A G E N D A
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Orlando, FL
Wednesday, February 15, 2023, 1:00 p.m. – 3:00 p.m. (EST)

Co-Chair:	**Christopher Dvorak, MD, University of California San Francisco Medical Center, San Francisco, CA;** **E-mail: christopher.dvorak@ucsf.edu**
Co-Chair:	**George Georges, MD, Fred Hutchinson Cancer Research Center, Seattle, WA;** **E-mail: ggeorges@fredhutch.org**
Co-Chair:	**Andrew Gennery, MD, Newcastle General Hospital / The Royal Victoria Infirmary, Newcastle, UK;** **E-mail: andrew.gennery@newcastle.ac.uk**
Scientific Director:	**Larisa Broglie, MD, MS, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: lbroglie@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: skim@mcw.edu**
Statistician:	**Charimar Santiago Parilla, MPH, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: csantiago@mcw.edu**

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1. **Introduction**
   a. **Minutes from February 2022 TCT Working Committee Session** (Attachment 1)

2. **Accrual Summary** (Attachment 2)

3. **Presentations, Published or Submitted Papers**
   a. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) ***Submitted.***
   b. **NM19-01** Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) ***Submitted.***
   c. **NM19-02** Marsh RA, Hebert K, Kim S, Dvorak CC, Aquino V, Baker KS, Chellapandian D, Saldana BD, Duncan C, Eckrich MJ, Georges GE, Olson TS, Pulsipher MA, Shenoy S, Stenger E, Lugt MV, Yu LC, Gennery A, Eapen M. A comparison of hematopoietic cell transplant conditioning regimens for hemophagocytic lymphohistiocytosis disorders. ***Journal of Allergy and Clinical Immunology. doi:10.1016/j.jaci.2021.07.031. Epub 2021 Aug 7.***
   d. **NM19-03** Cancio M, Hebert K, Kim S, Aljurf M, Olson T, Anderson E, Burroughs L, Vatsayan A, Myers K, Hashem H, Hanna R, Horn B, Prestidge T, Boelens JJ, Boulad F, Eapen M. Outcomes in hematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.10.009. Epub 2021 Oct 17.***

4. **Studies in progress** (Attachment 3)
   a. **NM15-01** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) **Manuscript Preparation.**
   b. **NM17-01** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) **Protocol Development.**
   c. **NM18-01** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) **Data File Preparation.**
   d. **NM20-01** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Data File Preparation.**
   e. **AC18-02** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) **Manuscript Preparation.**
   f. **NM22-01** Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis (H Rangarajan/P Satwani) **Protocol Development.**

5. **Future/proposed studies**
   a. **2205-02** Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD) (E Ayala) (Attachment 4)
   b. **2210-19/2210-60** Impact of RBC Factors (prior allo-immunization and donor-recipient ABO mismatch) on Outcomes Post-Allogeneic Hematopoietic Stem Cell Transplant in Patients with Hemoglobinopathies (E Elsabbagh / C McKinney /N Shah/H Rangarajan/) (Attachment 5)
   c. **2210-110/2210-183** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (A Rayes/ S Otoukesh/R Nakamura/M Pulsipher) (Attachment 6)
   d. **2210-131** Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia (N Gibson/J Oved) (Attachment 7)
   e. **2210-236/2210-283** Alternative Donor Choices for Hematopoietic Stem Cell Transplantation (HCT) in Children and Young Adults with Hemophagocytic Lymphohistiocytosis (HLH) and other Immune Dysregulatory Disorders, Non-SCID Primary Immunodeficiency Diseases, and Inherited Bone Marrow Failure disorders (M Lakkaraja/ L Burroughs/ K Scott Baker/ M Pereda/ C Mckinney/ M Verneris) (Attachment 8)

Dropped Proposed Studies

   a. **2205-01** Impact of Total Body Irradiation (TBI) Dose for Allogeneic Hematopoietic Stem Cell Transplantation in Severe Aplastic Anemia (SAA) *Dropped due to overlap with current BMT-CTN study.*
   b. **2209-02** A comparative study of the use of reduced-intensity and myeloabative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Diamond-Blackfan Anemia (DBA) *Dropped due to low sample size.*
   c. **2209-14** Trends of Early Mortality Within First Two Years Following Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents with Non-Malignant Disorders. *Dropped due to heterogeneity of diseases.*
   d. **2210-05** Sickle cell disease and CD34 positive cell for gene therapy. *Dropped as data not currently collected.*
   e. **2210-16** Impact of Donor/Recipient CMV serological status on survival and outcomes post allogeneic hematopoietic cell transplant in patients with hemoglobinopathies. *Dropped due to overlap with recent published study (PMID: 31495699).*

f. **2210-122** Evaluation of Allogeneic Hematopoietic Stem Cell Transplantation Outcomes and Prognostic Factors in X-linked lymphoproliferative disease type 1 (XLP1): A CIBMTR Analysis *Dropped due to overlap with recent published study* (*PMID: 34375618).*

g. **2210-151** Identify optimal rabbit ATG (Thymoglobuline) dosing in reduced intensity conditioning HCT to minimize graft failure in severe aplastic anemia: Exposure-response analysis using an established population PK model for rabbit ATG *Dropped due to overlap with recent published study* (*PMID: 28341733).*

h. **2210-210** Outcomes of stem cell transplantation for leukocyte adhesion deficiency and other syndromes of defective neutrophil adhesion. *Dropped due to small sample size.*

i. **2210-221** Analysis of Graft Failure in Hematopoietic Stem Transplants for Sickle Cell Disease. *Dropped due to small sample size.*

j. **2210-239** Long Term Impact of Allogeneic Stem Cell Transplantation on Pulmonary Hypertension and Renal Outcomes in Patients with Sickle Cell Disease. *Dropped due to overlap with current Late Effects Working Committee study.*

k. **2210-240** Post-transplant cyclophosphamide vs. TCR αβ/CD19 deplete Haploidentical Transplant in Non-Malignant Diseases: A Comparative Analysis. *Dropped due to overlap with current EBMT study.*

l. **2210-280 Outcomes** of allogeneic hematopoietic cell transplantation in aplastic anemia with post transplantation cyclophosphamide. *Dropped due to overlap with recent published study* (*PMID: 35907408).*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Salt Lake City, UT
Saturday, April 23rd, 2022, 12:15pm – 1:45pm MDT

Co-Chair:	**Christopher Dvorak, MD, University of California San Francisco Medical Center, San Francisco, CA;** **E-mail: christopher.dvorak@ucsf.edu**
Co-Chair:	**George Georges, MD, Fred Hutchinson Cancer Research Center, Seattle, WA;** **E-mail: ggeorges@fredhutch.org**
Co-Chair:	**Andrew Gennery, MD, Newcastle General Hospital / The Royal Victoria Infirmary, Newcastle, UK;** **E-mail: a.r.gennery@ncl.ac.uk**
Scientific Director:	**Larisa Broglie, MD, MS, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: lbroglie@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: skim@mcw.edu**
Statistician:	**Michael Heim, MS, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: miheim@mcw.edu**

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1. Introduction

The CIBMTR Working Committee for Non-Malignant Diseases met on Saturday, April 23rd, 2022, at 12:15pm. Dr. Larisa Broglie called the meeting to order and welcomed the audience. She introduced herself as the new scientific director for the working committee and shared that Dr. Mary Eapen decided to step away as to focus on the Cure Sickle Cell Initiative. Dr. Broglie also introduced the working committee's new statistician, Michael Heim, and the other working committee leadership which have not changed since last year. Dr. Chris Dvorak then walked the audience through the difference between TED and CRF data. He then shared that there are research datasets available for secondary analysis on the organization's website, including those specifically from the Non-Malignant Diseases Working Committee, and highlighted the website as a resource for additional information on the committee. Dr. Dvorak shared the goals, limitations, and expectations of the committee, and the rules for working committee membership and study authorship. Lastly, Dr. Dvorak explained the process for new working committee leadership before turning the floor over to Dr. Georges to share updates on accruals.

2. Accrual summary

Dr. Georges presented on the accruals. First, autoimmune diseases, of which the highest accrual is in multiple sclerosis, then scleroderma, and others which have low numbers. He also highlighted the number of cases with and without CRF data. In immune deficiencies the highest accrual is SCID with a high percentage on the CRF track. The rest are quite rare and have low accrual. In histiocytic disorders the highest accrual is FELH. In metabolic diseases each of the diseases is well-represented with high proportions having CRF data. Among all diseases, aplastic anemia has the highest number of cases as

well as a high proportion of CRF data. Red blood cell disorders including thalassemia, sickle cell disease, and Fanconi anemia all have high accrual.

3. Presentations, published or submitted papers

Dr. Larisa Broglie provided updates on the committee. The two committee publications from 2021 and one submitted paper are listed below:

a. **NM16-03:** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) ***Submitted*.**

b. **NM19-02:** Marsh RA, Hebert K, Kim S, Dvorak CC, Aquino V, Baker KS, Chellapandian D, Saldana BD, Duncan C, Eckrich MJ, Georges GE, Olson TS, Pulsipher MA, Shenoy S, Stenger E, Lugt MV, Yu LC, Gennery A, Eapen M. A comparison of hematopoietic cell transplant conditioning regimens for hemophagocytic lymphohistiocytosis disorders. **Journal of Allergy and Clinical Immunology. doi:10.1016/j.jaci.2021.07.031. *Epub 2021 Aug 7.***

c. **NM19-03:** Cancio M, Hebert K, Kim S, Aljurf M, Olson T, Anderson E, Burroughs L, Vatsayan A, Myers K, Hashem H, Hanna R, Horn B, Prestidge T, Boelens JJ, Boulad F, Eapen M. Outcomes in hematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia. **Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.10.009*. Epub 2021 Oct 17.***

4. Studies in progress

Dr. Broglie shared the studies in progress including three manuscripts in progress and other ongoing studies in protocol development or data file preparation. Dr. Broglie reminded the audience that collaborative studies with EBMT can take longer than other studies.

The following is the full list of the current status of the active committee studies:

a. **NM15-01:** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) ***Manuscript Preparation.***

b. **NM17-01:** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) ***Data File Preparation.***

c. **NM18-01:** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson) ***Data File Preparation.***

d. **NM19-01:** Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) ***Manuscript Preparation.***

e. **NM20-01:** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa) ***Protocol Development.***

f. **AC18-02:** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) ***Manuscript Preparation.***

5. Future/proposed studies

Dr. Larisa outlined the voting process for the attendees, explaining that voting should be based both on scientific impact and on feasibility using the CIBMTR data.

a. **2106-02:** Curability of non-hematologic autoimmune diseases (AID) with allogeneic hematopoietic cell transplantation (HCT) / Outcomes of allogeneic hematopoietic cell translation (HCT) performed for an autoimmune disease (AID) – joint EBMT & CIBMTR study (J Storek)

The proposal was presented by Dr. Jan Storek. The objective of this study is to examine the relapse incidence rate, non-relapse mortality, relapse-free and overall survival of patients undergoing a first allo HCT for an AID. The CIBMTR identified 56 patients who underwent an HCT for AID between 1989-2019, and EBMT has approximately 95 patients that fit the criteria for this study. There has been a recent study published by EBMTR of 128 patients receiving an HCT purely for the AID that demonstrated the efficacy and toxicity of the HCT were both high. The follow questions were answered during the Q&A:

i. *Is there data on the age of disease onset rather than the age at transplant? Teenagers that were transplanted for an AID have likely been sick for awhile and very likely have an underlying monogenetic etiology even if it has not been established. Dr. Storek responded that this would be part of the supplemental data collection, and hopefully since most of the transplants have been done after 2000 genetic analysis will be available in most of the cases.*

ii. *What is the general plan for supplemental data collection, including in terms of funding? Dr. Storek responded that since most cases come from EBMT there is not a need for supplemental funding. Supplemental funding would only be needed for CIBMTR, a minority of cases, and hopefully a government/industry/charitable sponsor would be willing to fund the study.*

iii. *Will we be diluting the study by including many diseases with inadequate numbers for analysis? Also, might we want to narrow the number of questions/objectives as collecting too much data supplementally is difficult and burdensome? Dr. Storek responded that most cases come from their own center, so centers would only have to share a lot of information on a single patient.*

iv. *A suggestion to exclude the cases before 2000 as they are old, there are only a couple cases, and data may be hard to collect. Dr. Storek responded that though that is correct, if we were able to obtain data on these cases and they were still in remission this would be quite informative.*

v. *Are cases scored on their disease status pre-transplant? This is not collected as part of the CIBMTR but would be part of the supplemental data collection and would be important to have.*

vi. *Due to the heterogeneity of the disease cohort, the variety of conditioning regimens and donor sources it seems like it would be difficult to come to any meaningful conclusions.* Dr.

Storek responded that it is true that we would likely not be able to address the factors influencing outcomes for the individual diseases, but even addressing these for all AID would be helpful.

vii. *A suggestion to group the cytopenias as one subgroup.*

viii. *A comment that this study will take a lot of curating and it may be difficult as the patients may be very different. For example, the autoimmune hemolytic anemia cases may undergo multiple transplants. Dr. Storek responded that in general, these cases go to transplant because they are incredibly sick, and we are only taking a spectrum of these disorders. We will be focusing on first transplants.*

ix. *The presentation slides showed that there were 42 cases from EBMT categorized as "other", what are these? Dr. Storek responded that they could fit into the other defined disease categories, we would have to ask centers to share this information.*

x. *How is the preliminary discussion with EBMT, how is this study different from the study published 2-3 years ago? Dr. Storek responded that the prior study did not exclude monogenetic disorders, and this is probably why the study found 4x lower relapse in children versus adults. The two chairs of the EBMT working party have been supportive and there are ongoing discussions about moving forward with an EBMT study.*

b. **2109-15:** Outcomes after second or greater allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA): a contemporary analysis (H Rangarajan/P Satwani)

Dr. Hemalatha Rangarajan presented the proposal. The objective of the study is to examine 2-year overall survival after a second or greater transplant for SAA. The secondary outcomes include examining neutrophil and platelet engraftment, incidence of graft failure, grades II-IV acute and chronic GVHD, non-relapse mortality, and GVHD-free survival. This would be a contemporary analysis that would include alternative donors as well as matched siblings (prior CIBMTR study included only matched siblings and HCTs were in an earlier era). The CIBMTR identified 492 patients undergoing a second or greater HCT for SAA between 2000-2019. The following questions were answered during the Q&A:

i. *Where do the haplo cases fall under the donor type? Dr. Rangarajan responded under the "other related" category.*

ii. *A suggestion that the hypothesis should be more bold; we should look to see if we should use a haplo donor for a second or greater HCT or use another unrelated. The hypothesis should be that haplos are the same as unrelated donors for a rescue HCT. Also, a recent study from the EBMT showed that BM is safer than PB for aplastic anemia patients, but does this still apply for rescue HCTs? Along these lines, if we increased the year range to 2021, we could capture more cases. Early rejections happen in the first 6 months and allow one year for follow-up.*

iii. *A comment that this is a burning question the community needs to know.*

iv. *Is it possible to look at those that don't go to second transplant, have the trends of using a second HCT in SAA increased in recent years with the use of haplos? Dr. Rangarajan responded maybe look at first HCT with graft failure and look at outcomes, do they go to second transplant, and have they changed in recent eras? Though, this could be a different study.*

v. *A haplo followed by another haplo is not useful? Dr. Rangarajan responded that we will look at the combination of donor for first HCT and donor for second HCT as a variable.*

vi. *Will this include PNH patients? Dr. Rangarajan responded that they are not included.*

vii. *Part of the hypothesis should be in the era of haplos the time to second transplant is quicker. This variable would be included.*

viii. *Is there data on the antibodies? If it is not available, then recipient gender and the relationship of the haplo can be predictive. Dr. Rangarajan responded that we will have to look to see if it is captured and how well it is captured, such as what time period.*

ix. *When there is acute rejection, most providers will intensify the therapy and often add radiation, but one of the challenges is late rejections when the first HCT did not ablate what is happening with aplastic anemia and partial chimerism occurs. If possible, the analysis should compare the first and the second transplant. Did they use the same regimen or intensify? Dr. Rangarajan responded that that is a great point.*

x. *Why are you only selecting patients that survive more than 1 or 2 years, this may not give a good picture of the outcomes as some patients may die before these times? Dr. Rangarajan responded that 2-years of follow up includes those that die before 2 years.*

xi. *Would you review TBI vs non-TBI conditioning? Dr. Rangarajan responded we would have to review the data; it can be looked into.*

c. **2110-118:** Pre-transplant factors associated with survival in older patients transplanted after 1st line of treatment for aplastic anemia (A Prabahran/D Ritchie)

The proposal was presented by Dr. Ashvind Prabahran. The objectives of the study are to evaluate the relationship between pre-transplant factors including recent or active infections, number of lines of prior therapies, use of mismatched donors, time from diagnosis to transplant, and inflammatory biomarkers EASIX and ferritin on overall survival. The CIBMTR identified 273 patients from 2009-2019. The following questions were answered during the Q&A:

i. *Would age be evaluated as discrete or continuous? Dr. Prabahran responded, I imagine discrete.*

ii. *Is there good data on prior immunosuppressive therapies? Please refer to the slides. Data has only been recently collected on eltrombopag.*

iii. *Would we examine just the number of lines of therapies or sequence? Dr. Prabahran responded that date of therapy is collected in some cases, so we could order first, second,*

third lines.

iv. *How will you collect the pre-transplant ferritin and the other measure? Dr. Prabahran responded that ferritin is captured on the CRF and EASIX can be calculated. These may have been added recently.*

v. *There may be patients that have received more than one type of a line of therapy, how will we separate these? It is also important to assess how the patient is coming into transplant, such as organ damage mainly in the ATG/cyclosporine group. Dr. Prabahran responded that we might have to just quantify the number of therapies rather than the types of therapy, and best response prior to transplant should be captured on the CRF. HCT-CI is also captured and can be a measure of comorbidity burden.*

vi. *Is there data on prior transfusions? We can analyze the number of lines of prior transfusions.*

vii. *How many of the subjects never receive therapy? Dr. Prabahran responded that a selection criteria is patients who have had at least one prior line of therapy.*

viii. *Is it worth comparing to those patients who did not have a prior therapy and went directly to HCT? Dr. Prabahran responded that it would be interesting, but we may not have the numbers in this age group.*

d. **2110-137:** Allogeneic hematopoietic cell transplantation for pure red cell aplasia (J Vaughn/B Shaffer)

Dr. John Vaughn presented the proposal virtually. The objectives of the study are to estimate the overall survival of patients receiving an allogeneic HCT for PRCA including a comparison between transplants before and after 2015, non-relapse mortality, and the cumulative incidence of primary engraftment failure, acute and chronic GVHD. The CIBMTR identified 243 congenital and acquired PRCA in the US and Canada from 2000-2019. There is a recent publication from EBMT in 2019 on the outcomes of acquired PRCA and in 2021 in Diamond-Blackfan anemia. The following questions were answered during the Q&A:

i. *Who are the patients with acquired PRCA? Are they post-transplant? Dr. Vaughn responded that those with acquired would not be those who had a prior transplant, they were acquired unrelated and then underwent an HCT.*

ii. *What can we find from the condition regimens used and the status/number of transfusions and iron load? Dr. Vaughn responded that we aren't sure yet as we only have preliminary tables so far, but these data would be good to examine. This granularity of the data is not available and may not be very reliable. It may be worth collecting this supplementally.*

iii. *A comment that in patients referred from outside the number of transfusions is not reliably available, maybe only above or below 50, though this should be good enough.*

6. Dropped proposed studies

The committee received the following additional study proposals, but these proposals were not selected for presentation at the Tandem meeting, for the reasons outlined below:

a. **2109-11:** A comparative study of the use of reduced-intensity and myeloabative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Diamond-Blackfan Anemia. ***Dropped due to low sample size.***

b. **PROP 2110-09:** Outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with Histiocytic Disorders. ***Dropped due to low sample size and overlap with recent publications.***

c. **2110-12:** Outcomes of hematopoietic cell transplantation in aplastic anemia with posttransplantation cyclophosphamide. ***Dropped due to overlap with current study in progress BMT-CTN 1502.***

d. **2110-44:** Haploidentical Donor Transplantation for Severe Aplastic Anemia. ***Dropped due to overlap with current study in progress BMT-CTN 1502.***

e. **2110-111:** Impact Of Preexisting RBCs Allo-Antibodies on The Outcome of Hematopoietic Stem Cell Transplantation for Patients with Sickle Cell Disease. ***Dropped due to low sample size/feasibility.***

f. **2110-175:** Outcomes after autologous hematopoietic stem cell transplant with cyclophosphamide and anti-thymocyte globulin (ATG) compared with carmustine, etoposide, cytarabine, and melphalan (BEAM) and ATG conditioning for the treatment of Multiple Sclerosis. ***Dropped due to low sample size.***

g. **2110-198:** Evaluation of Allogeneic Hematopoietic Stem Cell Transplantation Outcomes and Prognostic Factors in X-linked lymphoproliferative disease type 1 (XLP1): A CIBMTR Analysis. ***Dropped due to overlap with recent study NM19-02.***

h. **2110-252:** Trends of Early Mortality Within First Two Years Following Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents with Non-Malignant Disorders. ***Dropped due to heterogeneity of diseases.***

i. **2110-256:** Impact of Donor/Recipient CMV serological status on survival post allogeneic hematopoietic cell transplant in children with non-malignant disorders. ***Dropped due to heterogeneity of diseases.***

j. **2110-258** Impact of Donor and Recipient ABO incompatibility on Outcomes Post Allogeneic Stem Cell transplantation for Non-malignant Disorders in Children. ***Dropped due to heterogeneity of diseases.***

k. **2110-318:** Sickle cell disease-related symptom changes after allogeneic hematopoietic cell transplantation. ***Dropped due to overlap with recent studies and publications.***

7. Concluding Notes

a. Meeting adjourned at 1:30pm.

b. After the new proposals were presented, each participant in the meeting had an opportunity to score each proposal electronically using the Tandem app or website. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following proposal was accepted to move forward to be added to the committee's active studies:

2109-15: Outcomes after second or greater allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA): a contemporary analysis (H Rangarajan/P Satwani)

c. The following proposals were not accepted as studies, for the reasons specified:

2106-02: Curability of non-hematologic autoimmune diseases (AID) with allogeneic hematopoietic cell transplantation (HCT) / Outcomes of allogeneic hematopoietic cell translation (HCT) performed for an autoimmune disease (AID) – joint EBMT & CIBMTR study (J Storek). ***Dropped due to feasibility.***

2110-118: Pre-transplant factors associated with survival in older patients transplanted after 1st line of treatment for aplastic anemia (A Prabahran/D Ritchie). ***Dropped due to feasibility, timing of lines is not well-collected and eltrombopag has only been collected recently.***

2110-137: Allogeneic hematopoietic cell transplantation for pure red cell aplasia (J Vaughn/B Shaffer). ***Dropped due to recent overlapping EBMT publications.***

Working Committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM16-03: Results of transplants from genetically-identical twin donors in persons with aplastic anaemia	Manuscript Preparation	**3**
NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH	Protocol Development	**3**
NM18-01: Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease	Data file preparation	**2**
NM19-01: Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy	Manuscript Preparation	**1**
AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis	Manuscript Preparation	**1**
NM20-01: Hematopoietic Stem Cell Transplantation for Fanconi anemia	Protocol Development	**2**
NM22-01: Outcomes After Second or Greater Allogeneic Stem Cell Transplants in Patients with Severe Aplastic Anemia: A Contemporary Analysis	Protocol Pending	**2**

Working Assignments for Working Committee Leadership (May 2022)

George Georges	**NM16-03:**	Results of transplants from genetically-identical twin donors in persons with aplastic anaemia
	NM19-01:	Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy
	AC18-02:	Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis
Christopher Dvorak	**NM15-01:**	Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria
	NM17-01:	Late effects after hematopoietic stem cell transplantation in patients with HLH
	NM20-01:	Hematopoietic Stem Cell Transplantation for Fanconi anemia
Andrew Gennery	**NM18-01:**	Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease

Accrual Summary for the Non-Malignant Diseases Working Committee

Allogeneic Transplants for Immune Deficiencies reported to the CIBMTR from 2000-2022

Characteristic	CRF N	TED N	Total N
Number of patients	**2907**	**3983**	**6890**
Number of centers	185	272	301
Disease			
Acute megakaryoblastic leukemia (M7)	1 (0)	0 (0)	1 (0)
Immune Deficiencies (ID), NOS	27 (1)	93 (2)	120 (2)
SCID ADA deficiency	99 (3)	68 (2)	167 (2)
SCID absence of T and B cells	194 (7)	150 (4)	344 (5)
SCID absence of T, normal B cell SCID	223 (8)	150 (4)	373 (5)
Omenn syndrome	97 (3)	80 (2)	177 (3)
Reticular dysgenesis	11 (0)	6 (0)	17 (0)
Bare lymphocyte syndrome	40 (1)	88 (2)	128 (2)
SCID, NOS	149 (5)	145 (4)	294 (4)
SCID other, specify	325 (11)	224 (6)	549 (8)
Wiskott Aldrich syndrome	306 (11)	296 (7)	602 (9)
DiGeorge anomaly	8 (0)	9 (0)	17 (0)
Chronic granulomatous disease	312 (11)	355 (9)	667 (10)
Chediak-Higashi syndrome	31 (1)	67 (2)	98 (1)
Common variable immunodef	34 (1)	72 (2)	106 (2)
X-linked lymphoproliferative syndrome	69 (2)	113 (3)	182 (3)
Leukocyte adhesion deficiencies	49 (2)	57 (1)	106 (2)
Kostmann agranulocytosis	54 (2)	130 (3)	184 (3)
Cartilage hair hypoplasia	24 (1)	41 (1)	65 (1)
TED Immune deficiency plus neutropenia	0 (0)	1 (0)	1 (0)
CD40 ligand deficiency	27 (1)	81 (2)	108 (2)
Griscelli syndrome type 2	10 (0)	22 (1)	32 (0)
Combined immunodef dis (CID), NOS	7 (0)	5 (0)	12 (0)
CID other, specify	16 (1)	1 (0)	17 (0)
Other immunodeficiencies, specify	198 (7)	661 (17)	859 (12)
Histiocytic disorder, NOS	6 (0)	26 (1)	32 (0)
FELH Familial erythrohemophagocytic lymphohis	422 (15)	808 (20)	1230 (18)
Langerhans Cell Histiocytosis	34 (1)	58 (1)	92 (1)
Hemophagocytosis	81 (3)	110 (3)	191 (3)
Malignant histiocytosis	2 (0)	15 (0)	17 (0)
Other histiocytic disorders	51 (2)	51 (1)	102 (1)

*Only first transplants are included in this accrual.

*CRF patients are also eligible for TED-level studies.

Abbreviations: ADA = adenosine deaminase; NOS = not specified; SCID = severe combined immunodeficiency

Allogeneic Transplants for Inborn Errors of Metabolism reported to the CIBMTR from 2000-2022

Characteristic	CRF N	TED N	Total N
Number of patients	**1007**	**1082**	**2089**
Number of centers	125	174	206
Disease			
Inherited disorders of metabolism, NOS	3 (0)	21 (2)	24 (1)
Osteopetrosis	132 (13)	212 (20)	344 (16)
Lesch-Nyhan(HGPTR defic)	2 (0)	0 (0)	2 (0)
Neuronal ceroid lipofuscinosis	5 (0)	3 (0)	8 (0)
Other inherited metabolism disorders, specify	35 (3)	60 (6)	95 (5)
Mucopolysaccharidosis, NOS	7 (1)	12 (1)	19 (1)
IH Hurler syndrome	322 (32)	255 (24)	577 (28)
IS Scheie syndrome	0 (0)	2 (0)	2 (0)
II Hunter syndrome	26 (3)	24 (2)	50 (2)
III Sanfillippo	26 (3)	7 (1)	33 (2)
IV Morquio	0 (0)	3 (0)	3 (0)
VI Maroteaux-Lamy	25 (2)	18 (2)	43 (2)
VII B-glucuronidase deficiency	1 (0)	1 (0)	2 (0)
V Mucopolysaccharidosis	2 (0)	5 (0)	7 (0)
Other mucopolysaccharidosis	3 (0)	1 (0)	4 (0)
Mucolipidoses, NOS	3 (0)	1 (0)	4 (0)
Gaucher disease	4 (0)	10 (1)	14 (1)
Metachromatic leukodystrophy (MLD)	83 (8)	96 (9)	179 (9)
Adrenoleukodystrophy (ALD)	207 (21)	247 (23)	454 (22)
Globoid leukodystrophy/Krabbe disease	73 (7)	46 (4)	119 (6)
Neiman-Pick disease	12 (1)	11 (1)	23 (1)
I-cell disease	15 (1)	9 (1)	24 (1)
Wolman disease	6 (1)	6 (1)	12 (1)
Glucose storage disease	0 (0)	1 (0)	1 (0)
Other mucolipidoses	1 (0)	0 (0)	1 (0)
Asparty1 glucosaminuria	0 (0)	3 (0)	3 (0)
Fucosidosis	5 (0)	3 (0)	8 (0)
Mannosidosis	9 (1)	25 (2)	34 (2)

*Only first transplants are included in this accrual.

*CRF patients are also eligible for TED-level studies.

*Abbreviations: NOS = not specified

Allogeneic Transplants for non-malignant disorders reported to the CIBMTR from 2000-2022

Characteristic	CRF N	TED N	Total N
Number of patients	**7828**	**10004**	**17832**
Number of centers	338	440	481
Disease			
Paroxysmal nocturnal hemoglobinuria	201 (3)	284 (3)	485 (3)
NHL diffuse, large B-cell	1 (0)	0 (0)	1 (0)
Severe aplastic anemia unknown (095CORE)	26 (0)	556 (6)	582 (3)
Acquired Severe Aplastic Anemia, NOS	3913 (50)	4710 (47)	8623 (48)
Severe aplastic anemia secondary to hepatitis	183 (2)	241 (2)	424 (2)
Severe aplastic anemia secondary to toxin-other	88 (1)	71 (1)	159 (1)
Amegakaryocytosis(not congenital)	13 (0)	16 (0)	29 (0)
Schwachmann-Diamond	35 (0)	43 (0)	78 (0)
Acquired Pure Red Cell Aplasia	42 (1)	64 (1)	106 (1)
Dyskeratosis congenital	43 (1)	37 (0)	80 (0)
Other acquired cytopenic syndrome, specify	147 (2)	169 (2)	316 (2)
Inherited abnormal of erythrocyte differ, NOS	10 (0)	8 (0)	18 (0)
Fanconi anemia	757 (10)	744 (7)	1501 (8)
Diamond-Blackfan anemia (pure red cell aplasia)	145 (2)	196 (2)	341 (2)
Other constitutional anemia (not THALs)	64 (1)	114 (1)	178 (1)
Thalassemia, NOS	478 (6)	1215 (12)	1693 (9)
095 Type B+ Thalassemia major	1 (0)	6 (0)	7 (0)
095 Type B0 Thalassemia major	1 (0)	0 (0)	1 (0)
Sickle Thalassemia major	70 (1)	44 (0)	114 (1)
Sickle cell anemia	907 (12)	1026 (10)	1933 (11)
Beta thalassemia major	659 (8)	400 (4)	1059 (6)
Other hemoglobinopathy, specify	41 (1)	57 (1)	98 (1)
Missing	3 (0)	3 (0)	6 (0)

*Only first transplants are included in this accrual.

*CRF patients are also eligible for TED-level studies.

Abbreviations: NOS = not specified

Autologous Transplants for autoimmune diseases reported to the CIBMTR from 2000-2022

Characteristic	CRF N	TED N	Total N
Number of patients	**96**	**1347**	**1443**
Number of centers	41	111	124
Disease			
Autoimmune disease unclassified	0 (0)	24 (2)	24 (2)
Myasthenia gravis	1 (1)	17 (1)	18 (1)
Multiple sclerosis	40 (42)	872 (65)	912 (63)
Rheumatoid arthritis	3 (3)	5 (0)	8 (1)
Psoriatic arthritis or psoriasis	1 (1)	0 (0)	1 (0)
Systemic lupus erythematosis (SLE)	9 (9)	51 (4)	60 (4)
Polymyositis-dermatomyositis	0 (0)	5 (0)	5 (0)
System Scleroderma	29 (30)	240 (18)	269 (19)
Antiphospholipid syndrome	0 (0)	6 (0)	6 (0)
Other autoimmune disease, specify	0 (0)	13 (1)	13 (1)
Other arthritis, specify	0 (0)	2 (0)	2 (0)
Other Connective tissue dis	0 (0)	10 (1)	10 (1)
Churg-Strauss	0 (0)	1 (0)	1 (0)
Behcets Syndrome	0 (0)	2 (0)	2 (0)
JIA systemic	0 (0)	2 (0)	2 (0)
JIA Other, specify	0 (0)	1 (0)	1 (0)
Other neuro disorder, specify	7 (7)	38 (3)	45 (3)
ITP- Idiopathic thrombocytopenic purpura	2 (2)	2 (0)	4 (0)
Hemolytic anemia	0 (0)	1 (0)	1 (0)
Evan syndrome	0 (0)	1 (0)	1 (0)
Crohns disease	3 (3)	53 (4)	56 (4)
Other bowel disorder, specify	1 (1)	1 (0)	2 (0)

*Only first transplants are included in this accrual.

TO: Non-Malignant Diseases Working Committee Members

FROM: Larisa Broglie, MD, MS; Scientific Director for the Non-Malignant Diseases Working Committee

RE: Studies in Progress Summary

NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) The aim of the study is to describe the population of children or adults with Erythropoietic Porphyria who have undergone HCT and examine the outcomes post-transplant. U.S. data has been cleaned and prepared for presentation. European supplemental data has been collected and cleaned and analysis completed. Manuscript preparation is in progress by our European colleagues

NM16-03: What Causes Aplastic Anemia: Results of Transplants from Genetically-Identical Twins (RP Gale) The aim of this study is to examine the pathophysiology of acquired aplastic anemia by analyzing results of hematopoietic cells transplants between genetically-identical twins one of whom has aplastic anemia. The study describes outcomes of genetically-identical twin transplants with and without pretransplant conditioning and posttransplant immune suppression which may inform potential underlying etiology(ies). The manuscript has been completed and we are preparing for submission.

NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) The purpose of this study is to investigate the long-term outcomes and late effects of patients with hemophagocytic lymphohistiocytosis (HLH) who are survivors after hematopoietic cell transplantation (HCT). The main hypothesis is that HLH survivors will be at risk for significant long term medical and neuropsychological late effects that will be dependent upon pre-transplant disease related factors and the intensity of the BMT conditioning regimen. We were unable to collaborate with EBMT and so are working on updating the protocol. Protocol development is underway.

NM18-01: Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson) The purpose of this study is to compare outcomes following allogeneic HCT for pediatric patients with non-malignant disease based on the specific serotherapy used. Post-transplant outcomes, including overall survival, acute and chronic GVHD, graft failure, and graft-failure free survival will be compared between patients given alemtuzumab and patients given ATG. The focus will be on non-malignant diseases for which transplant is most commonly used as treatment to establish as much homogeneity as possible in the comparison. Work on preparation of the data file is underway, with significant progress made. The goal is to have the data file prepared for analysis by August 2023.

NM19-01: Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) The objective of this study is to explore the conditional probability at various time points of patients surviving at least one year after HCT for severe aplastic anemia. The trend in survival rates, conditional on surviving up to specific time points following transplant, will be assessed and compared to

conditional survival rates of severe aplastic anemia patients treated with immunosuppressive therapy. Preparation of the data file for transplant cases is in progress. The IST cases will require merging of data from the National Heart, Lung, and Blood Institute. The manuscript has been completed and we are preparing for submission.

NM20-01: Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa) This study aims to assess the impact of prognostic factors and describe the outcomes of patients undergoing transplant for Fanconi anemia, including overall survival, non-relapse mortality, and acute and chronic GVHD. Additionally, the study's goal is to obtain information on late effects including the rate of solid tumors and the association with radiation and GVHD. The protocol has been completed and data file preparation underway. The goal is to complete the analysis by June 2023.

AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) The objective of this study is to explore patient characteristics and post-transplant outcomes of patients undergoing autologous transplant for systemic sclerosis. Co-operation of the transplant centers treating these patients will be solicited for the collection of supplemental data of highest relevance for this specific autoimmune disease. Manuscript preparation is in progress. The goal is to submit the final manuscript by June 2023.

NM22-01: Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis (H Rangarajan/P Satwani) This study aims to evaluate outcomes of a contemporary cohort of patients with aplastic anemia who require second allogeneic transplantation. The protocol is under development and the goal is to have a completed data file for analysis by December 2023.

Response Summary:

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

Q1. Study Title

Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD)

Q2. Key Words

Metachromatic Leukodystrophy, Allogeneic

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Ernesto Ayala
Email address:	ayala.ernesto@mayo.edu
Institution name:	Mayo Clinic Florida
Academic rank:	Associate Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

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

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

None, currently

Q13. PROPOSED WORKING COMMITTEE:

- Non-Malignant Diseases

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

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

Christopher Dvorak and Andrew Gennery

Q15. RESEARCH QUESTION:

Allogenic Bone Marrow Transplantation is used for the treatment of MLD (rare indication), however very few systematic data is available to guide transplant physicians on regimen intensity, donor type, GVHD prophylaxis and expected outcomes.

Q16. RESEARCH HYPOTHESIS:

Allogeneic Bone Marrow Transplantation is able to stop the progression of MLD with limited morbidity and mortality.

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

Suggested word limit of 200 words:

Assess transplant related and functional neurological outcomes in patients with MLD undergoing allogeneic bone marrow transplantation.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Collected data will confirm/support the role of allogeneic bone marrow transplantation for the treatment of MLD and guide physicians on appropriate transplant strategies.

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

Published data on allogeneic transplantation is limited to case reports or small case series and frequently mixed with other storage diseases and leukoencephalopathies, making difficult to clearly define the role on MLD. The diagnosis of MLD is being done at earlier stages due to wider use of whole exome and targeted gene sequencing to assess patients with neurodegenerative disorders. A timely analysis is needed to review modern outcomes and establish appropriate transplant practices for these patients.

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

N/A

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

Patients that have undergone allogeneic bone marrow or peripheral blood stem cell transplantation for MLD from 2000 to 2020.
MLD must have been confirmed by biochemical or genetic based methods.
Analysis will be limited to Juvenile MLD (4 to 18 years at diagnosis) and adult onset MLD (more than 18 years at diagnosis). Groups will be analyzed independently.
An effort will be made to analyze functional outcomes as well as transplant related outcomes.

Q21. Does this study include pediatric patients?

- Yes

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

Patient: Age, sex, race/ethnicity, performance status
Disease: juvenile vs adult, neurological status, MRI findings
Transplant variables: Graft type, donor type, conditioning regimen with intensity, GVHD prophylaxis.

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

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

NA

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

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

NA

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

NA

Q26. **REFERENCES:**

Solders et al. Bone Marrow Transplantation 2014; 49: 1046-1051
Videbaek et al. JIMD reports 2021; 60: 96-104
Van Rappard et al. Blood 2016; 127: 3098-3101

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

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

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

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

N/A

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

Embedded Data:

N/A

Proposal 2205-02: Characteristics of patients who underwent first alloHCT for Metachromatic Leukodystrophy disease from 2008-2019 reported to CIBMTR

Characteristic	N (%)
No. of patients	87
Patient Related	
Recipient age - no. (%)	
Median (min-max)	6 (0-20)
0-5	46 (53)
6-11	32 (37)
12-17	5 (6)
18-21	4 (5)
Treatment Related	
Donor type - no. (%)	
HLA-identical sibling	10 (11)
Other related	4 (5)
Well-matched unrelated (8/8)	5 (6)
Partially-matched unrelated (7/8)	3 (3)
Unrelated (matching TBD)	4 (5)
Cord blood	61 (70)
Conditioning intensity as designated by center - no. (%)	
RIC / Non-Myeloablative	8 (9)
Myeloablative	69 (79)
To be determined following review	10 (11)
Graft source - no. (%)	
Bone marrow	20 (23)
Peripheral blood	6 (7)
Umbilical cord blood	61 (70)
Year of transplant - no. (%)	
2008-2009	18 (21)
2010-2011	15 (17)
2012-2013	17 (20)
2014-2015	12 (14)
2016-2017	18 (21)
2018-2019	7 (8)
Number of patients in the CRF Track - no. (%)	
CRF patients	41 (47)
Follow-up, months - median (range)	67 (3-168)

STUDY TITLE

Impact of RBC Factors (prior allo-immunization and donor-recipient ABO mismatch) on Outcomes Post-Allogeneic Hematopoietic Stem Cell Transplant in Patients with Hemoglobinopathies

PRINCIPAL INVESTIGATORS

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KEY WORDS

"ABO incompatibility", allo-immunization, "transplant", "hemoglobinopathies", "outcomes".

RESEARCH QUESTION:

Do pre-existing RBC allo-antibodies and Donor-Recipient ABO mismatch impact clinical outcomes post allogeneic hematopoietic stem cell transplantation (HCT) for patients with hemoglobinopathies?

RESEARCH HYPOTHESIS:

We hypothesize that pre-existing RBC allo-antibodies and Donor-Recipient ABO mismatch (**mm**) will be associated with a decreased 2-year Event Free Survival (EFS) post allogeneic HCT in patients with Hemoglobinopathies [Sickle cell disease (SCD) and Transfusion dependent β-thalassemia (TDT)]

SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED

Primary objective

- Determine and compare the 2-year EFS in the study population based on ABO status of donor and recipients (ABO matched, vs major mm vs minor mm vs bidirectional mm) and presence of RBCs allo-antibodies in the recipient (RBC alloimmunization (1, ≥2) vs

not RBC alloimmunization), and disease type (SCD and TDT). Events being death from any cause, recurrence of primary disease, graft rejection (GR), need for secondary interventions such as Donor lymphocyte infusion (DLI), CD34 stem cell boost or a 2nd HCT

Secondary Objectives

To determine the following outcomes stratified by the various sub-groups as defined above and also by disease subgroups (SCD and TDT)

- 2-year Overall Survival (OS) in study population stratified by disease type, presence of RBC alloimmunization and ABO matching between donor and recipient.
- Determine the baseline prevalence of RBC alloimmunization in patients with hemoglobinopathies undergoing HCT (clinically significant RBC allo-antibodies such as anti-C, anti-D, anti-E, anti-K, anti-Lewis, anti-Kidd, anti-Duffy, anti-MNSs)
- Days to RBC, neutrophil and platelet engraftment
- Incidence of GR: primary and secondary
- Incidence of pure red cell aplasia (PRCA).
- Day 100 Transplant related mortality (TRM)
- Incidence of need for second therapies (DLI or CD34 stem cell boost or 2nd transplant).
- Incidence of acute GvHD Grade I-II vs II-IV
- Incidence of chronic GvHD (NIH scoring mild/moderate/severe)
- GVHD free, rejection free survival (events include GR, grade II-IV aGVHD or extensive cGVHD requiring systemic treatment)
- Presence of mixed chimerism (MC: defined as < 95% donor in whole blood, CD3 or CD33) at 100 days, 1 year and 2 years post-HCT
- Incidence of autoimmune cytopenias post HCT

SCIENTIFIC IMPACT:

Allogeneic Hematopoietic Stem Cell transplant (HCT) is a curative option for patients with hemoglobinopathies. Given the increasing number of sibling and alternative (non-matched sibling) donor and the emerging role of reduced intensity conditioning (RIC) and non-myeloablative (NMA) regimens for HCT for hemoglobinopathies (SCD and TDT), it is imperative that donors are carefully chosen while weighing the risk of each type of transplant. It is unclear if ABO incompatibility and prior RBC alloimmunization is associated with adverse clinical outcomes post HCT in patients with hemoglobinopathies and whether it is of importance only when using haploidentical donors (irrespective of conditioning intensity) or NMA regimens (irrespective of donor type)?

Therefore our proposed study will provide insights into understanding the impact of RBCs factors on clinical outcomes of HCT. It may help with refining risk stratification of patients to help optimize selection of appropriate transplant candidates, provide timely guidance regarding optimum choice of donors, and could identify patients who may benefit from pre-transplant antibody depletion strategies for mitigating any increased risk associated with alloimmunization.

SCIENTIFIC JUSTIFICATION:

HCT is an evolving field wherein there is continuous attempt to study donor and recipient factors that can impact HCT outcomes. While the impact of some such as HLA compatibility, graft composition, donor-recipient age is well defined, other such as RBC factors are less well studied

and their impact on transplant outcomes remains ambiguous. [1].
Patients with non-malignant disorders (NMDs) especially hemoglobinopathies pose a unique scenario. Often these patients have an intact or hyperactive immune system and may have received PRBC transfusions pre-HCT and some also develop alloimmunization following chronic transfusions [2] and can cause several immune-hematological complications post-HSCT as prolonged reticulocytopenia with frequent RBC transfusion support [3]. Patients can also develop acute, life-threatening hemolysis [3]. These risks in turn may be amplified in the context of ABO incompatible transplants. The risk for becoming RBC allo-immunized is high in transfused patients with hemoglobinopathies compared to other transfused patient groups [4] even with leukocyte reduced products [5]. In some cohorts of adults with SCD, more than 25% had RBC alloantibodies [6,7] and the prevalence of alloimmunization among patients with thalassemia ranges from 3% to 42% [8].

Understanding how "RBC-related" factors; like ABO incompatibility and pre-existing RBCs Allo-antibodies, contribute to the main outcomes of HCT, such as risk of GR, poor graft function, pure red cell aplasia (PRA), autoimmune cytopenias, GvHD and overall survival OS, can help to better select both donors and BMT candidates and subsequently accomplish better HCT outcomes. Despite the risk of acute and delayed hemolytic reactions, delayed RBC engraftment and pure red cell aplasia (PRA) have been reported following ABO incompatible HCT, the latter's impact on outcomes such as engraftment, acute and chronic GvHD, OS and relapse rates have yielded inconsistent results across various studies [9]. In addition, while there is proved data of increased platelet transfusion requirements in myeloablative HCT with pre-existing HLA class I antibodies [10-12] and in HLA-disparate HCT, HLA alloimmunization increases the risk of graft rejection [13-17], the clinical significance of RBCs allo-antibodies in the context of HCT is not well described, particularly for patients with hemoglobinopathy undergoing different intensities of conditioning regimens from various degree of HLA-disparities HCT [18].

We searched PubMed for studies published up to October 1, 2022, using the search terms "ABO incompatibility", "hemoglobinopathy," "transplant," and "antibodies." We identified only one study that evaluated the impact of pre-existing RBCs allo-antibodies in 36 patients who received a HLA-matched HCT for SCD. The authors observed that RBC allo-immunized patients significantly required more RBC unit transfusions and had a trend towards lower donor T cell chimerism at the first year after HCT [18]. Also, the impact of ABO incompatibility on transplant outcomes in patients with NMDs have either been studied in isolation in only a few single center studies [19,20] or as part of a larger cohort of patients (mostly adults) with a variety of diseases [21-23]. Miller et al studied outcomes of 270 pediatric umbilical cord blood (UCB) HCT recipients with NMDs [19] stratified based on the donor recipient ABO incompatibility. In this study the authors observed an increased but not statistically significant risk of grade II-IV acute GVHD in recipients of major mismatched (mm) units. No other transplant outcomes were impacted by ABO incompatibility. However, in a study by Watz et al [21] of 310 recipients of RIC conditioning (including 60 patients with NMDs) presence of antibodies indicative of passenger lymphocyte syndrome (PLS) after minor ABO mm or persistence or recurrent recipient type ABO antibodies (PRABO) after major ABO mm were significant risk factors for decreased OS (0% vs 61% for with and without PLS and 17% vs 73% for with and without PRABO) and overall transplant related mortality (50% vs 21%). Both these studies did not include patients with hemoglobinopathies. Logan et al (23) in their single center study of 1737 patients which included NMDs [including hemoglobin disorders and very severe aplastic anemia (SAA): total number not specified] observed that patients with minor ABO mismatched HCT had an inferior and an increased risk of early non-relapse mortality.

Of relevance is the increasing use of RIC and NMA regimens for HCT in patients for SCD and TDT [24-26], Mixed chimerism (MC) is often seen post RIC and is universal following NMA conditioning [25] and is sufficient for the abrogation of the primary disease [27, 28]. However, this results in a state of simultaneous presence of host and donor immune cells which in turn can lead to the persistence of antibodies directed against target red cells. Interestingly, some studies utilizing NMA regimens for SCD have shown successful engraftment even across ABO barriers [25, 29] but other studies have excluded such patients [26] due to theoretical increased risk of GR.

In summary, the impact of the above-mentioned RBCs-related factors on transplant outcomes in patients with hemoglobinopathies is not well-studied. Therefore, we propose to utilize the large CIBMTR database to query if these RBCs- related factors increase the risk of adverse transplant outcomes in patients with hemoglobinopathies undergoing allogeneic HCT. The proposed study may fill the existing gap in literature and might help to change clinical and research practice.

PARTICIPANT SELECTION CRITERIA:

Inclusion criteria

- Diagnosis: SCD and TDT
- Any age had undergone 1st allogeneic HCT (or a 2nd HCT if same donor) for SCD and TDT between 1995-2021

Exclusion criteria

- Exclude non-consented patients

DATA REQUIREMENTS:

Patient

- Age at HCT: continuous and & ≤ 6, 7-12 and 13-21 years and & ≥ 21 years
- Sex: male vs. female
- Karnofsky/Lansky performance score: ≥90% vs. & ≤90%
- Donor/recipient (D/R) CMV status: +/+. -/-, +/-, -/+
- Donor/recipient ABO status: matched, major mm, minor mm & bidirectional
- Number of RBCs allo antibodies (patient with (1, ≥ 2 RBCs alloantibodies vs none) and specify type (anti-C, anti-D, anti-E, anti-K, anti-Lewis, anti-Kidd, anti-Duffy, anti-MNSs)
- Pre-HCT transfusion burden (1-5 vs. 6-10 vs. 11-20 vs. 21-30 vs. 31-40 vs. 41-50 vs. ≥ 51 vs. unknown)
- Infused total nucleated cell count (if available, CD34+ cell dose and CD3 dose).
- HCT- Comorbidity index 1-2 vs & ≥ 2 (or Pediatric comorbidity index if available)

Disease-related

- SCD or TDT

Treatment-related

- Conditioning regimen: MAC vs RIC vs NMA
- TBI with conditioning Y/N if Y dose
- Graft source: bone marrow vs. peripheral blood vs. cord blood
- Donor: HLA-identical sibling vs unrelated donor vs cord blood vs haploidentical donor
- HLA matching 8/8 vs 7/8 vs & ≤ 7/8

- GVHD prophylaxis: No GVHD prophylaxis, Ex-vivo T-cell depletion, Calcineurin inhibitors ± others, Sirolimus ± others, PTCY based ± others
- ATG/Campath: yes vs. no
- Year of alloHCT: 1995-1999 vs. 2000-2004 vs. 2005-2009 vs. 2010-2012 vs 2012-2021

Post-transplant

- Acute GVHD: Max grade of acute GVHD and site of aGVHD
- Chronic GVHD: Max grade of chronic GVHD: none vs. limited vs. extensive
- GR: primary or secondary, time from HCT to GR
- Pure red cell aplasia (Y/N)
- Days to RBCs, neutrophil, and platelet engraftment
- Chimerism at 100 days, 1 year and 2 years post-HCT
- Incidence of need for second therapies (DLI or CD34 stem cell boost or 2nd HCT)
- Alive at last follow up Y/N, If N Cause of Death
- Last follow up in months

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Proposals 2210-19 & 2210-60: Characteristics of patients who underwent first alloHCT for SCD and TDT from 2008-2019 reported to CIBMTR

Characteristic	N (%)
No. of patients	1451
Patient Related	
Recipient age - no. (%)	
Median (min-max)	10 (1-65)
<7	472 (33)
7-12	473 (33)
13-21	333 (23)
>21	173 (12)
Treatment Related	
Donor type - no. (%)	
HLA-identical sibling	812 (56)
Twin	3 (0)
Other related	285 (20)
Well-matched unrelated (8/8)	118 (8)
Partially-matched unrelated (7/8)	34 (2)
Mis-matched unrelated (<= 6/8)	3 (0)
Multi-donor	2 (0)
Unrelated (matching TBD)	56 (4)
Cord blood	138 (10)
Conditioning intensity as designated by center - no. (%)	
RIC / Non-Myeloablative	485 (33)
Myeloablative	963 (66)
To be determined following review	3 (0)
Graft source - no. (%)	
Bone marrow	942 (65)
Peripheral blood	371 (26)
Umbilical cord blood	138 (10)

Characteristic	**N (%)**
No. of patients	1451
Year of transplant - no. (%)	
2008-2009	80 (6)
2010-2011	23 (2)
2012-2013	81 (6)
2014-2015	326 (22)
2016-2017	372 (26)
2018-2019	569 (39)
Did the transfusion(s) induce red cell alloimmunization? - no. (%)	
No	438 (30)
Yes	103 (7)
Missing	674 (46)
Unknown	236 (16)
Follow-up, months - median (range)	26 (1-149)

Study Title: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant

Key Words: Severe aplastic anemia, hematopoietic stem cell transplantation, conditioning regimen, unrelated donor, HLA mismatch

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Research question:

1. Does the intensity of the preparative regimen for patients with SAA undergoing upfront URD or haploidentical HSCT impact rates of acute or late rejection and autoimmune cytopenias?

2. What is the impact of HLA mismatch on outcomes in patients with SAA receiving a contemporary conditioning regimen (ATG/fludarabine/cyclophosphamide/low-dose TBI: Flu/Cy/ATG/TBI200) with bone marrow or PBSC grafts and standard GVHD prophylaxis (calcineurin inhibitor, short course of methotrexate).

Research hypothesis

1. Patients with SAA who receive URD or haploidentical HSCT as initial treatment, in the face of active autoimmune process, have a higher incidence of graft rejection/failure and/or post-transplant autoimmune cytopenia compared to patients with refractory/relapsed SAA patients who failed IST receiving similar regimens for URD or haploidentical HSCT as second line therapy

2. Single allele HLA mismatch is not associated with inferior outcomes after HSCT when a contemporary conditioning regimen (Flu/Cy/ATG/TBI200) is used with bone marrow graft and standard GVHD prophylaxis.

Specific objectives/outcomes to be investigated:

Primary:

1. To estimate the 24-month CI of primary and secondary graft failure and severe autoimmune cytopenia by patient group (upfront vs second line), conditioning regimen (ATG or Campath, Cy dose, Flu dose, radiation dose), donor type/match (10/10 URD, 9/10 URD, Haplo) and GVHD prophylaxis strategy (MTX/CI, MMF/CI, PT-Cy).

2. To estimate the 24-month failure-free survival and overall survival by patient group (upfront vs second line), conditioning regimen, donor type/match (10/10 URD, 9/10 URD, Haplo) and GVHD prophylaxis strategy (MTX/CI, MMF/CI, PT-Cy).

Secondary:

1. To estimate the 6-month CI of acute GVHD (any grade, grade II-IV and III-IV) and 24-month CI of chronic GVHD (any cGVHD, moderate-severe, and severe) by GVHD prophylaxis strategy, conditioning regimen, donor type/match and patient group (upfront vs second line).
2. To estimate the 24-month incidence of immune-mediated cytopenia by conditioning regimen, GVHD prophylaxis strategy and patient group (upfront vs second line).
3. To estimate the median time to neutrophil and platelet recovery by conditioning regimen, GVHD prophylaxis strategy and patient group (upfront vs second line).
4. To determine whole blood, myeloid and T cell chimerisms at 100, 180, 365 days and 2-year post HSCT by conditioning regimen, GVHD prophylaxis strategy and patient group (upfront vs second line).
5. To test if early stable vs. worsening recipient chimerism is associated with early or late rejection or autoimmune cytopenias.
6. To test the effect of age of the recipient and infused cell dose on rates of rejection and severe acute/chronic GVHD.
7. To determine if the impact of HLA mismatch is significantly different in the recent era (with BM graft and Flu/Cy/ATG/TBI200 conditioning), by recipient age, and the use of PBSC grafts
8. To estimate the 5-year overall survival by patient group (upfront vs second line), conditioning regimen, donor type/match and GVHD prophylaxis strategy.
9. To estimate the 5-year GVHD-free failure-free survival by patient group (upfront vs second line), conditioning regimen, donor type/match and GVHD prophylaxis strategy.

Scientific Impact:
Conducting this research study will help us determine if increased conditioning regimen intensity is required for patients with SAA who are undergoing upfront URD HSCT compared to patients who are receiving transplant after they failed IST and if post-transplant cyclophosphamide or other GVHD prophylaxis approaches are associated with rejection and/or post-transplant autoimmunity. This study will also allow us to determine whether using a single HLA mismatched unrelated donor is a safe and effective approach.

Scientific justification:
Acquired severe aplastic anemia treatment focuses on disruption of an autoimmune destruction of hematopoietic stem cells or the bone marrow niche by use of either systemic immunosuppressive therapy (IST) or HSCT[1]. Historically, upfront HSCT was indicated only for patients with an HLA-matched related donor[1-3]. The outcomes of matched unrelated donor HSCT for SAA have significantly improved, with recent retrospective reviews and registry data suggesting that utilizing various reduced-intensity conditioning regimens, the outcomes of MUD transplants approaching that of MRD transplants, especially in children and adolescents[4-7]. Improvements in MUD BMT outcomes for SAA have been attributed to reduced doses of total body irradiation[8], the use of fludarabine with concomitant reduction in the dosage of cyclophosphamide, and improvements in supportive care[5,9]. Despite the improved outcomes, a standard of care has not been yet defined with no randomized studies determining whether pediatric and young adult patients would benefit from up-front URD HSCT compared to immune suppressive therapy.

For patients with SAA who failed first line immunotherapy, a BMT CTN prospective multicenter phase 1-2 study explored 4 cyclophosphamide doses (0, 50mg/kg, 100mg/kg, and 150mg/kg) in order to define an optimal preparative regimen for unrelated donor marrow transplantation. Cyclophosphamide at 50 mg/kg and 100 mg/kg with TBI 2 Gy, fludarabine, and anti-thymocyte globulin resulted in low graft failure rates and favorable overall survival[9]. No such study has been conducted to determine the optimal conditioning for upfront URD HSCT. In a retrospective analysis, Dufour et al. reported the outcomes of upfront-unrelated donor HSCT in pediatric SAA patients following FCC conditioning (fludarabine150 mg/m2, cyclophosphamide 120 mg/kg and alemtuzumab 0.9–1 mg/kg) with the addition of low dose total body irradiation (2–3 cGy) in two of the five MMUD HSCTs. Event-free survival in the upfront cohort was 92% compared to 87% in MSD and 74% in the unrelated donor HSCT post-IST failure controls[6]. In a retrospective study on behalf of the SAAWP registry of the European Blood and Marrow Transplantation, Petit et al. reported the outcomes of 65 young patients (median age 16 y) who received up-front URD HSCT in Europe utilizing ATG or Campath prep were analyzed. The two-year overall survival rate was 92% but failure occurred in 8% (1-15%) of the patients. GVHD-free/relapse-free was 87% (77-96%) at 2-years[10]. In another retrospective study by Shah et al. the authors described the use of fludarabine, Campath, and low-dose cyclophosphamide conditioning (FCC low) in 15 children undergoing related or unrelated donor transplants with total body irradiation of 2 Gy added for unrelated donor HSCT. The failure-free survival was 100%, with low rates of infection and toxicity and no occurrence of grade III to IV acute graft-versus-host disease[11]. Bejanyan et al. evaluated conditioning regimens for matched sibling and unrelated donor BMT. For URD recipients (median age 21 y) graft failure at 1 year did not differ according to conditioning regimen, 9%, 8%, 15% and 12% after Cy/ATG/TBI200 cGy, Flu/Cy/ATG/TBI 200 cGy, Flu/Cy/ATG, and

Cy/ATG. Data suggested that the risk of grade II to IV GVHD was lower with the Flu/Cy/ATG regimen compared with Cy/ATG/TBI 200 cGy. Additionally grade II to IV acute GVHD was lower with r-ATG independent of regimen[12]. While these approaches have helped define successful URD and haploidentical BMT approaches mainly in patients who have failed IST, there is not clear data about whether these approaches are sufficient to get a graft into someone who has newly diagnosed SAA and whose disease process may still be highly active.

While study numbers are very limited, there is some evidence that patients treated with HSCT as initial therapy for SAA may require more intensity for optimal engraftment. In a single center study, DeZern and colleagues demonstrated high success with patients who failed IST undergoing haploidentical HSCT using a preparative regimen of rATG, Cy 14.5mg/kgx2, fludarabine, and TBI 200cGy followed by post-transplant cyclophosphamide (19/20 engrafting). When they began to use this approach in newly diagnosed patients, 3/7 rejected, prompting them to increase their TBI dose to 400cGy. This seemed to address the problem by decreasing their rejection rate to 0 with 9 additional patients in the publication and additional unpublished patients[13]. The TransIT study, a multicenter pilot trial aimed at demonstrating feasibility of diagnosis, randomization, and initiation of URD BMT or IST within a clinically acceptable timeframe in children and young adults has recently analyzed 17 patients receiving URD BMT as first therapy using the BMT CTN rATG/flu/Cy 50mg/kg/TBI200 approach. Two of these 17 patients had early rejection and 2 developed severe autoimmune cytopenias after engraftment in the face of partial chimerism. The autoimmunity led to late rejection and an overall rejection rate of 23%[14]. For the newly opening TransIT phase III trial, the team is planning to decrease this rejection rate by increasing the dose to the 100mg/kg dose shown as safe and effective in the BMT CTN trial. These examples illustrate support the hypothesis that transplantation of upfront SAA may lead to increased rejection and post-transplant autoimmune cytopenia because ongoing autoimmunity in the patient has not been sufficiently suppressed by some of the non-myeloablative/reduced intensity regimens currently being used for patients failing IST. As the number of patients receiving HSCT from URD and haploidentical donors are increasing, it is critical that the field define whether there is truly a difference in rejection and autoimmunity in these patients and then define the least toxic preparative approaches that overcome that rejection/autoimmunity barrier.

Previous studies demonstrated that HLA mismatched unrelated donor transplant was associated with worse survival after allogeneic hematopoietic cell transplantation (HCT) in patients with aplastic anemia (AA)[15] however, these data are relatively old with HSCT performed over 1-2 decades ago. A relatively large study from the Japanese registry showed a single allele mismatch unrelated donor (MMUD) was not associated with inferior survival of acute GVHD[16]. More recent summary data (2009-2019) by the CIBMTR showed inferior survival in those who received MMUD in univariate analyses[17] while the same registry data show incremental improvement of survival in AA over the last two decades. More recently, the Johns Hopkins group and subsequently the BMT CTN group (CTN#1502) reported successful results of haploidentical donor BMT using post-transplant Cy (PTCy) as GVHD prophylaxis[18]. However, the controversy exists regarding the degree of HLA mismatch acceptable in BMT for patients with aplastic anemia with a significant knowledge gap in its impact when a contemporary conditioning regimen (ATG/fludarabine/cyclophosphamide/low-dose TBI) with bone marrow graft and standard GVHD prophylaxis (calcineurin inhibitor, short course of methotrexate) is used.

Participant selection criteria:

Inclusion criteria: All patients with acquired SAA who underwent first URD or haploidentical HSCT between January 2010 and December 2022.

Exclusion criteria:

1. Clonal cytogenetic abnormalities or Fluorescence In-Situ Hybridization (FISH) pattern consistent with pre- myelodysplastic syndrome (pre-MDS) or MDS on marrow examination.
2. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ.
3. Prior solid organ transplant.

Data requirements:

Patient related:

- Sex
- Race/Ethnicity
- Age at diagnosis (<20, 20-40, 40-60, >60)

Transplant related:

- Age at transplant
- Year of transplant
- Up front HSCT vs HSCT for failure of IST
- Interval from diagnosis to HSCT
- Duration of follow up
- HLA match
- Donor age, sex, ABO status
- Graft source
- Conditioning regimen (explore doses of fludarabine, cyclophosphamide, TBI) in the context of serotherapy (alemtuzumab vs. rATG)
- GVHD prophylaxis strategy
- Occurrence of primary or secondary graft failure
- Occurrence of autoimmune cytopenias (pancytopenia vs. isolated thrombocytopenia vs AIHA)
- Stem cell boost without conditioning date and outcome
- Repeat transplant with conditioning date and outcome
- Survival (last follow up) and cause of death
- Occurrence and grade/severity of acute and chronic GVHD
- Neutrophil and platelet engraftment
- Chimerism studies (whole blood, T-cell, Myeloid) at 100 days, 180 days and 1 year post transplant.

Patient reported outcome requirement: none

Sample requirement: none

Non-CIBMTR data source: none

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Proposals 2210-183 & 2210-110: Characteristics of patients who underwent first alloHCT for Aplastic Anemia from 2008-2019 reported to CIBMTR

Characteristic	N (%)
No. of patients	957
Patient Related	
Recipient age - no. (%)	
Median (min-max)	21 (0-74)
0-10	207 (22)
11-19	242 (25)
20-39	292 (31)
40-60	163 (17)
>60	53 (6)
Treatment Related	
Donor type - no. (%)	
Well-matched unrelated (8/8)	530 (55)
Other related	258 (27)
Partially-matched unrelated (7/8)	131 (14)
Unrelated (matching TBD)	29 (3)
Mis-matched unrelated (<= 6/8)	9 (1)
Conditioning intensity as designated by center - no. (%)	
RIC / Non-Myeloablative	581 (61)
Myeloablative	373 (39)
To be determined following review	3 (0)
Graft source - no. (%)	
Bone marrow	715 (75)
Peripheral blood	242 (25)
Year of transplant - no. (%)	
2008-2009	147 (15)
2010-2011	28 (3)
2012-2013	72 (8)
2014-2015	230 (24)
2016-2017	240 (25)
2018-2019	240 (25)

Characteristic	**N (%)**
No. of patients	957
Was therapy given prior to preparative regimen - no. (%)	
No	115 (12)
Yes	809 (85)
Missing	25 (3)
Unknown	8 (1)
Treatment ATG, ALS, ATS, ALG - no. (%)	
No	240 (25)
Yes	684 (71)
Missing	33 (3)
Treatment Cyclosporine - no. (%)	
No	238 (25)
Yes	686 (72)
Missing	33 (3)
Follow-up, months - median (range)	38 (1-147)

Response Summary:

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

Q1. Study Title

Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia

Q2. Key Words

severe congenital neutropenia, alloHCT, iBMF

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nora Gibson M.D.
Email address:	gibsonn1@chop.edu
Institution name:	Children's Hospital of Philadelphia
Academic rank:	Fellow, Pediatric Hematology & Oncology

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Joseph Hai Oved MD MA
Email address:	ovedj@mskcc.org
Institution name:	Memorial Sloan Kettering Cancer Center
Academic rank:	Assistant Member

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

ovedj@mskcc.org

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

N/A

LETTER OF COMMITMENT:

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

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

Was part of the recent study published by Daria Babushok in JCI Insights on 10/11/22 but am not currently involved in other CIBMTR projects

Q13. PROPOSED WORKING COMMITTEE:

- Non-Malignant Diseases

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

What is the best approach to conditioning for patients with SCN defined by outcomes including engraftment, treatment-related toxicity and overall & event free survival.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that a reduced toxicity approach utilizing busulfan/fludarabine regimen will have best outcomes by balancing need for durable efficient engraftment while minimizing treatment related toxicities.

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

Suggested word limit of 200 words:

The objectives of this proposal are to evaluate engraftment, OS, EFS and treatment-related toxicity associated with the many different conditioning regimens that have been reported for HCT in patients with SCN.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

In a recent literature review, we were unable to find a standard of care conditioning regimen approach to bone marrow transplant for patients with SCN. Instead we found a wide variety of approaches that ranged from maximally toxic (i.e. Bu/Cy) to reduced toxicity (Bu/Flu) and a variety of other regimens in between (including additional regimens that have two or more alkylators for conditioning). This study will attempt to define the optimal conditioning regimen that provides a high probability of success with minimal risk of treatment-related toxicity. By defining these parameters, this study can help either define a suggested standard of care for these patients or help in design of a future prospective clinical trial to determine the optimal conditioning regimen for this patient population.

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

Hematopoietic stem cell transplant (HSCT) is the only curative treatment option for SCN. Definitive reasons to pursue HSCT include failure to maintain appropriate ANC with GCSF, high G-CSF requirement, recurrent intractable infections or progression to MDS or leukemia.
As with many rare hematologic conditions, there remains a paucity of data on the most appropriate conditioning regimen for SCN patients. At this point, most patients who have had HSCT for SCN have received myeloablative conditioning with busulfan and cyclophosphamide, while others have received varied regimens with no standard of care (Please see attached document for literature review and data on this topic). This Bu/Cy myeloablative regimen carries numerous well-documented risks, including increased risk of veno-occlusive disease, pulmonary toxicity, infertility, and secondary malignancy. Numerous case reports suggest that a regimen including busulfan and fludarabine may produce similar outcomes in SCN patients and offer a way to mitigate the severe side effects associated with cyclophosphamide. Our institutional experiences concur that Bu/Flu may represent a better approach for SCN but these are based on small case series and will need larger numbers to define outcomes in a more rigorous manner.

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

[Click here]

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

Inclusion: All patients that received a first allogeneic transplant for severe congenital neutropenia.
Exclusion: Patients with MDS and/or Leukemia. Patients that received a previous transplant. Patients with other iBMF syndromes that have neutropenia as part of their constellation but is not the sole symptom.

Q21. Does this study include pediatric patients?

- Yes

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

1. Form 2402: Diagnosis, pre-HCT info
2. Form 2400: Donor, conditioning/prep regimen, clinical status, GVHD ppx, post-HCT therapy
3. Forms 2450 and 2100 (when applicable): Long term outcomes/toxicities, chimerism, lymphocyte subsets.

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

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

None required

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

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

None required

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

N/A

Q26. **REFERENCES:**

Please see attached table

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

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

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

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

N/A

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

Embedded Data:

N/A

Author Name	Title (abb)	Year	# of pts	Ind for txp	Conditioning	Outcome
Connelly	Hematopoietic stem cell transplant for severe congenital neutropenia (Review)	2012		N/A	Referenced bu/flu at institution but no published study	
Carlsson	Hematopoietic Stem Cell Transplantation in Severe Congenital Neutropenia. Pediatric	2018	8	MDS, G-CSF resistance, re-transplantation	3 pts got bu/cy, + melphalan in 2 1pt got bu/flu 3 got treosulfan/flu 1 retransplant got flu/cy	One needed 2nd txp All others alive and well
Choi	Stem cell transplantation in patients with severe congenital neutropenia with evidence of leukemic transformation.	2005	6	4 AML 2 MDS	Bu/cytarabine/cyclophos for 5 pts, one got cyclophos and TBI	MDS patients alive and well, all AML died
Cojean	Successful stem cell transplantation in an infant with severe congenital neutropenia complicated by pretransplant inflammatory pseudotumor of the liver	2006	1	Severe infections	Bu/cy/ATG	Alive and well
Dalloroso	Uneventful outcome of unrelated hematopoietic stem cell transplantation in a patient with leukemic transformation of Kostmann syndrome and long-lasting invasive	2003	1	AML	Bu/cy/mel	Alive and well

	pulmonary mycosis					
Ebihara	Allogeneic stem cell transplantation for patients with acute myeloid leukaemia.	2014	2	AML	TBI, Ara-C, cyclophos	One alive and well, one died of bronchiolitis obliterans 26m after txp
Ferry	Hematopoietic stem cell transplantation in severe congenital neutropenia: Experience of the French SCN register.	2005	9	4 had MDS or leukemia 4 had refractory neutropenia 1 had BMF	7 got bu/cy Others got cy/thiotepa, cy/TBI or cy/etoposide	ALL pt died 1 MDS pt died BMF pt died
Fioredda	Stem cell transplantation in severe congenital neutropenia: an analysis from the European Society for Blood and Marrow Transplantation	2015	136	G-CSF nonresponse or clonal transformation	Myeloablative (87%) RIC (13%)	
Fukano	Unrelated bone marrow transplantation using a reduced-intensity conditioning regimen for the treatment of Kostmann syndrome.	2006	1	Infection	Flu/mel/ATG	Alive and well
Hashem	Successful second hematopoietic cell transplantation in severe congenital neutropenia.	2018	1	Second transplant for rejection 6 months after first for pt with ELANE mutation	Bu/flu/ATG	Alive and well 1 year after txp, >95% chimerism
Kawaguch	Successful treatment with allogenic hematopoietic	2014	1	Failed GCSF, repeated infections	Flu/mel/ATG/TBI	Alive and well 15 months later

	stem cell transplantation of a severe congenital neutropenia patient harboring a novel ELANE mutation [Japanese]					
Lu	Hematopoietic stem cell transplantation for inherited bone marrow failure syndromes: alternative donor and disease-specific conditioning regimen with unmanipulated grafts		8	Infections	Bu/Ara-C/cy/ATG	All alive
Markel	Unrelated cord blood transplantation for severe congenital neutropenia: Report of two cases with very different transplant courses	2008	2	GCSF failure	Bu/cy/ATG	Pt 1 alive and well Pt 2 needed 2nd and 3rd transplants, now alive and well
Mino	Umbilical cord blood stem cell transplantation from unrelated HLA-matched donor in an infant with severe congenital neutropenia	2004	1	Refractory to GCSF	Bu/cy/ATG	Alive and well
Nakazawa	Successful unrelated cord blood transplantation using a reduced-intensity	2004	1	Severe infection	Flu/cy/TBI	Alive and well

	conditioning regimen in a 6-month-old infant with congenital neutropenia complicated by severe pneumonia					
Nino	Successful non-myeloablative allogenic bone marrow transplantation in a child with severe congenital neutropenia complicated by chronic pulmonary infection [Japanese]	2016	1	Infection	Flu/mel/TBI	Alive and well
Oshima	Hematopoietic stem cell transplantation in patients with severe congenital neutropenia: an analysis of 18 Japanese cases.	2010	18	"Reasons other than malignant transformation"	12 pts got bu/cy + ATG in 7 pts, +flu (1), +TLI (1) 1 pt got bu/flu/ATG (alive, no graft failure)	Bu/flu/ATG pt alive and well, engrafted
Osone	Case Reports of Severe Congenital Neutropenia Treated With Unrelated Cord Blood Transplantation With Reduced-intensity Conditioning	2006	3	Infections	Flu/mel/TBI	Alive and well
Rotulo	HSCT may lower leukemia risk in ELANE neutropenia: a before–after study from the French Severe Congenital	2020	16		9 got bu/cy/ATG 6 got bu/flu plus either ATG only, ATG/mel, or ATG/thiotepa One got TBI, cy, melphalan	All had full engraftment and chimerism One pt died of ALL One pt died of grade IV GVHD and TMA

	Neutropenia Registry					
Thachil	Non-Myeloablative Transplantation for Severe Congenital Neutropenia	2008	1	Infection	Flu/campath/thiotepa	Alive and well
Toyoda	Successful unrelated BMT in a patient with Kostmann syndrome complicated by pre-transplant pulmonary 'bacterial' abscesses	2001	1	Nonresponse to GCSF	TBI, ATG, cy, etoposide	Alive and well
Zeidler	Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation [could not access full article]	2000	11	Anything other than malignant transformation	1 got cy alone 10 got bu/cy	

Proposal 2210-131: Characteristics of patients who underwent first alloHCT for Kostmann Syndrome from 2008-2019 reported to CIBMTR

Characteristic	N (%)
No. of patients	87
Patient Related	
Recipient age - no. (%)	
Median (min-max)	2 (0-20)
0-5	59 (68)
6-11	18 (21)
12-17	5 (6)
18-21	5 (6)
Treatment Related	
Donor type - no. (%)	
HLA-identical sibling	27 (31)
Other related	11 (13)
Well-matched unrelated (8/8)	19 (22)
Partially-matched unrelated (7/8)	6 (7)
Multi-donor	1 (1)
Unrelated (matching TBD)	3 (3)
Cord blood	20 (23)
Conditioning intensity as designated by center - no. (%)	
RIC / Non-Myeloablative	18 (21)
Myeloablative	67 (77)
To be determined following review	2 (2)
Graft source - no. (%)	
Bone marrow	59 (68)
Umbilical cord blood	20 (23)
Peripheral blood	8 (9)
Year of transplant - no. (%)	
2008-2009	13 (15)
2012-2013	4 (5)
2014-2015	17 (20)
2016-2017	26 (30)
2018-2019	27 (31)
Number of patients in the CRF Track - no. (%)	
CRF patients	23 (26)
Follow-up, months - median (range)	49 (4-147)

QI. Study Title: Alternative Donor Choices for Hematopoietic Stem Cell Transplantation (HCT) in Children and Young Adults with Hemophagocytic Lymphohistiocytosis (HLH) and other Immune Dysregulatory Disorders, Non-SCID Primary Immunodeficiency Diseases, and Inherited Bone Marrow Failure disorders

Investigators:

Fred Hutchinson Cancer Center/ University of Washington of Medicine

Madhavi Lakkaraja, MD, MPH, Lauri Burroughs, MD, K. Scott Baker, MD, MS

University of Colorado

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Key Words
Hematopoietic Stem Cell Transplantation (HCT),
Haploidentical Donor,
Matched Unrelated Donor (MUD),
Matched Sibling Donor,
Mismatched Unrelated Donor (MMUD),
Cord HCT,
Pediatrics,
Young Adults,
Non-Malignant,
Bone Marrow Failures,
Primary immune deficiencies,
Hemophagocytic lymphohistiocytosis (HLH),
Immune dysregulation,
Overall Survival (OS),
Event free Survival (EFS),
Transplant Related mortality (TRM),
Graft versus Host Disease (GVHD),
GVHD free EFS

Q15. Research Question

What are the outcomes of hematopoietic stem cell transplantation using alternative donors in patients with nonmalignant disorders including primary immunodeficiencies (PID; non-severe combined immunodeficiency), Hemophagocytic lymphohistiocytosis (HLH), immune dysregulation, and inherited bone marrow failures (iBMF) (excluding aplastic anemia) disorders who lack a matched sibling (MSD) donor or matched unrelated donor (MUD)?

Q16. Research Hypothesis

We hypothesize that pediatric and young adult patients undergoing HSCT for PID, immune dysregulation disorders, HLH and iBMF using a cord blood graft, haploidentical graft or mismatched unrelated donor graft, have comparable outcomes to patients treated with MSD

grafts in a modern cohort (2010 – 2021). Moreover, early HSCT in these patients will prevent the development of comorbidities that may affect transplant outcomes.

Q17.Specific Objectives/Outcomes to be Investigated

Objective:

To assess outcomes of pediatric and young adult patients with PID (non SCID), HLH, immune dysregulation, and inherited bone marrow failure disorders undergoing alternative donor HCT, compared to MSD and MUD, between January 2010 to December 2021.

Outcomes to be investigated:

Primary Endpoint:

3-year Overall Survival (OS): Time to death from any cause. Patients who are alive will be censored at the time of last contact.

Secondary Outcomes:

1. Transplant related mortality (TRM): Time to death from any cause.
2. Incidence of graft failure.
3. Graft versus Host Disease (GVHD): Incidence of acute (grade II-IV) or extensive chronic GVHD requiring immune suppression.
4. Event free Survival (EFS). An event will be defined as death, rejection, or second transplant.
5. GVHD free EFS. GVHD will be defined as acute grade III-IV GVHD and extensive chronic GVHD requiring immune suppression.
6. Description of alternative donor type, HLA match and conditioning regimen used for transplantation and GVHD prophylaxis.
7. Description of other pre-transplant comorbidities (colitis, failure to thrive or malnutrition, liver or brain abscesses, lung disease).
8. Description of post-transplant number and sites of infections and description of active infections at the start of conditioning regimen.
9. Donor chimerism: Correlate rates (and kinetics) of full donor vs mixed chimerism based on disease [immune dysregulation disorders including HLH, primary immunodeficiencies: Chronic Granulomatous Disease (CGD), Wiskott Aldrich Syndrome (WAS), Leucocyte Adhesion Deficiency (LAD), CTLA4 deficiency, DOCK8 deficiency, GATA2 deficiency, LRBA deficiency) inherited bone marrow failures (Fanconi anemia, Amegakaryocytic thrombocytopenia, Diamond Blackfan anemia, Dyskeratosis congenita, Severe congenital neutropenia, Shwachman Diamon syndrome, Thrombocytopenia absent radii and others)], stem cell source, and conditioning regimen.

Q18. Scientific Impact

Reports of alternative donor transplant outcomes for PID, immune dysregulation disorders, HLH and iBMF are scarce and from small cohorts.[1-4] A recent retrospective report of the use of haploidentical HSCT in nonmalignant disorders included 16 patients with PID (3 patients with SCID) and the outcomes for the subgroup were encouraging with 2-y OS, EFS and GRFS of 100%, 94%, 88%, respectively. These cohort included few patients of each PID (4 CGD, 2 LAD, 2 SCN, 2 Hyper IgM, 1 ALPS, 1 Hyper IgE, 1 Gricelli syndrome). The heterogeneity of the

diseases as well as the small sample size precluded the group to provide recommendations regarding the best conditioning. Importantly, younger age at transplant (<4years) and PID was associated with better GRFS. [5]

In patients without a matched related donor, or from ethnically diverse groups which are under-represented in registries, finding a suitable donor remains a challenge. There is a need to assess the impact of alternate donor HCT in rare non-malignant disorders. A successful CIBMTR-data study of the use of alternative donor transplant in rare non-malignant disorders would provide relevant clinical information that may guide practice in the future.

Q19. Scientific Justification

There is only a 25% chance that a patient will have an HLA-matched sibling donor. In addition, many of the nonmalignant diseases that are treatable by HCT are genetic. As a result, the sibling may also have the same nonmalignant disease as the patient and therefore, not be a suitable donor. Over the last decade, there have been advancements in the prevention and treatment of graft versus host disease (GVHD) as well as supportive care which have resulted in improved outcomes following HCT including HCT using alternative donors. Alternative donor choices have emerged as a donor choice for ethnically underrepresented patients in the registry.

Haploidentical donors have advantages that include a ready available and committed donor, leading to shorter time between collection and infusion and ease of repeated donations,[6] but the need for ex vivo or in vivo T cell depletion, and use of aggressive immunosuppression leading to delayed immune reconstitution, and increased the risk of infections are some pitfalls.[7] Similarly, umbilical cord blood has been increasingly used for HCT in non-malignant disorders, as it is readily available, but higher immune mediated rejection with mismatched at 2 or more alleles, delayed immunological and hematopoietic recovery, and ability to select the best unit are some hurdles.[8,9]

In the recent survey of 315 clinicians conducted by the Center for International Blood and Marrow Transplantation Research (CIBMTR) across United States, clinicians predicted that the number of HCTs will increase for non-malignant disorders. They responded that matched related and MUD will continue being the preferred donor choice, there would be a rise in HCT using haploidentical donors and a reduction in cord HCT. Respondents also predicted that in children with PIDs in the absence of a matched related donor, donor choices would be in the following order of preference: MUD, haploidentical with graft manipulation, haploidentical with post-transplant cyclophosphamide (Pt-cy), cord and MMUD. [10,11] The worldwide network of blood and marrow transplantation recently assessed HCT trend worldwide between 2014 and 2016 and compared it to 2006 and reported that the number of HCT for non-malignant disorders had increased significantly and noted a rise in haploidentical HCT, plateau in unrelated donor HCT and decrease in cord blood HCT.[12]

Given the rising use of alternate donors, especially in ethnically underrepresented group in the donor pool, there is a need to assess the outcomes of HCT with alternate donors in a registry-based study. Here is a summary of the pertinent literature in patients with bone marrow failures, HLH, immune dysregulation non SCID-PID who underwent an alternate donor HCT.

In a European Society for Blood and Marrow Transplantation (EBMT) study, Zubicaray et al compared HCT outcomes of Fanconi anemia in pediatric patients between 2000 and 2018, using HLA- MMUD (n = 123) or haploidentical donor, with in vivo T cell depletion (*n* = 33) or in vivo T

cells depletion with ex vivo graft manipulation (n = 59). Event free survival (EFS) was higher in haploidentical donor patients with in-vivo T cell depletion compared to patients who received MMUD or to those who received haploidentical donor with ex vivo graft manipulation.[13]

Another study assessed the impact of alternative donor HCT (haploidentical donor, MUD, MMUD) with Pt-cy in 11 patients with PIDs, HLH, inherited bone marrow failures, lymphoproliferative disorder, and demonstrated that reduced intensity alternative donor HCT with high dose Pt-CY as GVHD prophylaxis has low TRM, low rates of infections and good engraftment. [14]

In 23 patients with nonmalignant disorders who underwent a haploidentical donor HCT (bone marrow and peripheral blood) with non-myeloablative conditioning and post-transplant cyclophosphamide, mycophenolate mofetil, tacrolimus, ± sirolimus, the 2-year OS was 91% ,2-year EFS was 78%, cumulative incidence of aGVHD II to IV was 78%, aGVHD III to IV was 26% at 100 days and cGVHD was 42% at 2 years. TRM at day 100 was 0%, suggesting that T-replete haploidentical donor HCT could be an option for patients with non-malignant diseases.[15]

A prospective study assessed haploidentical donor HCT in 6 nonmalignant disorders (chronic granulomatous disease (CGD), XIAP deficiency, Wiskott Aldrich Syndrome (WAS), bone marrow failure disorders and IL-10R deficiency, with Pt-CY and low dose antithymocyte globulin. Median time to engraftment was 14.5 days and no patient developed severe acute GVHD, or chronic GVHD and has stable mixed chimerism at the time of last follow up (range 282 to 1108 days), suggesting that haploidentical donor with low dose ATG with Pt-CY could be an option for HCT in these children with excellent outcomes.[16]

In a retrospective study of 45 children with HLH who underwent matched related donor HCT (n=17) , MUD (n=9), MMUD (n=7), haploidentical donor HCT (n=8) (with alpha beta depletion in 5, CD3/CD19 depletion in 1 and Pt-cy in 2), and umbilical cord HCT(n=4), with myeloablative (n=20) or reduced intensity conditioning (n=25), it was noted that the 5-year OS was 86% and EFS was 82%. Alternative donors (haploidentical donor, MMUD, cord) had higher rates of incomplete donor chimerism and inferior EFS 74% compared to matched donors 92%.[17]

A primary immune deficiency treatment consortium (PIDTC) report assessed the outcomes of 129 patients with WAS. In 84, patients who received alternate donor HCT (MUD, MMUD and unrelated cord blood), OS was nearly 90% and similar in all alternative donor HCT.[18]

Individual studies in smaller cohorts of patients with non-SCID PID, HLH and bone marrow failures assessing outcomes of alternative donors in HCT, have demonstrated promising results. However, as the number of HCTs continues to rise for patients with non-malignant indications with newer genetic disorders being recognized, there is an increasing need to assess the impact of different alternative donor sources on HCT outcomes in a registry-based study, especially in patients lacking a fully matched related or unrelated donor.

To accomplish this, we propose a CIBMTR registry-based analysis comparing outcomes of children and young adults with PID (excluding SCID), immune dysregulation, HLH, bone marrow failures (excluding aplastic anemia), undergoing their first allogeneic HCT with either MMUD, haploidentical, or cord blood donors, to patients undergoing their first allogeneic HCT with matched related donors/MUD.

Q20. Participant Selection Criteria

Inclusion Criteria:

1. Patients between 0 to 30 years of age

2. Underwent their first allogeneic HCT

3. Fanconi anemia, Amegakaryocytic thrombocytopenia, Diamond Blackfan anemia, Dyskeratosis congenita, Severe congenital neutropenia, Shwachman Diamon syndrome, Thrombocytopenia absent radii and other inherited bone marrow failure syndromes, X-Linked Lymphoproliferative Syndrome, chronic granulomatous disease, immune dysregulation disorders including HLH, primary immunodeficiencies: Chronic Granulomatous Disease (CGD), Wiskott Aldrich Syndrome (WAS), Leucocyte Adhesion Deficiency (LAD), CTLA4 deficiency, DOCK8 deficiency, GATA2 deficiency, LRBA deficiency) as indications for HCT.

4. Donor was MMUD, haploidentical, or cord blood

We will compare outcomes following alternative donor HCT to outcomes of patients who underwent a matched related donor vs. MUD HCT independently.

5. HCT occurred between January 2010 to December 2021.

Exclusion Criteria:

1.Patients who had undergone prior HCT

2. Ex vivo graft manipulation with alpha-beta T-cell depletion

3. Aplastic Anemia

4. Severe combined immunodeficiency (SCID)

5. Hemoglobinopathies

We are excluding the above diagnoses as there is literature in these cohorts of patients indicating the donor choices in the absence of matched sibling donor.[1-4] We are excluding ex vivo graft manipulation with alpha beta depletion since there may not be sufficient data available in the last ten years in the CIBMTR registry.

Data Requirements
Patient related:

Age: Continuous and categorical (0-10 ,11-20, 21-30 years)

Recipient Gender: Male, Female

Race: Caucasian, African American Asian Pacific Islander, Native America, Asian, Multiple races

Ethnicity: Hispanic/Latino, Non-Hispanic/Non-Latino, Non-resident of US, unknowing/missing

Performance status: 90-100, < 90

HCT- co-morbidity index (HCT-CI) :0,1-2, >=3

Disease Related:

Primary Disease:

Non - Malignant: Bone marrow failures, Immune dysregulation, HLH, PIDS (Non SCID)

Donor:

Stem cell source: MMUD, Haploidentical, Cord and for comparison MUD and matched sibling or related donor

Age

CMV serostatus

Sex/sex MM

Conditioning regimen intensity: Myeloablative, reduced intensity, non-myeloablative

Use of TBI: Yes vs No

Donor-recipient CMV status: -/- vs. -/+, +/-, +/+

GVHD prophylaxis:

PT-CY +/- others,

CNI + mycophenolate (MMF)

CNI + methotrexate,

CNI alone

CNI + others

Others

None

Serotherapy (ATG, campath vs. none)

T cell depletion, CD34 selection broad categories

We will perform a subgroup analysis within each GVHD prophylaxis strategy

Date of transplant:

Time dependent:

Neutrophil engraftment (Yes or No)

Acute GVHD (Yes or No)

- Grade II-IV

Chronic GVHD (Yes or No)

- Limited or Extensive

NRM (Yes or No)

Graft failure (Yes or No)

Death (Yes or No)

Causes of Death:

Infection

Progression of Disease

GVHD

Other

-2146 Fungal infections post-HSCT
-CMV/DBV/ADV/HHV-6/BK Viral Infection Diagnostic and Treatment Form 1.0
-2400 Pre-transplant essential data
-2055 Chronic granulomatous disease pre HSCT data
Disease assessment at diagnosis:
2. Pattern of CGD inheritance
Clinical Features Assessed between Diagnosis and the Start of the Preparative Regimen
26. Dihydrohodamine oxidation (DHR)
27. Specify stimulation index
34. Site of infection: adenitis
35. Organism
38. Site of infection: brain abscess, organism
42. Site of infection: cellulitis, organism
46. Site of infection: furuncles, organism
50. Site of infection: genitourinary, organism
62. Site of infection: liver abscess, organism
66. Site of infection: lung absess, organism
82. Site of infection: perirectal abscess, organism
86. Site of infection: pneumonia, organism
94. Site of infection: subcutaneous abscess, organism
Clinical status between diagnosis and preparative regimen
108. Is autoimmune hemolytic anemia present?
111. Is failure to thrive present?
114. Is gastric outlet obstruction resent?
120. Is inflammatory bowel disease present?

-2029 R2.0: Fanconi Anemia/Constitutional Anemia Pre-HSCT Data
31. Specify the presenting hematologic disorder
Specify cytopenia
32. Anemia
33. Thrombocytopenia
34. Neutropenia
Specify group testing: 80-87
117. Recipient status immediately prior to the preparative regimen?
Specify autoimmune/inflammatory disorders: 98-127

-2039 R2.0: Hemophagocytic Lymphohistiocytosis Pre-HCT Data

Specify genetic mutation: 13-18
Clinical features and laboratory studies at diagnosis: 23-46
Disease assessment between diagnosis and start of prep: 59-71
Therapy given prior BMT: 79-91
Clinical features prior BMT: 108-126
- 2129 R2.0: Fanconi Anemia / Constitutional Anemia Post-HSCT Data

- 2133 R3.0: Wiscott-Aldrich Syndrome Post-HSCT Data
- 2134 R3.0: X-Linked Lymphoproliferative Syndrome Post-HCT Data
-2134 R2.0: Congenital Amegakaryocytic Thrombocytopenia Post-HSCT Data

Q21. Patient-Reported Outcome (PRO) Requirements

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

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

Q22. Sample Requirements (if the study will use biologic samples from the CIBMTR Repository)

- If the study requires biologic samples from the CIBMTR Repository, the proposal should also include a detailed description of the proposed testing methodology and sample requirements and a summary of the investigator's previous experience with the proposed assay systems.

No samples will be requested

Q23. Non-CIBMTR Data Source, *if applicable*

- A description of the external data source to which the CIBMTR data will be linked.
- The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

Q24. References

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Proposals 2210-236 & 2210-283: Characteristics of patients who underwent first alloHCT for bone marrow failure syndromes, non-SCID primary immune deficiencies, immune dysregulation and HLH from 2008 to 2019 reported to CIBMTR

Characteristic	Bone marrow failure syndromes	Immune dysregulation and HLH	Non-SCID primary immune deficiencies
No. of patients	612	439	401
Patient Related			
Recipient age - no. (%)			
Median (min-max)	8 (0-29)	1 (0-29)	2 (0-29)
0-6	272 (44)	347 (79)	296 (74)
7-12	230 (38)	38 (9)	51 (13)
13-18	78 (13)	36 (8)	32 (8)
19-24	23 (4)	15 (3)	13 (3)
25-30	9 (1)	3 (1)	9 (2)
Treatment Related			
Graft source - no. (%)			
Bone marrow	263 (43)	189 (43)	165 (41)
Peripheral blood	156 (25)	89 (20)	81 (20)
Umbilical cord blood	193 (32)	161 (37)	155 (39)
Donor type - no. (%)			
Other related	199 (33)	106 (24)	89 (22)
Mis-matched unrelated (<= 7/8)	135 (22)	124 (28)	75 (19)
Unrelated (matching TBD)	85 (14)	48 (11)	82 (20)
Cord blood	193 (32)	161 (37)	155 (39)
Year of transplant - no. (%)			
2008-2009	93 (15)	68 (15)	56 (14)
2010-2011	92 (15)	76 (17)	61 (15)
2012-2013	91 (15)	64 (15)	76 (19)
2014-2015	115 (19)	79 (18)	68 (17)
2016-2017	125 (20)	67 (15)	76 (19)
2018-2019	96 (16)	85 (19)	64 (16)
Follow-up, months - median (range)	60 (3-169)	58 (3-163)	52 (3-167)

*Bone marrow failure syndromes: Shwachman Diamond syndrome, Dyskeratosis congenita, Fanconi anemia, Diamond Blackfan anemia, Severe congenital neutropenia, Amegakaryocytic thrombocytopenia, Thrombocytopenia absent radii and other inherited bone marrow failure syndromes

*Non-SCID primary immune deficiencies: Wiskott Aldrich Syndrome (WAS), Chronic Granulomatous Disease (CGD), Leucocyte Adhesion Deficiency (LAD)

* Immune dysregulation: X-Linked Lymphoproliferative Syndrome, HLH