-2013 (Maheen Abidi/ Parameswaran Hari) (PROP1510-16). We anticipate receiving the protocol by June 30, 2016 and having the data ready for manuscript by June 30 2017.

f. **IN16-02** Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections in the first 100 days after stem cell transplant (Christopher Dandoy/Paulina Daniels) (PROP 1511-85). We anticipate receiving the protocol by June 30, 2016 and having the final protocol by June 30 2017.
## Work Assignments for Working Committee Leadership (March 2016)

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<tr>
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<td>Outcomes of allogeneic hematopoietic stem cell transplantation for patients</td>
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<td>Caroline Lindemans</td>
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