Not for publication or presentation

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A G E N D A
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
San Antonio, TX
Friday, February 23, 2024, 1:00pm – 3:00pm CST

Co-Chair:	**Andrew Gennery, MD, Newcastle General Hospital / The Royal Victoria Infirmary, Newcastle, UK; E-mail: andrew.gennery@newcastle.ac.uk**
Co-Chair:	**George Georges, MD; Fred Hutchinson Cancer Research Center, Seattle, WA; E-mail: ggeorges@fredhutch.org**
Co-Chair:	**Kasiani Myers, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Phone: 513-226-4948; Email: kasiani.myers@cchmc.org**
Scientific Director:	**Larisa Broglie, MD; CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4108; E-mail: lbroglie@mcw.edu**
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1. **Introduction**
   a. Minutes from February 2023 TCT Working Committee Session (Attachment 1)
   b. Instructions for signing-in and voting
   c. Introduction of incoming WC Co-Chairs

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

3. **Presentations, published or submitted papers**
   a. **NM16-03b:** Gale RP, Hinterberger W, Young NS, Gennery AR, Dvorak CC, Hebert KM, Heim M, Broglie L, Eapen M. What causes aplastic anaemia? ***Leukemia. 2023 Jun 1; 37(6):1191-1193. doi:10.1038/s41375-023-01892-2. Epub 2023 Apr 27. PMC10353698.***
   b. **NM19-01:** Nakamura R, Patel BA, Kim S, Wong FL, Armenian SH, Groarke EM, Kessler DA, Hebert KM, Heim M, Eapen M, Young NS. Conditional survival and standardized mortality ratios of patients with severe aplastic anemia surviving at least one year after hematopoietic cell transplantation or immunosuppressive therapy. ***Haematologica. 2023 Dec 1; 108(12):3298-3307. doi:10.3324/haematol.2023.282781. Epub 2023 Jun 1. PMC10690917.***

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) **Protocol Development.**

d. **NM20-01:** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Manuscript 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. **Protocol Development.**
g. **NM23-01:** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant. **Protocol Development.**

5. **Future/proposed studies**
   a. **PROP 2309-09:** Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes (J Koo/ A Sabulski) (Attachment 4)
   b. **PROP 2309-12:** A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders (J Koo/ K Myers) (Attachment 5)
   c. **PROP 2310-143:** Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the Impact of conditioning regimens (H Rangarajan/ RA Arja/ J Kurtzberg/ P Satwani) (Attachment 6)
   d. **PROP 2310-205:** Impact of somatic mutations in aplastic anemia (AA) after allogeneic stem cell transplantation (B Ball) (Attachment 7)
   e. **PROP 2310-213/2310-255:** Comparison of Haploidentical Donor transplantation using post-transplant cyclophosphamide platform versus Matched Unrelated Donor transplantation in Severe Aplastic Anemia patients who lack a Matched Sibling Donor (Revision 1) / Assess impact of Post Transplant Cyclophosphamide as GVHD prophylaxis in aplastic anemia (N Khaire/ R Kumar/L Gowda/ S Mizra) (Attachment 8)

6. **Dropped proposed studies**
   a. **PROP 2309-06:** The impact of Transplant Conditioning Intensity (TCI) score on the prognosis of allogeneic hematopoietic cell transplantation for aplastic anemia and Fanconi anemia in children. *Dropped due to overlap with current ongoing study (NM 23-01).*
   b. **PROP 2310-26:** Second transplantations for severe aplastic anemia. *Dropped due to overlap with current ongoing study (NM 22-01).*
   c. **PROP 2310-90:** HSCT for DADA2 - Real World Experience from the CIBMTR. *Dropped due to low sample size.*
   d. **PROP 2310-88:** Allogeneic Hematopoietic Stem Cell Transplant in non-SCID Rare Inborn Errors of Immunity: Leukocyte Adhesion Deficiency (LAD) Type I and III and Cartilage Hair Hypoplasia (CHH). *Dropped due to recent EBMT publication of LAD.*
   e. **PROP 2310-109:** Outcomes following Allogeneic Hematopoietic Stem Cell Transplant in patients with hemophagocytic lymphohistiocytosis (HLH) and oculocutaneous manifestations (Chediak Higashi Syndrome and Griscelli syndrome). *Dropped due to low sample size.*
   f. **PROP 2310-126:** Pain and Physical Function post-HCT for SCD. *Dropped due to low sample size and only recent addition of questions to capture chronic pain on recent forms.*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Orlando, Florida
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**
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1. Introduction

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

The Non-Malignant Disease Working Committee (NMWC) met on Wednesday, February 15, 2023, at 1:03 p.m. Attendees were asked to have their name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.

As scientific director of the NMWC, Dr. Larisa Broglie called the meeting to order and welcomed the attendees on behalf of the working committee leadership.

Dr. Broglie started the welcome presentation by introducing each member of the working committee leadership. Dr. Broglie also introduced the working committee's new statistician, Charimar Santiago, and the other working committee leadership, which have not changed since last year. Dr. Broglie acknowledged Dr. Christopher Dvorak for all his effort during the past years as Co-Chair and introduced Dr. Kasiani Myers as the newly appointed Chair for the Working Committee starting March 1, 2023.

Dr. Broglie, then walked the audience through the sources of data and the difference between TED and CRF data. Additionally, cellular therapy data is collected and available.

Dr. Broglie talked about the CIBMTR's Patient-Reported Outcome (PRO) data collection effort. It collects survey data from HCT/CT patients who have agreed to be contacted by CIBMTR. We are currently collecting data from adult patients at 17 partnering centers, with plans to expand to pediatric patients in the future.

Dr. Larisa Broglie shared that there are publicly available datasets 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. Broglie then shared with the audience the new initiative called CIBMTR Working Committee Training and Leadership (CTL) Program. The program is offered to early career investigators who are interested in expanding their observational research skills as well as gaining exposure to CIBMTR and its Working Committee study portfolios.

Dr. George Georges shared the goals, limitations, and expectations of the committee, the rules for working committee membership and the rules of authorship. Dr. Georges emphasized all in person attendees that had the name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.

2. Accrual Summary (Attachment 2)

Dr. Georges presented the accruals summary. In non-malignant diseases, the highest accrual is in acquired aplastic anemia, followed by primary immune deficiencies, hemoglobinopathies, and bone marrow failure syndrome. Others have low numbers such as autoimmune diseases. It is expected that in the following years, this number will grow. Among patients with aplastic anemia, a large number have CRF forms completed, thus more granular data is available. Most patients with inherited bone marrow are under Fanconi Anemia, with half of the patients having CRF data available. Sickle Cell Anemia, and Beta Thalassemia comprised the majority of patients with hemoglobinopathies. In metabolic diseases, Hurler Syndrome, Osteopetrosis, MLD, and ALD have the highest proportions with high percentages on the CRF track. Among histiocytic diseases, the highest accrual is familial HLH, with a smaller contribution of the other causes. In Immune Deficiencies, the highest proportions are in SCID and CGD. Dr. Georges then turned the floor over to Dr. Andrew Gennery who explained the process for new working committee leadership.

3. Presentations, Published or Submitted Papers

Dr. Gennery provided updates on the committee. The two committee publications from 2021 and two submitted papers are listed below:

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)

Dr. Gennery shared the studies in progress including two manuscripts in progress and other ongoing studies in protocol development or data file preparation. 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) **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

Dr. Christopher Dvorak introduced the five proposals that were presented. Dr. Dvorak emphasized that each proposal had 5 minutes for presentation and ~10 minutes for discussion. D. Dvorak outlined the voting process for the attendees, explaining that voting should be based both on scientific impact and feasibility using the CIBMTR data.

a. **2205-02** Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD) (E Ayala) (Attachment 4)

The proposal was presented by Dr. Ernesto Ayala. The objective of this study is to examine the results of AlloHCT in the treatment of MLD in a modern cohort. The CIBMTR identified 87 patients who underwent an HCT for Metachromatic Leukodystrophy (MLD) 2008-*2019. The following questions were answered during the Q&A:*

I. *A comment was made that there's a center that has a group focusing on MLD, it's crucial to have that neurological outcome data. This center does extensive neuro-psych testing, both before and after transplant. And just having survival really won't be that impactful in the field. These are very challenging patients to transplant. There are three types, and they can present with different degrees of neurological decline before the transplant. Would this study lend to the body of information that's already known about an MLD?*
II. *Dr. Broglie commented that there are a few questions on the forms about MRI findings and certain neurologic testing that has been done and didn't know how reliably these questions have been answered. These questions are on the CRF forms, and we have only 41 patients that would potentially have that information available.*
III. *A comment was made that this study may be important because gene therapy will be coming for these diseases. CIBMTR might be able to provide what has happened so far and how does it compare with upcoming gene therapy options. The commenter thought it would be doable from a neurological standpoint, and it may form a platform for comparison later.*
IV. *Dr. Gennery commented that Gene therapy is here. This is a rare condition and there were probably not many centers that are looking after these patients. It's worth thinking about talking to EBMT, because there'll be a population of patients in Europe*

as well. And that will just give you more patients and therefore, a greater chance of being able to answer the questions you're asking.

V. *I think this is an example of a study that is worst done by CIBMTR in that we don't have the detail that you want to give a meaningful report of whether the intervention was successful or not. You can put two or three centers together and get the best report in a totally way.*

VI. *Dr. Broglie added that if there are any centers that see a lot of these patients and partnering with them to obtain more neurologic data might be a better option than to using the CIBMTR data that is currently available. CIBMTR can always try to supplement information, each transplant center can request data on their own patients back to them. This might be an alternative especially if there's a lot of concern from the group about the neurologic outcomes.*

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)

The proposal was presented by Dr. Erman Elsabbagh. The primary objective of this study is to determine and compare 2-year EFS based on the presence of RBC alloimmunization and ABO matching between donor and recipient. The CIBMTR identified 1451 patients who underwent an HCT for SCD and TDT between 2008-2019. The following questions were answered during the Q&A:

I. *How will you define the events? Dr.* Elsabbagh responded that the study will use any graft vs host disease or any graft failures as events.

II. *How will the missing alloimmunization data will be handled? Dr. Broglie replied to the number of missing data needs to be considered when choosing the study. The CIBMTR has asked the question for patients but is not always answered on the forms. If the group decide that we want to move the study forward, then CIBMTR will try to go back to the centers to ask them to fill out that form, this process will take time and potentially the N will increase but we anticipate that there's still going to be missing data that we will have to consider in the analysis.*

III. *Is this a CRF data study? Dr. Broglie confirmed this is a CRF-level study.*

IV. *Do the forms collect information about the treatments for alloimmunization? Dr. Broglie replied that CIBMTR does not collect this type of information.*

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)

The proposal was presented by Dr. Ahmad Rayes. The principal objective of this study is to examine the 24-month cumulative incidence (CI) of GF and autoimmune cytopenia. 24 month of OS and EFS. The CIBMTR identified 957patients who underwent an HCT for Aplastic Anemia between 2008-2019, The following questions were answered during the Q&A:

I. *Does this study overlap with a previous study published in Blood Advances in 2019? The current proposal is a subset of the patients that were published in 2019. The study proposal presented has a new question but most of the questions that are being asked*

including 8/8 vs 7 /8 mismatched were already published. Dr. Rayes responded that it is true, and that what hasn't been published is an overlook to see if all these centers doing different regimens, how are they comparing to each other in a longer time, and then dissecting early versus modern or contemporary regimens, which happened after 2015.

II. *A comment was made that it's difficult to select patients based on no therapy at all. The proposal has patients that have received cyclosporine, others who have received no ATG, etc. How are you going to select patients without any kind of therapy? What will be the definition of an upfront transplant? Dr. Broglie responded that a way we would have to do it's to look at the three main questions. Was therapy given prior to transplant? Did they receive ATG? And the treatment with cyclosporine? The study will only include patients that said 'no' to each of those questions.*

d. **2210-131** Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia (N Gibson/J Oved) (Attachment 7)

The proposal was presented by Dr. Nora Gibson. The objective of this study is to examine how outcomes of HSCT for SCN are impacted by age, donor source, and graft source. The CIBMTR identified 87 patients who underwent an HCT for Kostmann Syndrome between 2008-2019.The following questions were answered during the Q&A:

I. *Dr. Broglie shared additional data of the conditioning regimens: 26 patients received Bu/Cy, 36 received Flu/Bu and other regimens that had less than 10 patients in each.*

II. *Do all these patients presumably not have MDS and AML? Dr. Gibson responded that their understanding of the preliminary data for the 87 patients, their primary indication for transplant was not MDS or AML but SCN.*

III. *A question was made based on the numbers that Dr. Broglie shared. The patients that received Flu/Bu, were they defined as myeloablative? Dr. Broglie replied that the committee did not get a chance to review these numbers and there's probably a mixture within there of myeloablative and reduced intensity. Another question was made, what was the cut-off for Bu/Cy that the study will use for myeloablative vs nonmyeloablative? Dr. Dvorak responded that there's a standard CIBMTR definition for Bu/Cy dose that has been worked through well and CIBMTR knows what the doses are. Dr. Broglie added that CIBMTR should have what will be the planned therapy or their Bu/Cy dosing. The data will have to be reviewed and categorized.*

IV. *A comment was made that there might be an opportunity to collaborate with the severe congenital neutropenia registry because of what one of the things the study would like to conclude is that the transplant would protect from the malignancy risk over the long term.*

V. *Do we collect data on the underlying genetic abnormalities in these patients? Dr. Broglie responded that CIBMTR does not collect information on the mutation leading to severe congenital neutropenia if it is written in the 'other specified' field CIBMTR may have it, but it's not consistent. CIBMTR do have in the instructions that if a patient has MDS or AML, even with this underlying disorder, they fill out the indication for transplant as MDS or AML. These should be non-MDS or AML patients with SCN.*

VI. *Why not include the category of those patients who have or who had evidence of AML or MDS as a variable to see if the outcome is different? Dr. Gibson replied that this could make sense and that the study is primarily looking at SCN.*

VII. *A suggestion was made to have the Flu/Bu separated one way or another from the Bu/Cy, because they're going to end up falling together in the same subcategory.*

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)

The proposal was presented by Dr. Maria Pereda and Dr. Madhavi Lakkaraja. The objective of this study is to examine Overall Survival at 1-year post-HCT. The CIBMTR identified 612 patients who underwent an HCT for Bone marrow failure syndromes, 439 for Immune dysregulation and HLH and 401 for Non-SCID primary immune deficiencies between 2008-2019. The following questions were answered during the Q&A:

I. *On the first slide, you showed a survey and people voted that they slightly preferred ex vivo T cell depletion Haplo over PTCy Haplo, why are you excluding them? Dr. Broglie replied that CIBMTR doesn't have enough data about alpha beta T cell depletion but has T cell depletion. The alpha beta information was not added until more recent years and the numbers are small.*

II. *A comment was made regarding the heterogeneity of the study. The diseases are so different that one donor source might wash each other out and going up to age 30 doesn't add many numbers but adds a lot of heterogeneity. By the time you've got all the different diseases, all the different donors with potential things going in different directions, not sure this study is going to get a strong answer out of this bucket. Dr. Lakkaraja replied that given that there are such rare non-malignant disorders, maybe they could put them in a combined proposal and maybe have a subgroup analysis that could be informative.*

III. *A comment was made on another issue that could be that just looking at survival may not be enough when some of these diseases may not be fully corrected, by transplant. Do we have data on whether the disease itself and the manifestation of the disease is corrected? Dr. Broglie replied that CIBMTR does not have the data.*

IV. *A comment was received that it's not just the donor source as the GVHD prophylaxis and it's the preoperative therapy, there's been a lot of change in our community about how we're transplanting these patients. When you look at all these aspects, it'd be so noisy to get a measure of the impact of a certain factor.*

V. *A suggestion was made that Fanconi and DKC should be removed because you cannot give PT Cy for those graphs.*

VI. *A suggestion was made to narrow the scope of the study.*

6. 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).*

7. Concluding Notes

a. Meeting adjourned at 2:24 pm.
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:
    a. **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)

c. The following proposals were not accepted as studies, for the reasons specified:
    a. **2205-02** Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD) (E Ayala). **Dropped due to feasibility and need for supplemental data.**
    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/). **Dropped due supplemental/additional data needed.**
    c. 2210-131 Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia (N Gibson/J Oved). **Dropped due supplemental/additional data needed.**

d. **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). **Dropped due to heterogeneity of the population.**

Working Committee Overview Plan 2023-2024		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic CellTransplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM16-03: Results of transplants from genetically- identical twin donors in persons with aplastic anemia	In Press	**3**
NM17-01: Late effects after hematopoietic stem celltransplantation in patients with HLH	Protocol Development	**3**
NM18-01: Impact of choice of serotherapy in pediatricstem 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 leastone year after alloHCT or immunosuppressive therapy	Submitted Manuscript	**1**
AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for SystemicSclerosis	Manuscript Preparation	**1**
NM20-01: Hematopoietic Stem Cell Transplantation forFanconi anemia	Protocol Development	**2**
NM22-01: Outcomes After Second or Greater AllogeneicStem Cell Transplants in Patients with Severe Aplastic Anemia: A Contemporary Analysis	Protocol Development	**2**
NM23-01: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant	Protocol Pending	**3**

Allogeneic Transplants for Immune Deficiencies reported to the CIBMTR from 2000-2023

Characteristic	TED N	CRF N	Total
No. of patients	4296	2995	7291
No. of centers	279	186	307
ALL subdisease (2400 Q174) - no. (%)			
Immune Deficiencies (ID), NOS	101 (2.4)	27 (0.9)	128 (1.8)
SCID ADA deficiency	80 (1.9)	104 (3.5)	184 (2.5)
SCID absence of T and B cells	164 (3.8)	199 (6.6)	363 (5.0)
SCID absence of T, normal B cell SCID	156 (3.6)	231 (7.7)	387 (5.3)
Omenn syndrome	83 (1.9)	98 (3.3)	181 (2.5)
Reticular dysgenesis	6 (0.1)	11 (0.4)	17 (0.2)
Bare lymphocyte syndrome	102 (2.4)	39 (1.3)	141 (1.9)
SCID, NOS	162 (3.8)	159 (5.3)	321 (4.4)
SCID other, specify	244 (5.7)	330 (11.0)	574 (7.9)
Wiskott Aldrich syndrome	310 (7.2)	320 (10.7)	630 (8.6)
DiGeorge anomaly	9 (0.2)	8 (0.3)	17 (0.2)
Chronic granulomatous disease	385 (9.0)	334 (11.1)	719 (9.9)
Chediak-Higashi syndrome	69 (1.6)	32 (1.1)	101 (1.4)
Common variable immunodef	75 (1.7)	35 (1.2)	110 (1.5)
X-linked lymphoproliferative syndrome	125 (2.9)	70 (2.3)	195 (2.7)
Leukocyte adhesion deficiencies	63 (1.5)	49 (1.6)	112 (1.5)
Kostmann agranulocytosis	130 (3.0)	54 (1.8)	184 (2.5)
Cartilage hair hypoplasia	45 (1.0)	24 (0.8)	69 (0.9)
TED Immune deficiency plus neutropenia	1 (0.0)	0 (0.0)	1 (0.0)
CD40 ligand deficiency	87 (2.0)	27 (0.9)	114 (1.6)
Griscelli syndrome type 2	23 (0.5)	12 (0.4)	35 (0.5)
Combined immunodef dis (CID), NOS	5 (0.1)	7 (0.2)	12 (0.2)
CID other, specify	1 (0.0)	16 (0.5)	17 (0.2)
Other immunodeficiencies, specify	733 (17.1)	203 (6.8)	936 (12.8)
Histiocytic disorder, NOS	26 (0.6)	6 (0.2)	32 (0.4)
FELH Familial erythrohemophagocytic lymphohis	871 (20.3)	430 (14.4)	1301 (17.8)
Langerhans Cell Histiocytosis	63 (1.5)	34 (1.1)	97 (1.3)
Hemophagocytosis	111 (2.6)	81 (2.7)	192 (2.6)
Malignant histiocytosis	15 (0.3)	2 (0.1)	17 (0.2)
Other histiocytic disord	51 (1.2)	53 (1.8)	104 (1.4)

Allogeneic Transplants for Inborn Errors of Metabolism reported to the CIBMTR from 2000-2023

Characteristic	TED N	CRF N	Total
No. of patients	1129	1058	2187
No. of centers	181	126	210
ALL subdisease (2400 Q174) - no. (%)			
Inherited disorders of metabolism, NOS	23 (2.0)	4 (0.4)	27 (1.2)
Osteopetrosis	224 (19.8)	134 (12.7)	358 (16.4)
Lesch-Nyhan(HGPTR defic)	0 (0.0)	2 (0.2)	2 (0.1)
Neuronal ceroid lipofuscinosis	3 (0.3)	5 (0.5)	8 (0.4)
Other inherited metabolism disorders, specify	67 (5.9)	36 (3.4)	103 (4.7)
Mucopolysaccharidosis, NOS	12 (1.1)	7 (0.7)	19 (0.9)
IH Hurler syndrome	260 (23.0)	341 (32.2)	601 (27.5)
IS Scheie syndrome	2 (0.2)	0 (0.0)	2 (0.1)
II Hunter syndrome	25 (2.2)	26 (2.5)	51 (2.3)
III Sanfillippo	7 (0.6)	26 (2.5)	33 (1.5)
IV Morquio	3 (0.3)	0 (0.0)	3 (0.1)
VI Maroteaux-Lamy	18 (1.6)	25 (2.4)	43 (2.0)
VII B-glucuronidase deficiency	1 (0.1)	1 (0.1)	2 (0.1)
V Mucopolysaccharidosis	6 (0.5)	3 (0.3)	9 (0.4)
Other mucopolysaccharidosis	1 (0.1)	3 (0.3)	4 (0.2)
Mucolipidoses, NOS	1 (0.1)	3 (0.3)	4 (0.2)
Gaucher disease	10 (0.9)	4 (0.4)	14 (0.6)
Metachromatic leukodystrophy(MLD)	98 (8.7)	86 (8.1)	184 (8.4)
Adrenoleukodystrophy(ALD)	256 (22.7)	227 (21.5)	483 (22.1)
Globoid leukodystrophy/Krabbe disease	50 (4.4)	76 (7.2)	126 (5.8)
Neiman-Pick disease	11 (1.0)	12 (1.1)	23 (1.1)
I-cell disease	9 (0.8)	15 (1.4)	24 (1.1)
Wolman disease	7 (0.6)	6 (0.6)	13 (0.6)
Glucose storage disease	1 (0.1)	0 (0.0)	1 (0.0)
Other mucolipidoses	0 (0.0)	1 (0.1)	1 (0.0)
Asparty1 glucosaminuria	3 (0.3)	0 (0.0)	3 (0.1)
Fucosidosis	4 (0.4)	5 (0.5)	9 (0.4)
Mannosidosis	27 (2.4)	10 (0.9)	37 (1.7)

Allogeneic Transplants for non-malignant disorders reported to the CIBMTR from from 2000-2023

Characteristic	TED N	CRF N	Total
No. of patients	10300	8173	18473
No. of centers	452	342	489
ALL subdisease (2400 Q174) - no. (%)			
PNH Proxysmal nocturnal hemoglobinuria	284 (2.8)	201 (2.5)	485 (2.6)
NHL diffuse, large B-cell	0 (0.0)	1 (0.0)	1 (0.0)
Severe aplastic anemia unknown (095CORE)	556 (5.4)	26 (0.3)	582 (3.2)
Acquired Severe Aplastic Anemia, NOS	4980 (48.3)	4229 (51.7)	9209 (49.9)
SAA secondary to hepatitis	260 (2.5)	199 (2.4)	459 (2.5)
SAA secondary to toxin-other	71 (0.7)	90 (1.1)	161 (0.9)
Amegakaryocytosis(not congenital)	16 (0.2)	14 (0.2)	30 (0.2)
Schwachmann-Diamond	43 (0.4)	35 (0.4)	78 (0.4)
Acquired Pure Red Cell Aplasia	68 (0.7)	48 (0.6)	116 (0.6)
Dyskeratosis congenital	37 (0.4)	43 (0.5)	80 (0.4)
Other acquired cytopenic syndrome, specify	171 (1.7)	150 (1.8)	321 (1.7)
Inherited abnormal of erythrocyte differ, NOS	8 (0.1)	10 (0.1)	18 (0.1)
Fanconi anemia	744 (7.2)	757 (9.3)	1501 (8.1)
Diamond-Blackfan anemia (pure red cell aplasia)	196 (1.9)	145 (1.8)	341 (1.8)
Other constitutional anemia (not THALs)	114 (1.1)	64 (0.8)	178 (1.0)
Thalassemia, NOS	1215 (11.8)	478 (5.8)	1693 (9.2)
095 Type B+ Thalassemia major	6 (0.1)	1 (0.0)	7 (0.0)
095 Type B0 Thalassemia major	0 (0.0)	1 (0.0)	1 (0.0)
Sickle Thalassemia major	44 (0.4)	70 (0.9)	114 (0.6)
Sickle cell anemia	1026 (10.0)	907 (11.1)	1933 (10.5)
Beta thalassemia major	400 (3.9)	659 (8.1)	1059 (5.7)
Other hemoglobinopathy, specify	57 (0.6)	41 (0.5)	98 (0.5)
Not reported	4 (0.0)	4 (0.0)	8 (0.0)

Autologous Transplants for autoimmune diseases reported to the CIBMTR from from 2000-2023

Characteristic	TED N	CRF N	Total
No. of patients	1577	106	1683

Characteristic	TED N	CRF N	Total
No. of centers	118	43	131
ALL subdisease (2400 Q174) - no. (%)			
Autoimmune disease unclassified	24 (1.5)	0 (0.0)	24 (1.4)
Myasthenia gravis	20 (1.3)	1 (0.9)	21 (1.2)
Multiple sclerosis	1041 (66.0)	49 (46.2)	1090 (64.8)
Rheumatoid arthritis	6 (0.4)	3 (2.8)	9 (0.5)
Psoriatic arthritis or psoriasis	0 (0.0)	1 (0.9)	1 (0.1)
Systemic lupus erythematosis (SLE)	51 (3.2)	9 (8.5)	60 (3.6)
Polymyositis-dermatomyositis	6 (0.4)	0 (0.0)	6 (0.4)
System Scleroderma	276 (17.5)	30 (28.3)	306 (18.2)
Antiphospholipid syndrome	6 (0.4)	0 (0.0)	6 (0.4)
Other autoimmune disease, specify	19 (1.2)	0 (0.0)	19 (1.1)
Other arthritis, spec	2 (0.1)	0 (0.0)	2 (0.1)
Other Connective tissue dis	10 (0.6)	0 (0.0)	10 (0.6)
Churg-Strauss	1 (0.1)	0 (0.0)	1 (0.1)
Behcets Syndrome	2 (0.1)	0 (0.0)	2 (0.1)
JIA systemic	2 (0.1)	0 (0.0)	2 (0.1)
JIA Other, specify	1 (0.1)	0 (0.0)	1 (0.1)
Other neuro disorder, spec	48 (3.0)	7 (6.6)	55 (3.3)
ITP- Idiopathic thrombocytopenic purpura	2 (0.1)	2 (1.9)	4 (0.2)
Hemolytic anemia	1 (0.1)	0 (0.0)	1 (0.1)
Evan syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Crohns disease	56 (3.6)	3 (2.8)	59 (3.5)
Other bowel disorder, spec	1 (0.1)	1 (0.9)	2 (0.1)
Diabetes mellitustype I	1 (0.1)	0 (0.0)	1 (0.1)

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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.**

NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH (N Bhatt/KS Baker/R Marsh/J Talano) 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. The protocol has been undergone some updates to ensure homogeneity in disease and treatment approaches and the datafile is partially completed. **Protocol development is underway.**

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 study has completed analysis and the results presented at the American Society of Hematology Conference this past December. **The study is in manuscript preparation.**

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. Supplemental data collected and analysis complete. Study presented in 2021 and Manuscript **preparation is in progress.**

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.**

NM23-01: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (R Ahmad/O Salman). The study has 2 aims: 1) to assess rates of graft failure in patients receiving upfront alternative donor transplant, compared to those who receive transplant as salvage therapy, and 2) to assess outcomes using increased intensity regimens (Flu/Cy/ATG/TBI) for mismatched (related and unrelated) alternative donor transplantation. **The protocol is under development.**

Field	Response
Proposal Number	2309-09-KOO
Proposal Title	Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes
Key Words	inherited bone marrow failure syndrome, primary graft failure, secondary graft failure, hematopoietic stem cell transplant
Principal Investigator #1: - First and last name, degree(s)	Jane Koo, MD
Principal Investigator #1: - Email address	jane.koo@cchmc.org
Principal Investigator #1: - Institution name	Cincinnati Children's Hospital Medical Center
Principal Investigator #1: - Academic rank	Assistant Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Anthony Sabulski, MD
Principal Investigator #2 (If applicable): - Email address:)	anthony.sabulski@cchmc.org
Principal Investigator #2 (If applicable): - Institution name:	Cincinnati Children's Hospital Medical Center
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
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:	Jane Koo
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Larisa Broglie, MD (also discussed having Kasiani Myers, MD as the senior mentor on this study)

Field	Response
RESEARCH QUESTION:	What are the outcomes for patients with inherited bone marrow failure syndromes (IBMFS) who complete second allogeneic hematopoietic stem cell transplantation (HSCT) for graft failure?
RESEARCH HYPOTHESIS:	IBMFS patients who undergo second allo-HSCT for graft failure have different outcomes across primary diagnoses and these differences may guide clinical approaches to retransplantation in this population.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Aims: • To compare the overall survival (OS) and event-free survival (EFS) for patients with IBMFS who completed second allo-HSCT at 100 days, 6 months, 1-year, 2 years, 5 years and >5 years following HSCT Secondary Aims: • To determine the incidence of primary graft failure in IBMFS patients who completed first allo-HSCT • To evaluate the incidence of secondary graft failure in IBMFS patients who completed first allo-HSCT • To evaluate the patterns of neutrophil and platelet engraftment in IBMFS patients who completed second allo-HSCT • To evaluate the incidence of acute graft-vs-host-disease (aGVHD) and chronic GVHD (cGVHD) in IBMFS patients who completed second allo-HSCT • To evaluate the incidence of veno-occlusive disease (VOD) in IBMFS patients who completed second allo-HSCT for graft failure • To compare the frequency of mixed chimerism between the IBMFS patients who completed second allo-HSCT for graft failure • To evaluate the incidence of clinically significant infections in IBMFS patients who completed second allo-HSCT for graft failure • To determine the incidence and types of post-transplant malignancy after the 2nd allo-HSCT

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Published outcomes for second allo-HSCT in patients with IBMFS are diagnosis-specific and limited which restrict our ability to optimize and tailor second transplant strategies in this unique yet diverse population of patients. Our proposed study would be the first and largest comparative study to evaluate transplant outcomes in patients with IBMFS who completed second allo-HSCT for primary and secondary graft failure. Results from this study would inform us about specific treatment-related and disease risk factors in patients with IBMFS who suffered graft failure after their first allo-HSCT. For example, this study would evaluate whether conditioning regimen intensity, stem cell source, graft manipulation, graft versus host disease (GvHD) prophylaxis regimen, stem cell dose and time to retransplantation contribute to graft failure risk to equally across patients with different IBMFS diagnoses. This study would provide novel information on disease and treatment-related variables that need to be considered in IBMFS patients who require second allo-HSCT for graft failure.

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.	Allo-HSCT is a potentially curative treatment for patients with hematologic malignancies and non-malignant diseases. This is especially true for patients with IBMFS who develop bone marrow failure, including patients with Fanconi Anemia (FA), Dyskeratosis Congenita (DC), Shwachman Diamond Syndrome (SDS) and Diamond Blackfan Anemia (DBA)1. Conditioning regimen intensity limitations and graft manipulation strategies mitigate transplant-related toxicity in IBMFS patients and have dramatically improved HSCT outcomes2-5. However, these toxicity-sparing interventions significantly increase the risk of graft failure after HSCT, which must be addressed. Graft failure is a rare but significant life-threatening complication of allo-HSCT that has limited potential interventions and frequently requires retransplantation. Immune-mediated graft failure, also termed graft rejection, involves an intricate and poorly understood harmony of T-cell, NK-cell, and antibody interactions between donor and recipient cells6,7. The exact mechanism of immune-mediated graft failure is not known but is thought to be distinct from graft failure that occurs after an inadequate stem cell dose. HLA mismatch, ABO mismatch, ex vivo T cell depletion, and reduced intensity conditioning are known graft failure risk factors which makes graft failure highly relevant to IBMFS patients8,9. A prior study by our group identified fever kinetics and a triad of cytokines as novel biomarkers for immune-mediated graft failure in BMF patients which has increased our ability to detect graft failure and provided insight on potential targeted interventions10. Graft failure is also notably more common in patients with non-malignant disorders8. Successful second transplant can occur, but is frequently limited by donor availability and the underlying physical condition of the patient. This is especially true for patients with IBMFS as they are uniquely sensitive to treatment-related toxicity due to underlying defects in DNA repair. Time to second transplantation predicted subsequent episodes of graft failure and survival in a cohort of patients with FA who completed second allo-HSCT11. Graft failure rates in this study were higher in patients with FA when the second transplant occurred less than three months than the first transplant11. While data on second allo-HSCT exists for patients with FA, the study published by Ayas M et al's study was published in 2015 and transplant-related practices and supportive care procedures have evolved in the past decade. A significant gap in knowledge therefore exists due to the absence of published large cohort data that evaluate second allo-HSCT outcomes in patients with IBMFS who suffered graft failure. There is a critical need to understand the clinical variables and mechanisms

Field	Response
	that contribute to higher graft failure rates in patients with IBMFS in order to develop strategies to effectively reduce graft failure rates in this group.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	VI. Participant Selection Criteria: A. Inclusion Criteria: a. Patient must have primary diagnosis of inherited bone marrow failure syndromes (IBMFS): i. Fanconi Anemia (FA) ii. Dyskeratosis Congenita (DC) iii. Shwachman-Diamond Syndrome (SDS) iv. Diamond Blackfan Anemia (DBA) v. Other inherited marrow failures including severe congenital neutropenia (SCN), congenital sideroblastic anemia, and congenital dyserythropoietic anemia, Pearson syndrome, Thrombocytopenia Absent Radii (TAR), Amegakaryocytic thrombocytopenia vi. Patients with underlying IBMFS and a malignancy (such as AML) who develop graft failure following first HSCT are eligible b. Patient must have completed second allo-HSCT for primary or secondary graft failure between 1990 and 2022 c. Patients who underwent second allo-HSCT for poor graft function will be included but will be analyzed separately B. Exclusion Criteria: a. Patients who underwent second HSCT for relapse of their original malignancy i. This does not include patients with an IBMFS who develops malignancy who went for subsequent transplant for graft failure. b. Patients diagnosed with idiopathic aplastic anemia c. Patients diagnosed with paroxysmal nocturnal hemoglobinuria d. Patients with underlying malignancy diagnoses who proceeded to additional HSCT for relapse
Does this study include pediatric patients?	Yes

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Data Requirements: a. Outcomes to be compared between the primary IBMFS diagnoses who completed second allo-HSCT for IBMFS: • Graft failure: Primary and secondary graft failure will be defined as outlined in the consensus definitions12: o Primary Graft Failure For peripheral blood stem cell (PBSC): Lack of achievement of an absolute neutrophil count (ANC) ≥500/µL by day +30 with associated pancytopenia. For bone marrow (BM): lack of achievement of ANC≥500/µL by day +30 with associated pancytopenia. For umbilical cord blood (UCB): lack of achievement of ≥500/µL by day +42 with associated pancytopenia. o Secondary graft failure A decline in hematopoietic function (either involving hemoglobin and/or platelets and/or neutrophils) necessitating blood products or growth factor support after having met the standard definitions of neutrophil and platelet engraftment (detailed below). • Neutrophil engraftment: Neutrophil engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count ≥ 500/mm3 • Platelet engraftment: Platelet engraftment is defined as the first of 7 consecutive days with an absolute platelet count of ≥ 20 x 109/L with no transfusions in the prior 7 days. • Acute graft-vs-host disease (aGVHD)): Incidence of grade II-IV aGVHD and time to diagnosis of grade II-IV aGVHD. • Chronic graft-vs-host disease (cGVHD): Incidence of cGVHD and time to diagnosis of cGVHD. • Veno-occlusive disease (VOD)/Sinusoidal obstruction syndrome (SOS): Incidence of VOD/SOS and time to diagnosis of VOD/SOS • Infection: Time to diagnosis of clinically significant infection, organism/site of infection will be recorded for each patient. • Primary and secondary graft failure: Incidence of primary and secondary graft failure and time to diagnosis of primary and secondary graft failure after second allo-HSCT • Poor graft function: Incidence of poor graft function after second allo-HSCT • Mixed chimerism: Incidence of mixed chimerism. Mixed chimerism defined as whole blood chimerism <95% donor. Chimerism studies will be compared at day 100, 6 months, 1-year, 2-years and >2 years post-HSCT. • Overall survival (OS): Time to death, patients will be censored at last follow-up. We will compare OS between patients who received MAC vs RIC regimens at day 100, 6 months, 1-year and 2-years and >2 years after HSCT. • Event-free survival (EFS): Time to graft loss, relapse, malignancy or second transplant. We will compare EFS between patients who

	received MAC vs RIC regimens at day 100, 6 months, 1-year, 2-years, 5 years and >5 years after HSCT. • Post-transplant malignancy: Time to diagnosis from 2nd allo-HSCT, malignancy diagnosis, OS and EFS at 1-year, 2-years, 5-years from malignancy diagnosis b. Patient-related variables i. Primary diagnosis: 1. Fanconi Anemia 2. Dyskeratosis Congenita 3. Shwachman Diamond Syndrome 4. Diamond Blackfan Anemia 5. Other IBMFS: Other inherited marrow failures including: severe congenital neutropenia (SCN), congenital sideroblastic anemia, and congenital dyserythropoietic anemia, Pearson syndrome, Thrombocytopenia Absent Radii (TAR), Amegakaryocytic thrombocytopenia ii. Sex: male vs female iii. Disease status at time of transplant c. Transplant related variables for second transplant: i. Year of second transplant ii. Time to second transplant 1. <3 months vs >3 months iii. Donor type: HLA-matched sibling, haploidentical relative, unrelated donor iv. Degree of HLA match v. Sex-match, recipient-donor: female-female, female-male, male-female, male-male vi. Different Donor from first HSCT: yes or no vii. CMV status, recipient donor: -/-; -/+; +/-; +/+ viii. Stem cell source: bone marrow, peripheral blood, cord blood ix. Stem cell dose (CD34+ cells/kg) x. Cryopreservation or fresh stem cell product xi. GVHD prophylaxis for second allo-HSCT xii. Conditioning regimen for second allo-HSCT: myeloablative or reduced intensity. Regimen intensity was classified as myeloablative or reduced intensity. Myeloablation was defined as busulfan dose >8 mg/kg or melphalan dose >140 mg/m2 or thiotepa dose >10mg/kg or total body irradiation (fractionated) ≥1000 cGy. All other regimens were considered reduced intensity. xiii. Radiation: Yes vs No xiv. Chimerism: full, mixed xv. Follow-up time (months) xvi. Survival status at the end of the reporting period xvii. Cause of death if applicable xviii. Post-transplant malignancy: 1. Time to diagnosis 2. Type of malignancy d. Transplant related variables for first transplant: i. Year of transplant ii. Time to transplant iii. Donor type: HLA-matched sibling, haploidentical relative, unrelated donor iv. Degree of HLA match v. Sex-match,

Field	Response
	recipient-donor: female-female, female-male, male-female, male-male vi. CMV status, recipient donor: -/-; -/+; +/-; +/+ vii. Stem cell source: bone marrow, peripheral blood, cord blood viii. GVHD prophylaxis ix. Conditioning regimen for first allo-HSCT: myeloablative or reduced intensity. Regimen intensity was classified as myeloablative or reduced intensity. Myeloablation was defined as busulfan dose >8 mg/kg or melphalan dose >140 mg/m2 or thiotepa dose >10mg/kg or total body irradiation (fractionated) ≥1000 cGy. All other regimens were considered reduced intensity. x. Radiation: Yes vs No
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 desc	No
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	None
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.	None

REFERENCES:	1. Peffault de Latour R, Peters C, Gibson B, et al. Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. Bone Marrow Transplant. 2015;50(9):1168-1172. 2. Myers K, Hebert K, Antin J, et al. Hematopoietic Stem Cell Transplantation for Shwachman-Diamond Syndrome. Biol Blood Marrow Transplant. 2020;26(8):1446-1451. 3. Nichele S, Bonfim C, Junior LGD, et al. Hematopoietic cell transplantation for telomere biology diseases: A retrospective single-center cohort study. Eur J Haematol. 2023;111(3):423-431. 4. Mehta P, Locatelli F, Stary J, Smith FO. Bone marrow transplantation for inherited bone marrow failure syndromes. Pediatr Clin North Am. 2010;57(1):147-170. 5. Diaz-de-Heredia C, Bresters D, Faulkner L, et al. Recommendations on hematopoietic stem cell transplantation for patients with Diamond-Blackfan anemia. On behalf of the Pediatric Diseases and Severe Aplastic Anemia Working Parties of the EBMT. Bone Marrow Transplant. 2021;56(12):2956-2963. 6. Kiessling R, Hochman PS, Haller O, Shearer GM, Wigzell H, Cudkowicz G. Evidence for a similar or common mechanism for natural killer cell activity and resistance to hemopoietic grafts. Eur J Immunol. 1977;7(9):655-663. 7. Murphy WJ, Kumar V, Bennett M. Acute rejection of murine bone marrow allografts by natural killer cells and T cells. Differences in kinetics and target antigens recognized. J Exp Med. 1987;166(5):1499-1509. 8. Olsson R, Remberger M, Schaffer M, Berggren DM, Svahn BM, Mattsson J, Ringden O. Graft failure in the modern era of allogeneic hematopoietic SCT. Bone Marrow Transplant. 2013;48(4):537-543. 9. Mattsson J, Ringden O, Storb R. Graft failure after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2008;14(1 Suppl 1):165-170. 10. Sabulski A, Myers KC, Duell A, Lane A, Teusink-Cross A, Davies SM, Jodele S. Graft Rejection Markers in Children Undergoing Hematopoietic Cell Transplant for Bone Marrow Failure. Blood Adv. 2021. 11. Ayas M, Eapen M, Le-Rademacher J, et al. Second Allogeneic Hematopoietic Cell Transplantation for Patients with Fanconi Anemia and Bone Marrow Failure. Biol Blood Marrow Transplant. 2015;21(10):1790-1795. 12. Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf

Field	Response
	of the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2021;27(8):642-649.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Proposal 2309-09: Characteristics of Patients with Graft Failure Undergoing Second AlloHCT for Inherited Bone Marrow Failure from 2000-2021 reported to CIBMTR

Characteristic	N (%)
No. of patients	227
Patient Related	
Recipient age - no. (%)	
Median (min-max)	8.6 (0.8-39.5)
0-5	52 (22.9)
5-10	91 (40.1)
10-18	58 (25.6)
>=18	26 (11.5)
Treatment Related	
Sex - no. (%)	
male	131 (57.7)
female	95 (41.9)
not reported	1 (0.4)
type of bone marrow failure - no. (%)	
Schwachmann-Diamond:	10 (4.4)
Dyskeratosis congenital:	14 (6.2)
Fanconi anemia:	144 (63.4)
Diamond-Blackfan anemia (pure red cell aplasia):	24 (10.6)
Kostmann agranulocytosis:	35 (15.4)
Donor type - no. (%)	
HLA-identical sibling	48 (21.1)
Other related	52 (22.9)
Well-matched unrelated (8/8)	41 (18.1)
Partially-matched unrelated (7/8)	22 (9.7)
Mis-matched unrelated (<= 6/8)	3 (1.3)
Multi-donor	4 (1.8)
Unrelated (matching TBD)	21 (9.3)
Cord blood	35 (15.4)
Not reported	1 (0.4)
Conditioning intensity as designated by center - no. (%)	
RIC / Non-Myeloablative	91 (40.1)
Myeloablative	89 (39.2)
Unknown	47 (20.7)
Conditioning regimen - no. (%)	
TBI/Cy	5 (2.2)

Characteristic	N (%)
TBI/Cy/Flu	27 (11.9)
TBI/Cy/Flu/TT	1 (0.4)
TBI/Cy/TT	1 (0.4)
TBI/Mel	1 (0.4)
TBI/Flu	23 (10.1)
TBI/other(s)	12 (5.3)
Bu/Cy	9 (4.0)
Flu/Bu/TT	1 (0.4)
Flu/Bu	7 (3.1)
Flu/Mel/TT	3 (1.3)
Flu/Mel	5 (2.2)
FCR	1 (0.4)
Cy/Flu	24 (10.6)
Cy alone	5 (2.2)
Treosulfan	1 (0.4)
TLI	1 (0.4)
Other(s)	43 (18.9)
None	30 (13.2)
Missing	27 (11.9)
GVHD prophylaxis - no. (%)	
None	22 (9.7)
Ex-vivo T-cell depletion	9 (4.0)
CD34 selection	35 (15.4)
PtCy + other(s)	17 (7.5)
TAC + MMF +- other(s) (except PtCy)	13 (5.7)
TAC + MTX +- other(s) (except MMF, PtCy)	9 (4.0)
TAC + other(s) (except MMF, MTX, PtCy)	4 (1.8)
TAC alone	8 (3.5)
CSA + MMF +- other(s) (except PtCy,TAC)	18 (7.9)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	19 (8.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	20 (8.8)
CSA alone	26 (11.5)
Other(s)	3 (1.3)
Missing	24 (10.6)
TED or RES track - no. (%)	
Ted (registration) patient	93 (41.0)
cRF (Research) patient	119 (52.4)
cRF changed to Ted track	6 (2.6)

Characteristic	**N (%)**
Ted change to CRF patient for FN2	9 (4.0)
Year of transplant - no. (%)	
2000-2009	123 (54.2)
2010-2021	104 (45.8)
Follow-up, months - median (range)	70.0 (0.0-221.0)

Field	Response
Proposal Number	2309-12-KOO
Proposal Title	A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders
Key Words	telomere biology disorder, myeloablative, reduced-intensity, hematopoietic stem cell transplant
Principal Investigator #1: - First and last name, degree(s)	Jane Koo, MD
Principal Investigator #1: - Email address	jane.koo@cchmc.org
Principal Investigator #1: - Institution name	Cincinnati Children's Hospital Medical Center
Principal Investigator #1: - Academic rank	Assistant Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Kasiani Myers, MD
Principal Investigator #2 (If applicable): - Email address:)	kasiani.myers@cchmc.org
Principal Investigator #2 (If applicable): - Institution name:	Cincinnati Children's Hospital Medical Center
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Jane Koo
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Larisa Broglie, MD

Field	Response
RESEARCH QUESTION:	Are outcomes for transplanted for Telomere Biology Disorders (TBDs) patients equivalent for those patients who receive reduced toxicity or reduced intensity conditioning (RIC)/non-myeloablative (NMA) regimens compared to patients who receive myeloablative conditioning (MAC) regimens?
RESEARCH HYPOTHESIS:	Outcomes for patients with TBD who completed allogeneic hematopoietic stem cell transplant (allo-HSCT) using RIC/NMA regimens are superior to to outcomes for patients with TBD who underwent HSCT utilizing MAC regimens.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Aims: • To compare the overall survival (OS) and event-free survival (EFS) between transplanted patients with TBDs who received MAC vs RIC/NMA regimens at day 100, 6 months, 1-year, 2-years and >2 years following HSCT. o To compare outcomes in transplanted patients with TBD who received MAC vs RIC/NMA regimens in the different eras of transplant (1990 to 1997, 1998 to 2005 and 2006 to 2022) • To compare the rates of primary and secondary graft failure between transplanted patients with TBDs who received MAC vs reduced toxicity/RIC regimens o Also, to compare outcomes in transplanted patients with TBD who received MAC vs RIC/NMA regimens in the different eras of transplant (1990 to 1997, 1998 to 2005 and 2006 to 2022) Secondary Aims: • To compare the patterns of neutrophil and platelet engraftment between transplanted patients with TBDs who received MAC vs reduced toxicity/RIC regimens • To compare the incidence of aGVHD and cGVHD between transplanted patients with TBDs who received MAC vs RIC regimens • To compare the incidence of veno-occlusive disease (VOD) between TBD transplanted patients who received MAC vs reduced toxicity/RIC regimens • To compare the frequency of mixed chimerism between transplanted patients with TBD who received MAC vs RIC/NMA regimens • To compare the incidence of primary and secondary graft failure between transplanted patients with TBD who received MAC vs RIC/NMA regimens • To compare the incidence of clinically significant infections between transplanted patients with DC who received MAC vs RIC/NMA regimens. • To compare pulmonary function between transplanted patients with TBD who received MAC vs RIC/NMA regimens • To compare liver function and issues between transplanted patients with TBD who received MAC vs RIC/NMA regimens • To compare the incidence of secondary malignancies between transplanted patients with TBD who received MAC vs RIC/NMA regimens

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	There is no standardized consensus on the best conditioning regimen for patients transplanted for bone marrow failure in patients with TBDs. Results from this study would be the largest comparative study analyzing outcomes of transplanted patients with TBDs who received RIC or NMA regimens. Results from this study would inform us about additional disease and treatment-related risk factors that need to be considered to determine the ideal conditioning regimen for use in allogeneic HSCTs for patients with TBDs. Longer follow-up of patients with TBD who have completed HSCT will guide future treatment protocols and research.

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.	Telomere Biology Disorders (TBDs) encompass a group of disorders caused by germline pathogenic variants in genes involved in repair and maintenance of telomeres1. Dyskeratosis congenita (DC) is the prototypical TBD2. TBDs are cancer predisposition syndromes and can present with bone marrow failure (BMF), lung and liver diseases. Patients with DC have very short telomeres resulting from various mutations in telomere biology genes, including DKC1, TERC, TERT and RTEL13,4. Patients with TBDs are at risk for BMF, myelodysplastic syndrome (MDS)/leukemia and other types of cancers5. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for severe BMF or MDS/leukemia in these patients6,7. While HSCT repairs the underlying hematopoietic stem cell defect, it does not alter the other multisystemic features of the disease including pulmonary fibrosis and liver cirrhosis8,9. HSCT outcomes for patients with DC have been historically poor, especially with the use of myeloablative conditioning regimens10,11. Complications from HSCT in patients with DC include graft failure, graft-vs-host-disease, VOD/SOS or liver cirrhosis. Increasingly in the last decade, RIC regimens have been used increasingly and more readily at institutions with improvement in overall outcomes for DC9,12-19. Some of these studies report the successful use of fludarabine-based approaches, while others report outcomes using radiation-containing conditioning regimens13,19. However, the ideal conditioning regimen that optimizes engraftment and long-term survival, while minimizing organ toxicity for patients with TBD is yet to be determined. Most of the data on survival and outcomes for patients with TBD following HSCT are limited to small, single-center retrospective cohort studies11,13-20. To date there have been two larger retrospective studies examining the outcome of HSCT in patients with DC specifically21,22. In the study completed by Gadalla SM et al, the authors used data acquired from the CIBMTR database to describe the outcomes of 34 patients with DC who underwent transplantation between 1981 and 2009. They found transplantation regimen intensity and mismatched donors attributed to early mortality and pulmonary complications attributed to late mortality22. Additionally, Fioredda F et al described data accumulated from the databases of the Severe Aplastic Anaemia Working Party (SAAWP), European Blood and Marrow Transplantation (EBMT) and European Working Group of Myelodysplastic Syndrome of Childhood (EWOG-MDS) from first transplants completed in patients (n=94) with DC between 1979 and 2015. This study primarily focused only on patients who received

Field	Response
	NMA regimens. This study showed HLA matched transplants and patients younger than 20 years old21. Since both of these studies have been published, further data has been published which has looked at outcomes of patients with TBD and using RIC regimens. Additionally, these studies focused primarily on patients with a confirmed diagnosis of DC11,13,17,20,21. More recent and comprehensive studies incorporating updated data on patients treated using RIC regimens are required to compare transplant-related outcomes for patients with TBD who undergo allo-HSCT.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion Criteria: • Patients who received allo-HSCT for TBD as diagnosed by their treating physician transplanted between 1990 and 2022 Exclusion Criteria: • Previous allogeneic or autologous stem cell transplant • Patients with other constitutional bone marrow failure syndromes • Patients with idiopathic aplastic anemia • Patients with bone marrow failure or aplastic anemia resulting from an environmental agent • Patient with diagnosis of paroxysmal nocturnal hemoglobinuria
Does this study include pediatric patients?	Yes

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	7. Data Requirements: 7.1. Outcomes to be compared between transplanted patients with TBD who received MAC vs RIC/NMA regimens • Telomere Biology Disorder: As recorded in the pre-HSCT baseline CIBMTR forms, the patient must have a diagnosis of Dyskeratosis congenita. We will include patients that had confirmed TERC/TERT positive gene testing. To broadly include patients with TBD we will also include DC patients with negative and unknown TERC/TERT testing with bone marrow failure and completed HSCT • Neutrophil engraftment: Neutrophil engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count ≥ 500/mm3 • Platelet engraftment: Platelet engraftment is defined as the first of 7 consecutive days with an absolute platelet count of ≥ 20 x 109/L with no transfusions in the prior 7 days. • Acute graft-vs-host disease (aGVHD): Incidence of grade II-IV aGVHD and time to diagnosis of grade II-IV aGVHD. • Chronic graft-vs-host disease (cGVHD): Incidence of cGVHD and time to diagnosis of cGVHD. • Veno-occlusive disease (VOD)/Sinusoidal obstruction syndrome (SOS): Incidence of VOD/SOS and time to diagnosis of VOD/SOS • Infection: Time to diagnosis of clinically significant infection, organism/site of infection will be recorded for each patient. • Primary and secondary graft failure: Incidence of primary and secondary graft failure and time to diagnosis of primary and secondary graft failure. • Mixed chimerism: Incidence of mixed chimerism. Mixed chimerism defined as whole blood chimerism <95% donor. Chimerism studies will be compared at day 100, 6 months, 1-year, 2-years and >2 years post-HSCT. • Overall survival (OS): Time to death, patients will be censored at last follow-up. We will compare OS between patients who received MAC vs RIC regimens at day 100, 6 months, 1-year and 2-years and >2 years after HSCT. • Event-free survival (EFS): Time to graft loss, relapse, malignancy or second transplant. We will compare EFS between patients who received MAC vs RIC regimens at day 100, 6 months, 1-year, 2-years and >2 years after HSCT. • Pre-transplant and post-transplant lung abnormalities: NIH lung scores, pulmonary function testing (FEV1%), causes of lung abnormalities (including lung fibrosis, lung parenchymal disease) • Pre-transplant and post-transplant liver abnormalities: NIH liver scores, causes of liver abnormalities (including abdominal ultrasonography, computed tomography scan and hepatic profile) • Post-transplant malignancies: Incidence and

Field	Response
	types of malignancy will be evaluated at 1-year, 2-years and >2 years after HSCT 7.2. Patient-related variables • Age at transplant (continuous) • Sex: male vs. female • Disease status at time of HSCT o History of androgen use 7.3. Transplant related variables • Year of transplant • Donor type: HLA-matched sibling, haploidentical relative, unrelated donor • Degree of HLA match • Sex-match, recipient-donor: female-female, female-male, male-female, male-male • CMV status, recipient donor: -/-; -/+; +/-; +/+ • Stem cell source: bone marrow, peripheral blood, cord blood • GVHD prophylaxis • Conditioning regimen: myeloablative or reduced intensity. Regimen intensity was classified as myeloablative or reduced intensity. Myeloablation was defined as busulfan dose >8 mg/kg or melphalan dose >140 mg/m2 or thiotepa dose >10mg/kg or total body irradiation (fractionated) ≥1000 cGy. All other regimens were considered reduced intensity. • Chimerism: full, mixed • Follow-up time (months) • Pulmonary function: pre-HSCT and post-HSCT • Liver function: pre-HSCT and post-HSCT • Malignancy diagnosis • Survival status at the end of the reporting period • Cause of death if applicable
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 desc	No
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	None
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.	None

REFERENCES:	11. References: 1. Armando RG, Mengual Gomez DL, Maggio J, Sanmartin MC, Gomez DE. Telomeropathies: Etiology, diagnosis, treatment and follow-up. Ethical and legal considerations. Clin Genet. 2019;96(1):3-16. 2. Sarek G, Marzec P, Margalef P, Boulton SJ. Molecular basis of telomere dysfunction in human genetic diseases. Nat Struct Mol Biol. 2015;22(11):867-874. 3. Savage SA, Bertuch AA. The genetics and clinical manifestations of telomere biology disorders. Genet Med. 2010;12(12):753-764. 4. Mason PJ, Bessler M. The genetics of dyskeratosis congenita. Cancer Genet. 2011;204(12):635-645. 5. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol. 2010;150(2):179-188. 6. Calado RT, Yewdell WT, Wilkerson KL, et al. Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. Blood. 2009;114(11):2236-2243. 7. Khincha PP, Wentzensen IM, Giri N, Alter BP, Savage SA. Response to androgen therapy in patients with dyskeratosis congenita. Br J Haematol. 2014;165(3):349-357. 8. Diaz de Leon A, Cronkhite JT, Katzenstein AL, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLoS One. 2010;5(5):e10680. 9. de la Fuente J, Dokal I. Dyskeratosis congenita: advances in the understanding of the telomerase defect and the role of stem cell transplantation. Pediatr Transplant. 2007;11(6):584-594. 10. Yabe M, Yabe H, Hattori K, et al. Fatal interstitial pulmonary disease in a patient with dyskeratosis congenita after allogeneic bone marrow transplantation. Bone Marrow Transplant. 1997;19(4):389-392. 11. Barbaro P, Vedi A. Survival after Hematopoietic Stem Cell Transplant in Patients with Dyskeratosis Congenita: Systematic Review of the Literature. Biol Blood Marrow Transplant. 2016;22(7):1152-1158. 12. Berthou C, Devergie A, D'Agay MF, et al. Late vascular complications after bone marrow transplantation for dyskeratosis congenita. Br J Haematol. 1991;79(2):335-336. 13. Nelson AS, Marsh RA, Myers KC, et al. A Reduced-Intensity Conditioning Regimen for Patients with Dyskeratosis Congenita Undergoing Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016;22(5):884-888. 14. Dietz AC, Orchard PJ, Baker KS, et al. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. Bone Marrow Transplant.

Field	Response
	2011;46(1):98-104. 15. Nishio N, Takahashi Y, Ohashi H, et al. Reduced-intensity conditioning for alternative donor hematopoietic stem cell transplantation in patients with dyskeratosis congenita. Pediatr Transplant. 2011;15(2):161-166. 16. Vuong LG, Hemmati PG, Neuburger S, et al. Reduced-intensity conditioning using fludarabine and antithymocyte globulin alone allows stable engraftment in a patient with dyskeratosis congenita. Acta Haematol. 2010;124(4):200-203. 17. Bhoopalan SV, Wlodarski M, Reiss U, Triplett B, Sharma A. Reduced-intensity conditioning-based hematopoietic cell transplantation for dyskeratosis congenita: Single-center experience and literature review. Pediatr Blood Cancer. 2021;68(10):e29177. 18. Ayas M, Nassar A, Hamidieh AA, et al. Reduced intensity conditioning is effective for hematopoietic SCT in dyskeratosis congenita-related BM failure. Bone Marrow Transplant. 2013;48(9):1168-1172. 19. Kharfan-Dabaja MA, Otrock ZK, Bacigalupo A, Mahfouz RA, Geara F, Bazarbachi A. A reduced intensity conditioning regimen of fludarabine, cyclophosphamide, antithymocyte globulin, plus 2 Gy TBI facilitates successful hematopoietic cell engraftment in an adult with dyskeratosis congenita. Bone Marrow Transplant. 2012;47(9):1254-1255. 20. Nichele S, Bonfim C, Junior LGD, et al. Hematopoietic cell transplantation for telomere biology diseases: A retrospective single-center cohort study. Eur J Haematol. 2023. 21. Fioredda F, Iacobelli S, Korthof ET, et al. Outcome of haematopoietic stem cell transplantation in dyskeratosis congenita. Br J Haematol. 2018;183(1):110-118. 22. Gadalla SM, Sales-Bonfim C, Carreras J, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. Biol Blood Marrow Transplant. 2013;19(8):1238-1243.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Proposal 2309-12: Characteristics of patients with Telomere Biology Disorders who underwent myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes from 2000-2021 reported to CIBMTR

Characteristic	RIC / Non-Myeloablative	Myeloablative	Total
No. of patients	170	60	230
Patient Related			
Recipient age - no. (%)			
Median (min-max)	12.6 (0.9-63.1)	12.1 (1.7-39.1)	12.4 (0.9-63.1)
0-5	42 (24.7)	13 (21.7)	55 (23.9)
5-10	31 (18.2)	11 (18.3)	42 (18.3)
10-18	44 (25.9)	24 (40.0)	68 (29.6)
>=18	53 (31.2)	12 (20.0)	65 (28.3)
Treatment Related			
Sex - no. (%)			
Male	110 (64.7)	37 (61.7)	147 (63.9)
Female	60 (35.3)	23 (38.3)	83 (36.1)
Donor type - no. (%)			
HLA-identical sibling	19 (11.2)	15 (25.0)	34 (14.8)
Other related	14 (8.2)	6 (10.0)	20 (8.7)
Well-matched unrelated (8/8)	75 (44.1)	20 (33.3)	95 (41.3)
Partially-matched unrelated (7/8)	28 (16.5)	4 (6.7)	32 (13.9)
Mis-matched unrelated (<= 6/8)	1 (0.6)	0 (0.0)	1 (0.4)
Unrelated (matching TBD)	12 (7.1)	9 (15.0)	21 (9.1)
Cord blood	20 (11.8)	6 (10.0)	26 (11.3)
Not reported	1 (0.6)	0 (0.0)	1 (0.4)
Conditioning intensity as designated by center - no. (%)			
RIC / Non-Myeloablative	170 (100)	0 (0.0)	170 (73.9)
Myeloablative	0 (0.0)	60 (100)	60 (26.1)
GVHD prophylaxis - no. (%)			
Ex-vivo T-cell depletion	2 (1.2)	2 (3.3)	4 (1.7)
CD34 selection	5 (2.9)	2 (3.3)	7 (3.0)
PtCy + other(s)	12 (7.1)	4 (6.7)	16 (7.0)
TAC + MMF +- other(s) (except PtCy)	29 (17.1)	4 (6.7)	33 (14.3)
TAC + MTX +- other(s) (except MMF, PtCy)	8 (4.7)	1 (1.7)	9 (3.9)
TAC + other(s) (except MMF, MTX, PtCy)	2 (1.2)	2 (3.3)	4 (1.7)

Characteristic	RIC / Non-Myeloablative	Myeloablative	Total
TAC alone	5 (2.9)	2 (3.3)	7 (3.0)
CSA + MMF +- other(s) (except PtCy,TAC)	77 (45.3)	14 (23.3)	91 (39.6)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	14 (8.2)	15 (25.0)	29 (12.6)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	5 (2.9)	2 (3.3)	7 (3.0)
CSA alone	2 (1.2)	2 (3.3)	4 (1.7)
Missing	9 (5.3)	10 (16.7)	19 (8.3)
TED or RES track - no. (%)			
TED	92 (54.1)	35 (58.3)	127 (55.2)
CRF (RES)	74 (43.5)	23 (38.3)	97 (42.2)
moved CRF (RES) to TED	3 (1.8)	2 (3.3)	5 (2.2)
moved TED to CRF (RES)	1 (0.6)	0 (0.0)	1 (0.4)
Year of transplant - no. (%)			
2000-2009	22 (12.9)	19 (31.7)	41 (17.8)
2010-2021	148 (87.1)	41 (68.3)	189 (82.2)
Follow-up, months - median (range)	51.5 (0.0-143.7)	55.9 (0.0-217.9)	55.8 (0.0-217.9)

Field	Response
Proposal Number	2310-143-RANGARAJAN
Proposal Title	Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the Impact of conditioning regimens.
Key Words	Transplant, Hurler's syndrome, Contemporary cohort
Principal Investigator #1: - First and last name, degree(s)	Hemalatha Rangarajan MD
Principal Investigator #1: - Email address	hemalatha.rangarajan@nationwidechildrens.org
Principal Investigator #1: - Institution name	Nationwide Children's Hospital, Columbus Ohio
Principal Investigator #1: - Academic rank	Clinical Associate Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	2. Rolla Abu Arja MD 3, Joanne Kurtzberg MD 4. Prakash Satwani MD
Principal Investigator #2 (If applicable): - Email address:)	2. Rolla.Abu-Arja@nationwidechildrens.org 3. joanne.kurtzberg@duke.edu 4. Satwani, Prakash ps2087@cumc.columbia.edu
Principal Investigator #2 (If applicable): - Institution name:	2. Nationwide Children's Hospital 3. Duke University School of Medicine 4. Columbia University Medical Center
Principal Investigator #2 (If applicable): - Academic rank:	2. Associate Professor of Pediatrics 3. Professor of Pediatrics 4. Professor of Pediatrics
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	Yes
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:	Hemalatha Rangarajan

Field	Response
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. I have completed the following study with CIBMTR IB17-02: Outcomes of Pediatric patients with JMML following unrelated donor transplant: The impact of Donor KIR Gene Content and KIR Ligand Matching Manuscript Published. Transplantation and Cellular Therapy. PMID: 34407489. Role : Principal investigator The following proposals that I have submitted have been accepted and are at varying stages of development. I am a co-principal investigator on all these protocols. 1. IN20-01: Incidence, Risk Factors, and Outcomes of Infections post CD19 CAR T therapies. February 2020. Data analysis is ongoing. 2. CT20-02: Resource utilization in patients receiving CAR-T Therapy. February 2020. Data analysis ongoing 3. PC19-03: Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with AML and CNS involvement. February 2019. Data analysis is ongoing. 4. NM22-01:Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis: Protocol development 5. RRT: 2110-80:Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database: Protocol Development 6. PC23-01: Post-transplant cyclophosphamide vs. TCR αβ/CD19+ deplete approaches for haploidentical transplant in pediatric patients with acute leukemias and myelodysplastic syndrome: Protocol Development 7. HS22-01:Study Title: Health Care Utilization And Costs Of Haploidentical Allogeneic Stem Cell Transplants In A Contemporary Cohort Of Pediatric Patients With Acute Leukemia And Myelodysplastic Syndrome: Protocol Development.
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Is the outcome of Busulfan cyclophosphamide (BuCY) vs Busulfan Fludarabine (BuFlu) based conditioning regimens comparable in patients with Hurlers syndrome post allogeneic hematopoietic cell transplantation (HCT)?

Field	Response
RESEARCH HYPOTHESIS:	We hypothesize that BuFlu based regimens though associated with decreased toxicity compared to historical BuCY based regimens for Hurler syndrome, will be associated with increased incidence of second interventions.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary objective 1. To estimate the 2-year Overall Survival (OS) of patients with Hurlers syndrome who have undergone HCT between BuCY vs BuFlu based conditioning regimens. Secondary objective 1. To compare the Event Free survival (events= death, second interventions: second HCT, DLI, CD34 boost) of patients with Hurlers syndrome who have undergone HCT between BuCY vs BuFlu based conditioning regimens. 2.To compare the difference in incidence of GF (primary or secondary) between the two regimes 3. To identify trends in graft source utilization for Hurlers syndrome Exploratory objective 1. To characterize the outcomes of patients who have undergone 2nd HCT for Hurler's syndrome
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Hematopoietic stem cell transplantation (HSCT) is the standard of care in children with Hurler syndrome as it is the only therapy that can arrest disease progression. However there remains ambiguity in field with regards to the optimum conditioning regimen while balancing toxicity with efficacy. Reduced toxicity regimens such as vs Busulfan Fludarabine (BuFlu) though associated with decreased toxicity are now being shown to be associated with increased risk of graft failure (GF) and need for second interventions. The outcome 2nd HCT in such patients have also not been studied using a registry-based data. It is unknown if there has been a shift /trend towards use of cord blood as a graft source for this disease due to prior CIBMTR report demonstrating better results with use of cord blood grafts[1]. With the implementation of NBS we are now able to take patients to HCT in the first few months of life and the current cohort of patients may be relatively younger than historical patients. Hence, since the CIBMTR report published in 2013[1], there may have been several changes in the field that merit consideration of analysis of contemporary cohort of Hurlers patients undergoing HCT. Through our proposal we seek to address these questions in this field. Our proposal is also of relevance as it will also provide the background data that is required for comparison with gene therapy [2, 3] a possible upcoming curative option for this rare metabolic disorder.

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.	Allogeneic stem cell transplant for Hurler's syndrome, requires a myeloablative platform to ensure durable engraftment. The landmark CIBMTR paper published in 2013 by Boelens et al [1], established the superiority of a matched 6/6 unrelated cord blood over other donor/graft sources including a matched sibling carrier donor. UCB HCT were observed to be associated with improved post-HCT enzyme levels and full donor chimerism compared to other graft sources. Notably patients in this CIBMTR cohort (1995-2007) were transplanted at a median of 16.7 months (range 2.1 to 228 months) with a predominantly Busulfan cyclophosphamide (BuCY) based regimen (83%). Event Free survival (EFS) was also better in patients transplanted less than 16.7 months (71%) compared to > 16.7 months (55%). Since the publication of this report, there continues to remain several areas of unmet research needs as detailed below. Choice of conditioning regimen: Although historically BuCY was the most favored regimen, increasingly BuFlu based regimens have gained more popularity due to decreased risk of toxicity. In an earlier study comparing BuCy vs BuFlu based regimens [4], the OS and EFS was comparable between both regimens in patients with both malignant and non-malignant diseases (included 32 patients with metabolic diseases). Notably the BuFlu arm had lower rates of non-infectious lung injury, veno-occlusive disease (VOD) , chronic graft-versus-host disease (cGVHD) adenovirus infection , and human herpesvirus 6 infection reactivation. A recent CIBMTR study [5] comparing both regimens in pediatric allogeneic HCT recipients also showed decreased toxicity with BuFlu regimens in patients with non-malignant diseases. The overall mortality was comparable for children with nonmalignant conditions who received BuFlu or BuCy however the BuFlu recipients had lower incidences of sinusoidal obstruction syndrome, hemorrhagic cystitis, and chronic graft-versus-host disease. This study included 65 patients with metabolic disease in the Bu CY arm and 24 in the BuFlu arm . However the study did not shed led light on event free survival or incidence of GF between both arms in non-malignant cohort. Gupta and colleagues recently in their single center study[6] have shown that although BuFlu was associated with decreased toxicity in patients with metabolic diseases, it was associated with increased need for second inventions. In this study UCB was the most common graft source (74%). The 1-year OS and EFS was similar between BuCY and BuFlu groups with similar incidence of acute and chronic GVHD. Neutrophil and platelet recovery was shorter in the BuFlu arm but the

	cumulative incident of GF was higher with BuFlu group (29% vs 14%, p= 0.08). Significantly higher rates of second HCT was noted following BuFlu cohort (27% vs. 3%, p= 0.001). However the incidence of adenoviral infection (14% vs. 0%, p=0.02) and hemorrhagic cystitis (23% vs. 3%, p=0.01) were higher in the BuCy group. The authors concluded that alternative immunosuppressive agents and novel techniques should be considered to minimize toxicities and reduce complications in this population. Therefore, there remains ambiguity with regards to the best choice of conditioning regimen for metabolic diseases including Hurlers syndrome. Is UCB still the best graft source? Along the same lines, It is also unclear whether the publication of the CIBMTR report[1], has led to shift in the use of UCB graft source over time. UCB traditionally have been associated with increased frisk of GF. The main criticism for the CIBMTR report is that testing for the enzyme level was done at different laboratories by different methods [7]. In a study where testing was uniformly done at a single center, the authors demonstrated in a predominantly UCB HCT cohort that irrespective of graft source it was patients with mixed chimerism who had lower enzyme levels[7]. Therefore, the authors concluded that graft source does not matter as much as HLA matching and conditioning regimen to ensure full donor chimerism. Impact of Newborn screening: Since 2016, based on the federal Recommended Uniform Screening Panel (RUSP) as many as 30 states have implement newborn screening for Hurler's syndrome (https://everylifefoundation.org/newborn-screening-take-action/mucopolysaccharidosis-i-mps-i/). Therefore, it is possible that the current cohort of patients in the CIBMTR database may include a relatively younger age group than historical controls. We will attempt to capture this cohort indirectly by analyzing outcomes of patients transplanted based on age cut off as follows: < 3 months, 3-6 months, >6-12 months and >12 months. Outcomes of 2nd HCT: Finally, outcomes of 2nd HCT for this cohort of patients can also be gleaned only from a single study reported by Lum et al, who reported on outcomes from two centers of patients transplanted from 1983 to 2016 [8]. With the implementation of busulfan pharmacokinetic monitoring started in 2004 in the authors observed improved outcomes (n=131 pre 2004 vs n=109 post-2004). GF was significantly lower in the current era compared with the historical era (37.2% vs 10.1%, respectively). All the 11 GF in the current era occurred in recipients of cord blood transplants (7 aplasia and 4 autologous reconstitution). The outcomes of 2nd HCT 48 patients (39 in historical era and 9 in current ear) in these patients had improved, with 89% of

Field	Response
	such patients alive and engrafted in the current era compared with 58% in the historical era. For patients undergoing second HCT, the estimated 5-year OS was 70.1% (historical era 66.7% vs current era 85.7%, P = 0.24). T our knowledge there has been no large registry-based data analyzing outcomes of 2nd HCT for patients with Hurler's syndrome. For all the above reasons, this may be the appropriate time to analyze the outcomes of contemporary cohort of patients with Hurlers syndrome. Specifically, we hope our proposal will help questions that warrant further research 1. Impact of conditioning regimens in current era 2. The impact of younger age at transplant (possible impact of NBS screening) 3. Trends in utilization of cord blood over time 4. Finally, the outcomes of patients who have undergone second transplant. Feasibility We looked at the NMD CIBMTR meeting minutes of 2023 and noted that there are 577 transplants for patients with Hurlers syndrome. This included 255 on TED and 322 on CRF tracks. Therefore, we think that this is a feasible proposal if approved by the Working committee.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion Criteria • Diagnosis of Hurlers syndrome • Year of Transplant 2000 to 2022 • Undergoing 1st allogenic HCT Exclusion criteria • Non consent patients • Those with incomplete forms
Does this study include pediatric patients?	Yes

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient • Age at HCT • Sex • HCT CI index (Pediatric CI index) if available • Race/Ethnicity • Enzyme replacement therapy before HCT Y/N if Y duration of ERT Donors • Graft source BM/PBSC/UCB • Matching HLA matching (Cords: 4/6, 5/6, 6/6), others (10/10, 9/10 , < 9/10), Haplo (2 antigen mismatched 5/10 vs > 5-8/10) • Donor MSD/MUD/MMUD, Haploidentical donor • Donor/Recipient CMV Status Transplant • Year of transplant • Conditioning regimen • GVHD prophylaxis: Calcineurin inhibitor (CNI) only, CNI/steroid, CNI /MTX, CNI/MMF, PTCY based • Ex vivo T cell depletion Y/N if Y specify which type • Serotherapy :ATG/Campath • Rituximab as part conditioning Y/N • Chimerism at day 100 , and 1 year if available? Outcomes • Time to neutrophil and platelet recovery • Chimerism at Day +100 • Acute GVHD Grade I-II vs II-IV • Chronic GVHD: NIH scoring mild/moderate /severe • Autoimmunity post HCT Y/N • Graft failure (GF) Y/N If Y Primary or Secondary Time from HCT to GF Second interventions Y/N, If Y 2nd HCT/Cd34 boost/DLI Time to second intervention Conditioning for 2nd intervention GVHD Y/N post 2nd intervention GF Y/N post 2nd intervention • Organ Toxicity VOD Y/N TA-TMA Y/N Pulmonary: IPS Y/N Neurological : PRES Y/N Cardiac toxicity Y/N Survival • Follow up • Survival Status Alive Y/N • Cause of death
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 desc	Not applicable
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	Not applicable

Field	Response
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 o	Not applicable
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.	Not applicable
REFERENCES:	1. Boelens, J.J., et al., Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Blood, 2013. 121(19): p. 3981-7. 2. Hurt, S.C., P.I. Dickson, and D.T. Curiel, Mucopolysaccharidoses type I gene therapy. J Inherit Metab Dis, 2021. 44(5): p. 1088-1098. 3. Tucci, F., et al., Current and Future Perspective in Hematopoietic Stem Progenitor Cell-gene Therapy for Inborn Errors of Metabolism. Hemasphere, 2023. 7(10): p. e953. 4. Bartelink, I.H., et al., Fludarabine and exposure-targeted busulfan compares favorably with busulfan/cyclophosphamide-based regimens in pediatric hematopoietic cell transplantation: maintaining efficacy with less toxicity. Biol Blood Marrow Transplant, 2014. 20(3): p. 345-53. 5. Harris, A.C., et al., Comparison of pediatric allogeneic transplant outcomes using myeloablative busulfan with cyclophosphamide or fludarabine. Blood Adv, 2018. 2(11): p. 1198-1206. 6. Gupta, A., et al., Reduced-Toxicity (BuFlu) Conditioning Is Better Tolerated but Has a Higher Second Transplantation Rate Compared to Myeloablative Conditioning (BuCy) in Children with Inherited Metabolic Disorders. Biol Blood Marrow Transplant, 2020. 26(3): p. 486-492. 7. Orchard, P.J., et al., Hematopoietic stem cell transplant for Hurler syndrome: does using bone marrow or umbilical cord blood make a difference? Blood Adv, 2022. 6(23): p. 6023-6027. 8. Lum, S.H., et al., Changes in the incidence, patterns and outcomes of graft failure following hematopoietic stem cell transplantation for Hurler syndrome. Bone Marrow Transplant, 2017. 52(6): p. 846-853.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Proposal 2310-143: Characteristics of patients with Hurler's syndrome who underwent first alloHCT with Bu/CY or Bu/Flu conditioning regimen from 2000-2021 reported to CIBMTR

Characteristic	Bu/Cy	Bu/Flu	Total
No. of patients	319	99	418
Patient Related			
Recipient age - no. (%)			
Median (min-max)	1.3 (0.2-5.1)	1.3 (0.2-3.2)	1.3 (0.2-5.1)
0-5	318 (99.7)	99 (100)	417 (99.8)
5-10	1 (0.3)	0 (0.0)	1 (0.2)
Treatment Related			
Sex - no. (%)			
male	160 (50.2)	60 (60.6)	220 (52.6)
female	159 (49.8)	39 (39.4)	198 (47.4)
Sub disease - no. (%)			
IH Hurler syndrome:	319 (100)	99 (100)	418 (100)
Donor type - no. (%)			
HLA-identical sibling	23 (7.2)	7 (7.1)	30 (7.2)
Other related	10 (3.1)	1 (1.0)	11 (2.6)
Well-matched unrelated (8/8)	36 (11.3)	15 (15.2)	51 (12.2)
Partially-matched unrelated (7/8)	12 (3.8)	1 (1.0)	13 (3.1)
Mis-matched unrelated (<= 6/8)	3 (0.9)	1 (1.0)	4 (1.0)
Unrelated (matching TBD)	14 (4.4)	0 (0.0)	14 (3.3)
Cord blood	221 (69.3)	74 (74.7)	295 (70.6)
Conditioning intensity as designated by center - no. (%)			
Myeloablative	319 (100)	99 (100)	418 (100)
Conditioning regimen - no. (%)			
Bu/Cy	319 (100)	0 (0.0)	319 (76.3)
Flu/Bu	0 (0.0)	99 (100)	99 (23.7)
GVHD prophylaxis - no. (%)			
Ex-vivo T-cell depletion	12 (3.8)	0 (0.0)	12 (2.9)
CD34 selection	5 (1.6)	3 (3.0)	8 (1.9)
PtCy + other(s)	2 (0.6)	1 (1.0)	3 (0.7)
TAC + MMF +- other(s) (except PtCy)	13 (4.1)	15 (15.2)	28 (6.7)
TAC + MTX +- other(s) (except MMF, PtCy)	8 (2.5)	2 (2.0)	10 (2.4)
TAC + other(s) (except MMF, MTX, PtCy)	4 (1.3)	5 (5.1)	9 (2.2)
TAC alone	2 (0.6)	1 (1.0)	3 (0.7)
CSA + MMF +- other(s) (except PtCy,TAC)	98 (30.7)	26 (26.3)	124 (29.7)

Characteristic	Bu/Cy	Bu/Flu	Total
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	18 (5.6)	13 (13.1)	31 (7.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	45 (14.1)	25 (25.3)	70 (16.7)
CSA alone	2 (0.6)	4 (4.0)	6 (1.4)
Other(s)	3 (0.9)	1 (1.0)	4 (1.0)
Missing	107 (33.5)	3 (3.0)	110 (26.3)
TED or RES track - no. (%)			
TED	120 (37.6)	42 (42.4)	162 (38.8)
CRF (RES)	188 (58.9)	54 (54.5)	242 (57.9)
moved CRF (RES) to TED	10 (3.1)	3 (3.0)	13 (3.1)
moved TED to CRF (RES)	1 (0.3)	0 (0.0)	1 (0.2)
Year of transplant - no. (%)			
2000-2009	160 (50.2)	4 (4.0)	164 (39.2)
2010-2021	159 (49.8)	95 (96.0)	254 (60.8)
Follow-up, months - median (range)	86.3 (0.0-241.0)	60.0 (0.0-217.3)	71.3 (0.0-241.0)

Field	Response
Proposal Number	2310-205-BALL
Proposal Title	Impact of somatic mutations in aplastic anemia (AA) after allogeneic stem cell transplantation
Key Words	Aplastic anemia, somatic mutation, clonal hematopoiesis, CHIP, CCUS
Principal Investigator #1: - First and last name, degree(s)	Brian Ball, MD
Principal Investigator #1: - Email address	brball@coh.org
Principal Investigator #1: - Institution name	City of Hope National Medical Center
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Ryotaro Nakamura, MD
Principal Investigator #2 (If applicable): - Email address:)	rnakamura@coh.org
Principal Investigator #2 (If applicable): - Institution name:	City of Hope National Medical Center
Principal Investigator #2 (If applicable): - Academic rank:	Professor, Transplant Center Director
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Prop 2210-259: I am the principal investigator. The study seeks to perform next generation sequencing on pre-conditioning peripheral blood specimens for patients with post-aplastic anemia MDS.
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Larisa Broglie and Stephen Spellman
RESEARCH QUESTION:	What is the impact of somatic mutations in aplastic anemia recipients aged ≥ 20 years on survival after allogeneic stem cell transplant
RESEARCH HYPOTHESIS:	Somatic mutations in AA recipients impact post-transplant outcomes

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Objective 1) To evaluate if the presence of somatic mutation detected in AA recipients is associated with overall survival after alloHCT 2) To evaluate if the presence of high-risk somatic mutations (DNMT3A, ASXL1, TP53, RUNX1, CSMD1) detected in AA recipients is associated with overall survival after alloHCT Secondary Objective: 1) To evaluate the impact of any somatic mutation or high-risk somatic mutations on GVHD incidence, primary and secondary graft failure, GVHD-failure free survival, and failure free survival 2) To evaluate the impact of mutation burden or any or high risk mutations on OS, GVHD incidence, primary and secondary graft failure, failure free survival 3) To evaluate the impact of the number of mutations on OS, GVHD incidence, primary and secondary graft failure, GVHD-failure free survival, failure free survival
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	AlloHCT is a curative approach for patients with AA who do not respond to immunosuppressive therapy. Complications of alloHCT, including graft vs. host disease, graft failure, and disease relapse remain barriers to improving long-term survival in patients with AA and post-AA MDS. Here, we propose NGS of preconditioning peripheral blood specimens from recipients aged 20 years and older with AA or post-AA MDS to determine the impact of somatic mutations on survival, relapse and treatment related mortality after alloHCT. These findings will directly impact patient care and enable more personalized transplant approaches, tailoring the timing, conditioning regimen, and type of graft vs. host disease regimen to mitigate the risk associated with particular somatic mutations.

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.	Acquired aplastic anemia (AA) is a bone marrow failure disorder arising from immune mediated destruction of hematopoietic stem and progenitor cells. Allogeneic stem cell transplantation (AlloHCT) is a potential curative approach but its use is limited by transplant associated complications. Although younger (age < 20 years) patients with AA undergoing alloHCT have long-term OS 90%, elderly patients (age > 40 years) have inferior survival with 5-year OS ~60%. The leading causes of death for these patients are graft vs. host disease (GVHD), infection, graft failure, and organ toxicity. As immunosuppressive therapy (IST) with horse ATG, cyclosporine and eltrombopag yields high rates of response and long-term survival, IST is the preferred frontline treatment for older patients (aged ≥ 40 years) or younger patients without matched sibling donors. However, among those receiving IST, somatic mutations or clonal hematopoiesis (CH) is common, occurring in 36% of patients at diagnosis and has prognostic implications. Whereas PIGA, BCOR, BCORL1 mutations are associated with improved responses to IST, DNMT3A, ASXL1, TP53, RUNX1, and CSMD1 are associated with lower response rates and inferior survival. Additionally progression to a myeloid neoplasm (MN) such as post-AA MDS or AML occurs in about 13% of patients with AA. For those with AA and post-AA MDS after IST, alloHCT remains a potentially curative approach. However, somatic mutations, which are likely to be enriched in older adults with AA, may negatively impact survival after transplant. In non-transplanted patients, CH is an age-related condition, which confers an increased risk of progression to MN and all-cause mortality, especially cardiovascular disease. Transmission of donor DNMT3A CH to alloHCT recipients was associated with reduced relapse risk and increased risk of chronic GVHD. In contrast, among patients undergoing autologous transplant for lymphoma, CH is associated with increased non-relapse mortality and death from ischemic cardiovascular disease (CVD). In alloHCT recipients, the effects of pre-existing CH, including accelerated aging, inflammation and CVD may predispose to increased transplant associated toxicity and treatment related mortality. Additionally, as non-myeloablative conditioning intensity is used in aplastic anemia, CH may persist and contribute to treatment failure and possible progression to myeloid malignancies. Here, we propose next generation-sequencing (NGS) of preconditioning peripheral blood specimen in recipients with AA to determine the prognostic impact of somatic mutations on survival after alloHCT.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Adult patients (age ≥ 20 years) enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR) Repository Patients with aplastic anemia, who underwent allogeneic stem cell transplant during 2001-2023 Pre-conditioning peripheral blood sample available Patients with progression to a myeloid neoplasm (MDS, MDS/MPN, MPN, AML) are excluded
Does this study include pediatric patients?	No
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient related variables (age, Sex, race, Karnofsky performance status, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Disease-related factors (Prior therapies, response to prior therapies, Time from diagnosis to HCT, cytogenetics) Transplant-related factors (conditioning regimens, Graft type, donor type, GVHD prophylaxis, in-vivo T-cell depletion, ex-vivo T-cell depletion, Year of transplant
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 desc	NA
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	NA
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 o	Aliquots of Whole Blood in anticoagulant citrate dextrose solution collected and stored according to the CIBMTR research sample repository.
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.	None

Field	Response
REFERENCES:	1. Young NS. Aplastic Anemia. New England Journal of Medicine 2018;379:1643-56. 2. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. New England Journal of Medicine 2017;376:1540-50. 3. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia. New England Journal of Medicine 2015;373:35-47. 4. Gurnari C, Pagliuca S, Prata PH, et al. Clinical and Molecular Determinants of Clonal Evolution in Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2022:Jco2200710. 5. Sun L, Babushok DV. Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria. Blood 2020;136:36-49. 6. Kim SY, Le Rademacher J, Antin JH, et al. Myelodysplastic syndrome evolving from aplastic anemia treated with immunosuppressive therapy: efficacy of hematopoietic stem cell transplantation. Haematologica 2014;99:1868-75. 7. Bernard E, Tuechler H, Greenberg Peter L, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evidence 2022;1:EVIDoa2200008. 8. Mei M, Pillai R, Kim S, et al. The mutational landscape in chronic myelomonocytic leukemia and its impact on allogeneic hematopoietic cell transplantation outcomes: a Center for Blood and Marrow Transplantation Research (CIBMTR) analysis. Haematologica 2022.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Proposal 2310-205. Population characteristics for patient receiving a first allogeneic hematopoietic cell transplantation for severe aplastic anemia with available cryopreserved peripheral blood mononuclear cells (PBMC) or whole blood sample available in CIBMTR repository, 2001-2021.

Variable	20-39 years old N (%)	>=40 years old N (%)
Number of patients	553	476
Source of data		
CRF	327 (59)	286 (60)
TED	226 (41)	190 (40)
Number of centers	128	97
Unrelated recipient PBMC available		
No	433 (98)	394 (98)
Yes	11 (2)	10 (2)
Unrelated recipient whole blood available		
No	11 (2)	10 (2)
Yes	433 (98)	394 (98)
Related recipient whole blood available		
Yes	109 (100)	72 (100)
Recipient age at transplant		
18-29 years	360 (65)	0
30-39 years	193 (35)	0
40-49 years	0	150 (32)
50-59 years	0	162 (34)
60-69 years	0	130 (27)
70+ years	0	34 (7)
Median (Range)	27 (20-40)	56 (40-77)
Recipient race		
White	427 (77)	405 (85)
Black or African American	52 (9)	28 (6)
Asian	31 (6)	15 (3)
Native Hawaiian or other Pacific Islander	2 (<1)	1 (<1)
American Indian or Alaska Native	8 (1)	3 (1)
More than one race	3 (1)	5 (1)
Missing	30 (5)	19 (4)
Recipient ethnicity		
Hispanic or Latino	96 (17)	64 (13)
Non-Hispanic or non-Latino	440 (80)	396 (83)
Non-resident of the U.S.	4 (1)	1 (<1)
Missing	13 (2)	15 (3)
Recipient sex		
Male	295 (53)	235 (49)
Female	258 (47)	241 (51)
Disease at transplant		
Severe aplastic anemia	553 (100)	476 (100)

Variable	20-39 years old N (%)	>=40 years old N (%)
Karnofsky score		
10-80	190 (34)	244 (51)
90-100	347 (63)	220 (46)
Missing	16 (3)	12 (3)
GvHD Prophylaxis		
No GVHD prophylaxis	1 (<1)	2 (<1)
Ex vivo T-cell depletion	3 (1)	2 (<1)
CD34 selection	7 (1)	4 (1)
Post-CY + other(s)	54 (10)	62 (13)
Tacrolimus + MMF +- others	65 (12)	64 (13)
Tacrolimus + MTX +- others (except MMF)	211 (38)	214 (45)
Tacrolimus + others (except MTX, MMF)	19 (3)	13 (3)
Tacrolimus alone	13 (2)	18 (4)
CSA + MMF +- others (except Tacrolimus)	19 (3)	13 (3)
CSA + MTX +- others (except Tacrolimus, MMF)	128 (23)	64 (13)
CSA + others (except Tacrolimus, MTX, MMF)	6 (1)	4 (1)
CSA alone	14 (3)	7 (1)
Other GVHD prophylaxis	10 (2)	7 (1)
Missing	3 (1)	2 (<1)
HLA-A B DRB1 groups - low resolution		
<=3/6	16 (3)	10 (2)
4/6	26 (5)	6 (1)
5/6	63 (11)	36 (8)
6/6	442 (80)	415 (87)
Missing	6 (1)	9 (2)
High-resolution HLA matches available out of 8		
<=5/8	43 (8)	15 (3)
6/8	14 (3)	9 (2)
7/8	67 (12)	49 (10)
8/8	406 (73)	387 (81)
Missing	23 (4)	16 (3)
High resolution release score		
N	221 (40)	204 (43)
Y	332 (60)	272 (57)
Graft type		
Marrow	411 (74)	301 (63)
PBSC	113 (20)	166 (35)
UCB	18 (3)	4 (1)
BM+PBSC	1 (<1)	0
PBSC+UCB	9 (2)	5 (1)
UCB+Others	1 (<1)	0
Conditioning regimen		
Myeloablative	240 (43)	156 (33)

Variable	20-39 years old N (%)	>=40 years old N (%)
RIC/Nonmyeloablative	312 (56)	319 (67)
Missing	1 (<1)	1 (<1)
Donor group		
HLA-identical sibling	76 (14)	54 (11)
Twin	1 (<1)	2 (<1)
Other related	32 (6)	16 (3)
Well-matched unrelated (8/8)	335(60)	336(70)
Partially matched unrelated (7/8)	66 (12)	47 (10)
Mis-matched unrelated (<= 6/8)	14 (3)	7 (1)
Unrelated (matching TBD)	1 (<1)	5 (1)
Cord blood	28 (5)	9 (2)
Donor age at donation		
To Be Determined/NA	17 (3)	3 (1)
0-9 years	11 (2)	2 (<1)
10-17 years	13 (2)	0
18-29 years	283 (51)	246 (52)
30-39 years	130 (24)	109 (23)
40-49 years	71 (13)	66 (14)
50+ years	28 (5)	50 (11)
Median (Range)	28 (0-69)	30 (2-73)
Donor/Recipient CMV serostatus		
+/+	198 (36)	172 (36)
+/-	43 (8)	30 (6)
-/+	159 (29)	173 (36)
-/-	121 (22)	83 (17)
CB - recipient +	19 (3)	7 (1)
CB - recipient -	8 (1)	2 (<1)
CB - recipient CMV unknown	1 (<1)	0
Missing	4 (1)	9 (2)
Donor/Recipient sex match		
Male-Male	192 (35)	168 (35)
Male-Female	155 (28)	148 (31)
Female-Male	88 (16)	64 (13)
Female-Female	90 (16)	87 (18)
CB - recipient M	15 (3)	3 (1)
CB - recipient F	13 (2)	6 (1)
Year of transplant		
2001	3 (1)	3 (1)
2002	1 (<1)	1 (<1)
2003	0	1 (<1)
2004	5 (1)	5 (1)
2005	17 (3)	5 (1)
2006	29 (5)	11 (2)

Variable	20-39 years old N (%)	>=40 years old N (%)
2007	15 (3)	17 (4)
2008	24 (4)	17 (4)
2009	19 (3)	15 (3)
2010	25 (5)	17 (4)
2011	33 (6)	16 (3)
2012	22 (4)	21 (4)
2013	41 (7)	35 (7)
2014	44 (8)	25 (5)
2015	46 (8)	42 (9)
2016	27 (5)	40 (8)
2017	38 (7)	54 (11)
2018	46 (8)	35 (7)
2019	40 (7)	31 (7)
2020	43 (8)	37 (8)
2021	35 (6)	48 (10)
Follow-up among survivors, Months		
N Eval	438	293
Median (Range)	43 (2-219)	40 (3-169)

Study Title	The outcomes of PTCY based GVHD prophylaxis for Allogeneic Stem Cell Transplantation in patients with Severe Aplastic Anemia patients who lack a HLA-Matched Sibling Donor
Key Words	PTCY, SAA
Investigators	Niranjan Khaire, Lohith Gowda, Abu-Sayeef Mirza and Rajat Kumar
Corresponding PI	Niranjan Khaire
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	No
PROPOSED WORKING COMMITTEE:	Non-malignant Diseases
RESEARCH QUESTION	1) In the real world setting what is the current impact of PTCY based GVHD prophylaxis across various donor types (haploidentical, MUD and MMUD) in Severe Aplastic Anemia a) What is the proportion of PTCY based GVHD prophylaxis use across donor types. 2) Head-to-head comparison in these subgroups a) Are the outcomes of Allogeneic Stem Cell Transplantation (Allo-SCT) for Severe Aplastic Anemia (SAA) using a PTCY- haploidentical platform comparable to MUD transplantation? (PTCY-Haplo vs all MUD and PTCY-Haplo vs PTCY-MUD). b) What are the outcomes of PTCY based GVHD prophylaxis as compared with conventional non PTCY based GVHD prophylaxis in MUD and MMUD transplants (PTCY-MUD vs non PTCY-MUD; PTCY-MMUD vs non PTCY-MMUD)
RESEARCH HYPOTHESIS	With the development of PTCY based transplant platforms for Severe aplastic anemia over the past decade we hypothesize that post-transplant outcomes have improved across all donor types. In the unrelated donor setting we hypothesize that use of PTCY based GVHD prophylaxis has the potential to further improve the outcomes of an already safe and effective transplant regimen. More importantly we hypothesize that use of PTCY based platform for haploidentical donor has the potential to provide a transplant option with outcomes comparable with the use of MUD donor and may allow us to offer haplo transplantation earlier in the treatment algorithms.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) (Suggested word limit 200 words)	AIM 1 : Assessing outcomes of PTCY in SAA across all donor types (Haploidentical, MUD, MMUD) AIM 2 : Comparing outcomes of haplo-PTCY transplants for SAA with MUD transplants for SAA. Primary Outcome: Overall survival Secondary Outcomes: Timing of neutrophil engraftment Timing of platelet engraftment; Graft failure; Transplant related Mortality at D100 and D365; acute GVHD; chronic GVHD; Infectious complications (Cumulative risk of Viral Infections / bacterial infections) , Graft Failure free Survival

	(Defined as patients alive and without primary or secondary graft failure); GRFS (GVHD and Relapse free survival) Optional Outcomes (if data is available): Chimerism; Immune reconstitution such as T cell subsets; Late effects such as fertility , premature ovarian failure, secondary cancers, cataracts, etc.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	The standard treatment strategy for severe aplastic anemia is HSCT from a HLA-matched sibling donor for adults aged < 40. However, 70% of those who require a transplant do not have a matched sibling donor available. With improving outcomes of MUD transplant these are also considered first line for young adults. However, until a decade ago there was no standardized and safe option for haploidentical transplantation in SAA. This is particularly concerning for non-Caucasian ethnicities such as Asians and African Americans where MUD availability is very low, ranging from 15 to 30% (1) and prevalence aplastic anemia is almost two to three-fold higher (2) The significant cost of a MUD donor (upto $30000) also is another barrier to transplantation especially in the LMIC and LIC countries. The development of a safe and effective transplant-based platform for SAA in patients lacking a MSD donor will improve timely access of this curative procedure to a vast majority of patients across the globe. In fact the 2014 BMT CTN Scientific Symposium identified this patient population as an important area of need. (3) The development of PTCY based transplantation in the past decade has the potential to address this important area of need. In the setting of the MUD transplantation, it has the potential to improve outcomes over the conventional non PTCY based transplants. As for the haploidentical setting, this retrospective analysis can help establish a standard platform for haplo transplants which could be offered earlier in the treatment algorithm rather than being used an option of last resort.

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.	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. The adaptation of PTCY based haploidentical donor transplantation, spearheaded by the John Hopkins group in the 2000s has been a major advancement in the field. This approach used a conditioning regimen of Fludarabine, Cyclophosphamide, ATG and TBI and a GVHD prophylaxis of post-transplant Cyclophosphamide, cyclosporine and MMF. The initial Hopkins experience of 37 patients (r/r and treatment naïve) transplanted with this approach showed a 2 year OS of 94% with a aGVHD rate of 11% and cGVHD rate of 11%. (4) These findings were validated by the same group in a multicenter phase 2 trial of 31 patients with a one year overall survival of 81% , aGVHD rate of 16% and cGVHD rate of 26%. (5) Recently the group reported upfront use of the transplant protocol in haplo transplants and demonstrated the importance of the 400cGY radiation which showed 100% survival in 20 patients (6)As expected approximately 40 percent of participants in both these studies self-identified as nonwhites. With the success of this approach there is concerted approach towards using PTCY based transplantation for SAA across diverse donor types including even other donor types such as MUD and MSD. (7) However, the exact role of PTCY especially in a real world setting with the variation in regional resources, practices, expertise remains to be defined. We propose this study to examine the role of PTCY based transplantation in Sever aplastic anemia in contemporary practice. In the setting of the MUD and MMUD transplantation, there is an increased use of PTCY based GVHD prophylaxis in the recent years in a few centres. The expectation for this approach is that the benefits of lower rates of GVHD that PTCY provides will make it an even safer procedure. On the other hand, we have to consider the risks of increased risk of rejection, infections, secondary malignancies and late effects of transplantation that may come along with the Baltimore approach. The data on this PTCY based approach for MUD and MMUD donors is exceedingly sparse and almost no head to head study. A retrospective CIBMTR study looking at outcomes of PTCY across different donor types can answer a lot of clinically important questions.

	The biggest potential impact of our proposal will be in the field of haploidentical transplantation. Whereas the GIAC protocol has been used since two decades in China, the concerns about use of Busulfan in a non-malignant condition, the use of a combined BM and PB graft as well as rates of acute as well as chronic GVHD reaching around 40% has led to a reluctance to use this protocol outside China. (8) In contrast there has been a rapid adoption of Baltimore protocol. However, the performance of this platform outside of the trial setting remains to be seen. Even in the experience of the Baltimore group the outcomes the Multicentre study were slightly inferior to the single centre study and there were more challenges in procuring a good quality BM graft when the protocol was expanded to centers with less experience. (4,5) A report from the Brazilian society of SCT reported 87 cases transplanted with the Baltimore protocol and reported a 2 year OS of 79%. (9) Different groups from other centres in UK, Brazil and India have reported their experience of the use of this platform for haploidentical transplant, however these are usually small single centre studies and with additional modifications of the conditioning regimens. (10-12) A review of EBMT data also showed excellent outcomes of HLA-haploidentical transplantation among a small number of aplastic anemia (N=33) patients given the regimen developed by Johns Hopkins (N=16 ; 2 yr OS 93%), while patients given other regimens fared far worse(N=17 ; 2 yr OS 64%) (13) In summary the Baltimore approach of haploidentical transplant has shown excellent results and is becoming more widely used. However, the data comes from relatively small studies with no robust head to head comparison of outcomes with the conventional transplant outcoems in MSD or MUD donors. There are also numerous variations of the protocols used by various centers and we do not yet have a firm consensus on which protocol would give the optimal outcomes. We are aware of a similar proposal being considered by the Non Malignant Diseases Committee in 2020, however we believe that the clinical practice in the field of Aplastic anemia has evolved since then. The numbers of transplants available for analysis will be higher, the experience of centers will be more mature, and we believe that it is the appropriate time to revisit this question. An analysis of the of haploidentical transplantation outcomes for SAA from CIBMTR database (HaploPTCY vs all MUD and Haplo PTCY vs Haplo MUD) has the potential to provide a globally acceptable Haplo platform leading to earlier referral to transplant centers as well as availability of this life saving procedure to a huge majority of underserved minorities, especially in the LMIC and LIC regions. References

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PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion : 1. Underwent first Allo HCT for SAA 2. Use of non MSD donor (MUD, MMUD, haploidentical donor) 3. All types of graft source, ex vivo graft manipulation, conditioning regimen and GVHD prophylaxis regimen to be included.

	Comparator Groups : 1. HAPLO-PTCY vs MUD (ALL) 2. HAPLO-PTCY vs MUD-PTCY 3. MUD PTCY vs MUD-NON PTCY 4. MMUD-PTCY vs MMUD- NON PTCY 5. MUD-PTCY vs MMUD-PTCY vs HAPLO-PTCY Exclusion criteria : Inherited BM failure syndrome ; UCD ; Second transplant.
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses.	Patient Variable : Age , Sex, HCT-CI , KPS Disease variable : Duration of diagnosis before transplant , Lines of RX before SCT , Transfusion load before transplant Infusion Variables : D/R CMV , D/R sex , D/R ABO , Graft source , Graft manipulation , Conditioning regimen , GVHD prophylaxis, Use of PTCy, Use of ATG/Campath, Use of TBI, Transplant year
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS:	No
MACHINE LEARNING:	No
SAMPLE REQUIREMENTS:	Nil
NON-CIBMTR DATA SOURCE:	Nil
CONFLICTS OF INTEREST	Nil

Proposal 2310-213/2310-255: Characteristics of patients with Severe Aplastic Anemia who lack a HLA-Matched Sibling Donor with PTCY based GVHD prophylaxis for Allogeneic Stem Cell Transplantation from 2010-2021 reported to CIBMTR

Characteristic	MUD	haplo	MMUD	Total
No. of patients	748	520	180	1448
Patient Related				
Recipient age - no. (%)				
Median (min-max)	23.6 (0.3-77.4)	22.2 (0.7-73.6)	18.9 (1.4-72.1)	22.4 (0.3-77.4)
0-10	149 (19.9)	99 (19.0)	57 (31.7)	305 (21.1)
10-21	184 (24.6)	140 (26.9)	42 (23.3)	366 (25.3)
21-40	188 (25.1)	167 (32.1)	45 (25.0)	400 (27.6)
40-60	143 (19.1)	86 (16.5)	25 (13.9)	254 (17.5)
>60	84 (11.2)	28 (5.4)	11 (6.1)	123 (8.5)
Treatment Related				
Sex - no. (%)				
Male	402 (53.7)	297 (57.1)	89 (49.4)	788 (54.4)
Female	346 (46.3)	223 (42.9)	91 (50.6)	660 (45.6)
Country - no. (%)				
US/Canada	623 (83.3)	326 (62.7)	155 (86.1)	1104 (76.2)
Other International Centers	125 (16.7)	194 (37.3)	25 (13.9)	344 (23.8)
Type of sub disease - no. (%)				
SAA idiopathic:	748 (100)	520 (100)	180 (100)	1448 (100)
Donor type - no. (%)				
Other related	0 (0.0)	520 (100)	0 (0.0)	520 (35.9)
Well-matched unrelated (8/8)	748 (100)	0 (0.0)	0 (0.0)	748 (51.7)
Partially-matched unrelated (7/8)	0 (0.0)	0 (0.0)	169 (93.9)	169 (11.7)
Mis-matched unrelated (<= 6/8)	0 (0.0)	0 (0.0)	11 (6.1)	11 (0.8)
Conditioning intensity as designated by center - no. (%)				
RIC / Non-Myeloablative	748 (100)	520 (100)	180 (100)	1448 (100)
GVHD prophylaxis - no. (%)				
None	1 (0.1)	2 (0.4)	2 (1.1)	5 (0.3)
Ex-vivo T-cell depletion	18 (2.4)	1 (0.2)	10 (5.6)	29 (2.0)
CD34 selection	14 (1.9)	4 (0.8)	6 (3.3)	24 (1.7)
PtCy + other(s)	51 (6.8)	379 (72.9)	35 (19.4)	465 (32.1)
PtCy alone	2 (0.3)	2 (0.4)	0 (0.0)	4 (0.3)
TAC + MMF +- other(s) (except PtCy)	54 (7.2)	29 (5.6)	12 (6.7)	95 (6.6)

Characteristic	MUD	haplo	MMUD	Total
TAC + MTX +- other(s) (except MMF, PtCy)	259 (34.6)	38 (7.3)	48 (26.7)	345 (23.8)
TAC + other(s) (except MMF, MTX, PtCy)	13 (1.7)	1 (0.2)	1 (0.6)	15 (1.0)
TAC alone	36 (4.8)	2 (0.4)	1 (0.6)	39 (2.7)
CSA + MMF +- other(s) (except PtCy,TAC)	33 (4.4)	12 (2.3)	15 (8.3)	60 (4.1)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	205 (27.4)	42 (8.1)	42 (23.3)	289 (20.0)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	8 (1.1)	0 (0.0)	2 (1.1)	10 (0.7)
CSA alone	40 (5.3)	5 (1.0)	6 (3.3)	51 (3.5)
Other(s)	13 (1.7)	3 (0.6)	0 (0.0)	16 (1.1)
Missing	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Graft source - no. (%)				
Bone marrow	567 (75.8)	323 (62.1)	126 (70.0)	1016 (70.2)
Peripheral blood	181 (24.2)	197 (37.9)	54 (30.0)	432 (29.8)
Follow-up, months - median (range)	39.9 (0.0-146.3)	28.2 (0.0-144.2)	48.0 (0.0-147.0)	36.7 (0.0-147.0)