Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Salt Lake City, Utah
Saturday, April 23, 2022, 12:15 PM – 1:45 PM

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1. **Introduction**
   a. Minutes from February 2021 TCT Working Committee Session (Attachment 1)

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

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

4. **Studies in progress** (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) **Data File Preparation**
c. **NM18-01** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) **Data File Preparation**
d. **NM19-01** Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) **Manuscript Preparation**
e. **NM20-01** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Protocol Development**
f. **AC18-02** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) **Manuscript Preparation**

5. Future/proposed studies

a. **2106-02** Curability of Non-Hematologic Autoimmune Disease (AID) with Allogeneic Hematopoietic Cell Transplantation (HCT) (J Storek) (Attachment 4)
b. **2109-15** Outcomes After Second or Greater Allogeneic Stem Cell Transplants In Patients With Severe Aplastic Anemia: A Contemporary Analysis. (H Rangarajan/ P Satwani) (Attachment 5)
c. **2110-118** Pre-Transplant Factors Associated with Survival in Older Patients transplanted after 1st Line Treatment for Aplastic Anemia (A Prabahran/ D Ritchie) (Attachment 6)
d. **2110-137** Allogeneic Hematopoietic Cell Transplantation for Acquired Pure Red Cell Aplasia (J Vaughn/ B Shaffer) (Attachment 7)

6. Dropped proposed studies

a. **2109-11** A comparative study of the use of reduced-intensity and myeloabative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Diamond-Blackfan Anemia
Dropped due to low sample size
b. **2110-09** Outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with Histiocytic Disorders
Dropped due to low sample size and overlap with recent publications
c. **2110-12** Outcomes of hematopoietic cell transplantation in aplastic anemia with posttransplantation cyclophosphamide.
Dropped due to overlap with current study in progress BMT-CTN 1502
d. **2110-44** Haploidentical Donor Transplantation for Severe Aplastic Anemia
Dropped due to overlap with current study in progress BMT-CTN 1502
e. **2110-111** Impact Of Preexisting RBCs Allo-Antibodies on The Outcome of Hematopoietic Stem Cell Transplantation for Patients with Sickle Cell Disease.
Dropped due to low sample size/feasibility
f. **2110-175** Outcomes after autologous hematopoietic stem cell transplant with cyclophosphamide and anti-thymocyte globulin (ATG) compared with carmustine, etoposide, cytarabine, and melphalan (BEAM) and ATG conditioning for the treatment of Multiple Sclerosis.
Dropped due to low sample size
g. **2110-198** Evaluation of Allogeneic Hematopoietic Stem Cell Transplantation Outcomes and Prognostic Factors in X-linked lymphoproliferative disease type 1 (XLP1): A CIBMTR Analysis.
Dropped due to overlap with recent study NM19-02
h. **2110-252** Trends of Early Mortality Within First Two Years Following Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents with Non-Malignant Disorders
Dropped due to heterogeneity of diseases

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

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

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

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

Accrual Summary for the Non-Malignant Diseases Working Committee

Allogeneic Transplants for Immune Deficiencies reported to the CIBMTR from 2000-2019

Characteristic	CRF N	TED N
Number of patients	**2855**	**5834**
Number of centers	186	277
Disease		
Immune Deficiencies (ID), NOS	26 (0.9)	98 (1.7)
SCID ADA deficiency	94 (3.3)	141 (2.4)
SCID absence of T and B cells	176 (6.2)	293 (5)
SCID absence of T, normal B cell SCID	234 (8.2)	338 (5.8)
Omenn syndrome	100 (3.5)	164 (2.8)
Reticular dysgenesis	11 (0.4)	14 (0.2)
Bare lymphocyte syndrome	42 (1.5)	111 (1.9)
SCID, NOS	146 (5.1)	251 (4.3)
SCID other, specify	323 (11.3)	456 (7.8)
Wiskott Aldrich syndrome	292 (10.2)	534 (9.2)
DiGeorge anomaly	8 (0.3)	15 (0.3)
Chronic granulomatous disease	258 (9)	520 (8.9)
Chediak-Higashi syndrome	31 (1.1)	90 (1.5)
Common variable immunodef	36 (1.3)	91 (1.6)
X-linked lymphoproliferative syndrome	68 (2.4)	154 (2.6)
Leukocyte adhesion deficiencies	53 (1.9)	98 (1.7)
Kostmann agranulocytosis	59 (2.1)	177 (3)
Cartilage hair hypoplasia	26 (0.9)	53 (0.9)
TED Immune deficiency plus neutropenia	0	1 (0)
CD40 ligand deficiency	27 (0.9)	93 (1.6)
Griscelli syndrome type 2	11 (0.4)	21 (0.4)
Combined immunodef dis (CID), NOS	7 (0.2)	12 (0.2)
CID other, specify	17 (0.6)	17 (0.3)
Other immunodeficiencies, specify	198 (6.9)	651 (11.2)
Histiocytic disorder, NOS	5 (0.2)	30 (0.5)
FELH Familial erythrohemophagocytic lymphohis	427 (15)	1025 (17.6)
Langerhans Cell Histiocytosis	37 (1.3)	86 (1.5)
Hemophagocytosis	88 (3.1)	189 (3.2)
Malignant histiocytosis	3 (0.1)	15 (0.3)
Other histiocytic disorders	52 (1.8)	96 (1.6)

*Only first transplants are included in this accrual.

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

Allogeneic Transplants for Inborn Errors of Metabolism reported to the CIBMTR from 2000-2019

Characteristic	CRF N	TED N
Number of patients	**1015**	**1875**
Number of centers	123	195
Disease		
Inherited disorders of metabolism, NOS	3 (0.3)	24 (1.3)
Osteopetrosis	141 (13.9)	317 (16.9)
Lesch-Nyhan(HGPTR defic)	2 (0.2)	2 (0.1)
Neuronal ceroid lipofuscinosis	5 (0.5)	7 (0.4)
Other inherited metabolism disorders, specify	40 (3.9)	82 (4.4)
Mucopolysaccharidosis, NOS	7 (0.7)	16 (0.9)
IH Hurler syndrome	323 (31.8)	523 (27.9)
IS Scheie syndrome	1 (0.1)	1 (0.1)
II Hunter syndrome	25 (2.5)	40 (2.1)
III Sanfillippo	27 (2.7)	32 (1.7)
VI Maroteaux-Lamy	25 (2.5)	41 (2.2)
VII B-glucuronidase deficiency	1 (0.1)	2 (0.1)
V Mucopolysaccharidosis	1 (0.1)	6 (0.3)
Other mucopolysaccharidosis	3 (0.3)	4 (0.2)
Mucolipidoses, NOS	3 (0.3)	4 (0.2)
Gaucher disease	4 (0.4)	14 (0.7)
Metachromatic leukodystrophy(MLD)	87 (8.6)	163 (8.7)
Adrenoleukodystrophy(ALD)	199 (19.6)	395 (21.1)
Globoid leukodystrophy/Krabbe disease	67 (6.6)	106 (5.7)
Neiman-Pick disease	11 (1.1)	22 (1.2)
I-cell disease	16 (1.6)	24 (1.3)
Wolman disease	6 (0.6)	11 (0.6)
Glucose storage disease	0	1 (0.1)
Other mucolipidoses	1 (0.1)	1 (0.1)
Asparty1 glucosaminuria	0	3 (0.2)
Fucosidosis	5 (0.5)	6 (0.3)
Mannosidosis	12 (1.2)	28 (1.5)

*Only first transplants are included in this accrual.

Allogeneic Transplants for non-malignant disorders reported to the CIBMTR from 2000-2019

Characteristic	CRF N	TED N
Number of patients	**7317**	**16108**
Number of centers	330	447
Disease		
Paroxysmal nocturnal hemoglobinuria	242 (3.3)	473 (2.9)
Severe aplastic anemia	3558 (45.9)	8324 (51.7)
Amegakaryocytosis	11 (0.2)	23 (0.1)
Shwachman-Diamond	37 (0.5)	75 (0.5)
Acquired Pure Red Cell Aplasia	31 (0.4)	86 (0.5)
Dyskeratosis congenita	39 (0.5)	75 (0.5)
Other acquired cytopenic syndrome, specify	135 (1.8)	281 (1.7)
Inherited abnormalities of erythrocyte differentiation, not otherwise specified	10 (0.1)	18 (0.1)
Fanconi anemia	801 (10.9)	1506 (9.3)
Diamond-Blackfan anemia	149 (2)	332 (2.1)
Other constitutional anemia	65 (0.9)	175 (1.1)
Thalassemia	1214 (16.6)	2744 (17)
Sickle cell disease	1025 (14)	1996 (12.4)

*Only first transplants are included in this accrual.

Autologous Transplants for autoimmune diseases reported to the CIBMTR from 2000-2019

Characteristic	CRF N	TED N
Number of patients	**129**	**781**
Number of centers	44	108
Disease		
Autoimmune disease unclassified	0	24 (3.1)
Myasthenia gravis	2 (1.6)	10 (1.3)
Multiple sclerosis	70 (54.3)	382 (48.9)
Rheumatoid arthritis	3 (2.3)	7 (0.9)
Psoriatic arthritis or psoriasis	1 (0.8)	1 (0.1)
Systemic lupus erythematosis (SLE)	9 (7)	60 (7.7)
Polymyositis-dermatomyositis	0	2 (0.3)
System Scleroderma	31 (24)	193 (24.7)
Antiphospholipid syndrome	0	5 (0.6)
Other arthritis, specify	0	1 (0.1)
Other Connective tissue dis	0	9 (1.2)
Churg-Strauss	0	1 (0.1)
Behcets Syndrome	0	2 (0.3)
JIA systemic	0	2 (0.3)
JIA Other, specify	0	1 (0.1)
Other neuro disorder, specify	7 (5.4)	33 (4.2)
ITP- Idiopathic thrombocytopenic purpura	2 (1.6)	4 (0.5)
Evan syndrome	0	1 (0.1)
Crohns disease	3 (2.3)	41 (5.2)
Other bowel disorder, specify	1 (0.8)	2 (0.3)

*Only first transplants are included in this accrual.

TO: Non-Malignant Diseases Working Committee Members

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

RE: Studies in Progress Summary

NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) The aim of the study is to describe the population of children or adults with Erythropoietic Porphyria who have undergone HCT and examine the outcomes post-transplant. U.S. data has been cleaned and prepared for presentation. European supplemental data has been collected and cleaned. Manuscript preparation is in progress. The goal is to submit the final manuscript by June 2022.

NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) The purpose of this study is to investigate the long-term outcomes and late effects of patients with hemophagocytic lymphohistiocytosis (HLH) who are survivors after hematopoietic cell transplantation (HCT). The main hypothesis is that HLH survivors will be at risk for significant long term medical and neuropsychological late effects that will be dependent upon pre-transplant disease related factors and the intensity of the BMT conditioning regimen. The study is beginning data file preparation. The goal is to have the data file prepared for analysis by August 2022.

NM18-01: Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson) The purpose of this study is to compare outcomes following allogeneic HCT for pediatric patients with non-malignant disease based on the specific serotherapy used. Post-transplant outcomes, including overall survival, acute and chronic GVHD, graft failure, and graft-failure free survival will be compared between patients given alemtuzumab and patients given ATG. The focus will be on non-malignant diseases for which transplant is most commonly used as treatment to establish as much homogeneity as possible in the comparison. Work on preparation of the data file is underway, with significant progress made. The goal is to have the data file prepared for analysis by August 2022.

NM19-01: Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) The objective of this study is to explore the conditional probability at various time points of patients surviving at least one year after HCT for severe aplastic anemia. The trend in survival rates, conditional on surviving up to specific time points following transplant, will be assessed and compared to conditional survival rates of severe aplastic anemia patients treated with immunosuppressive therapy. Preparation of the data file for transplant cases is in progress. The IST cases will require merging of data from the National Heart, Lung, and Blood Institute. Manuscript preparation is in progress. The goal is to submit the final manuscript by June 2022.

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 goal is to complete protocol development and have a sizeable portion of data file preparation complete by June 2022.

AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) The objective of this study is to explore patient characteristics and post-transplant outcomes of patients undergoing autologous transplant for systemic sclerosis. Co-operation of the transplant centers treating these patients will be solicited for the collection of supplemental data of highest relevance for this specific autoimmune disease. Manuscript preparation is in progress. The goal is to submit the final manuscript by June 2022.

EBMT/CIBMTR Study Proposal

Study Title:
Outcomes of Allogeneic Hematopoietic Cell Transplantation (HCT) Performed for an Autoimmune Disease (AID)

1st PI Information:
PI Name: Jan Storek
Degree(s): MD, PhD
Academic Rank: Professor
Junior Investigator (yes/no): No
Email Address: jstorek@ucalgary.ca
Institution Name: University of Calgary, Alberta, Canada

2nd PI Information:
PI Name (First, Middle, Last): Raffaella Greco
Degree(s): MD, PhD
Academic Rank: Associate Professor?
Junior Investigator (yes/no), *if applicable*: No
Email Address: greco.raffaella@hsr.it
Institution Name: San Raffaele Scientific Institute in Milano, Italy

Other Investigators:
Joerg Henes (Tuebingen), Andrew Gennery (Newcastle), Christopher Dvorak (San Francisco), Larisa Broglie (Milwaukee), John Snowden (Sheffield), Tobias Alexander (Berlin), ….

Research Hypothesis:
1. After alloHCT, 2-year relapse-free survival (RFS) is >50% for the following AIDs refractory to conventional therapy: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile inflammatory arthritis (JIA), systemic sclerosis (SSc), vasculitis including Behcet's disease (Vasc), Crohn's disease (CD), other inflammatory bowel disease including ulcerative colitis (IBDnonCD), neuromyelitis optica spectrum disorder (NMOSD), and immune cytopenia (Cytop). Relapse is defined as AID activity after HCT.
2. For each of the AIDs, the curability is >50%. Curability is defined as the percent of patients without relapse among patients who relapsed at any time after HCT or were followed for at least 1 year after discontinuation of systemic immunosuppressive therapy (IST).

Specific Aims:
1. For each of the AIDs, determine
    a. PFS
    b. OS
    c. Survival free of progression, moderate-severe GVHD, or a new AID
    d. Curability (defined above)
    e. Relapse incidence
    f. Non-relapse mortality (NRM)
    g. Incidence of significant HCT complications, i.e., graft failure, grade 2-4 or 3-4 aGVHD, moderate-severe cGVHD, new AID requiring systemic immunomodulatory treatment, new malignancy (other than nonmelanoma skin cancer or carcinoma in situ),

fatal infection (other than preceded by relapse, grade 2-4 aGVHD, moderate-severe cGVHD, new AID requiring systemic immunomodulatory treatment, or new malignancy). In case of a small number of events for each AID, this Specific Aim may instead be determined for the whole cohort of AID patients.

2. For each AID, generate hypotheses on factors associated with the above outcomes. The following factors will be evaluated:
    a. Patient Age
        i. Hypothesis: Higher curability in younger patients
    b. Duration of AID before HCT
        i. Hypothesis: Higher curability in patient with less established disease
    c. Pretransplant therapy for the AID (including the lines of therapy the patient has failed)
        i. Hypothesis: Higher curability in patients who failed fewer lines of therapy
    d. Donor HLA
        i. Hypothesis: For AIDs genetically influenced by HLA, eg, DRB1 for rheumatoid arthritis, higher curability if the donor has a protective or neutral HLA than HLA predisposing to the AID
    e. Donor non-HLA polygenic risk score (PRS), i.e., the magnitude of the genetic risk of developing the AID. This is an optional goal that will be pursued only if a sufficient number of specimens is available from NMDP/other repositories or from patients who are complete chimeras posttransplant and willing to donate buccal swab and blood specimens.
        i. Hypothesis: in patients who become complete chimeras, higher curability with donors with low PRS
    f. Conditioning
        i. Hypothesis: Higher curability in patients conditioned with a higher intensity conditioning
    g. GVHD prophylaxis
        i. Hypothesis: Higher curability in patients with ex vivo or in vivo lymphocyte depletion
    h. GVHD
        i. Hypothesis: Higher curability in patients who developed grade 2-4 acute GVHD or moderate-severe chronic GVHD
    i. Chimerism
        i. Hypothesis: Higher curability in patients who became complete chimeras compared to patients who became mixed chimeras or rejected the graft
    j. AID subcategory
        i. Hypothesis: Higher curability for certain AID subcategories, eg, ACPA+ compared to ACPA- RA.
    k. AID activity score (maximum ever, or immediately pretransplant), eg, SLEDAI-2K for lupus, DAS28-CRP for rheumatoid arthritis, CDAI for Chrohn's disease, or EDSS for multiple sclerosis
        i. Hypothesis: Lower curability for AID with a higher activity score)

Scientific Impact:

The knowledge on the incidence of the above outcomes and the potential factors associated with the outcomes are important for

1. Whether to design a prospective study of allogeneic HCT for an AID (yes if curability >50%).

2. Inform the eligibility criteria for such a prospective study/studies. For example, if the curability is substantially higher in RA patients with than without anti-citrullinated protein antibodies (ACPA), the initial prospective study will be only for patients with ACPA+ RA. For another example, if the PFS in CD is substantially higher in younger than older patients, the initial prospective study will be only for younger CD patients.
3. Inform the HCT protocol for the prospective studies. For example, if in the retrospective study there is no association between the remission of an AID and complete chimerism, the prospective study protocol will not include any intervention like donor lymphocyte infusion for mixed chimerism.
4. Improve knowledge on AID pathogenesis. For example, it is possible that among RA patients with complete hematolymphatic chimerism postHCT, there will be patients with relapse as well as patients in long-term remission post IST discontinuation. It will be concluded that in the latter patients, the hematolymphatic cells may play a key role in the pathogenesis of RA, whereas in the former group, the non-hematolymphatic cells (eg, synoviocytes) may play the primary role, perhaps by steering healthy T or B cells toward autoimmunity. This will generate hypotheses for mechanistic studies to be included in the prospective studies.

Scientific Justification:

In experimental animals, AIDs are highly curable with allogeneic hematopoietic cell transplantation (HCT).[1-4] Whether this applies to humans is less clear. Case reports, case series, and registry studies have described both patients whose AID relapsed after HCT as well as those whose AID entered a long-term remission free of anti-AID drugs ("cure").[5-8] Aggregate data on all AIDs suggest that the cumulative incidence of relapse (CIR) after HCT performed for the AID is approximately 22% to 45%.[5-7,9] However, there are significant limitations of the information published so far, which make it difficult or impossible to decide whether a patient should be offered HCT for an AID or whether to design a prospective study of alloHCT for an AID:

1. Data on relapse rates (or CIR) for individual AIDs (e.g., SLE, psoriasis, or UC) are scarce.
2. The scarce data are in the form of case reports/small series, which suffer from publication bias (higher likelihood of reporting "cures" than relapses).
3. Factors influencing the likelihoods of relapse for individual AIDs are unknown.

To overcome these limitations, we propose to take advantage of the fact that ~300 alloHCTs performed for an AID have been reported to EBMT and CIBMTR. Thus, we estimate that for each of the most frequent AIDs/disease categories (SLE, RA, JIA, SSc, Vasc, CD, IBDnonCD, NMOSD, Cytop), the results of 10-30 alloHCTs are known.

Patient Eligibility Population:

Eligibility for initial inclusion into study:
- First allogeneic HCT performed for an AID.

Eligibility for analysis (evaluable patients):
- Sufficient data available for categorizing patients as posttransplant relapse vs remission of AID.

Data Requirements:

If supplemental data is required, please review data collection forms at:
http://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx

Data from CIBMTR/EBMT:
- An identifier (eg, CRID) allowing each center to find supplemental data

- Date of HCT
- Age at HCT
- Sex
- Diagnosis for which HCT was done
- Date of the diagnosis for which HCT was done
- Disease stage (if hematologic disease)
- Donor HLA match and relation
- HLA of donor
- HLA of recipient
- Conditioning (myeloablative vs reduced intensity)
- GVHD prophylaxis, including serotherapy
- Graft failure? If yes, when?
- New malignancy (except for PTLD, non-melanoma skin cancer, or carcinoma in situ)? If yes, when and which histology and location?
- Was PTLD diagnosed? If yes, then date of diagnosis and treatment (modality, from when till when)
- Max overall grade aGVHD
- Max global score cGVHD (or limited/extensive)
- Date of discontinuation of systemic IST (if interrupted and later restarted, then the date of the discontinuation of the last IST course)
- Chimerism (all available) – % donor among which cells, when determined, method of determination
- Died? Yes/No
- Date of death or last follow up for survival (per registry record)

<u>Supplementary Data</u>:

- Date of AID diagnosis (Y / N / Insufficient information)
- Was AID diagnosis definite (per pre-specified criteria)? (Y / N / Insufficient information)
- Which drugs/modalities have been used to treat the AID?
- What was the AID subcategory? (per pre-specified criteria, eg, organ(s) involved in SLE or SSc, or ACPA/other autoantibody status in RA
- Highest activity/severity score, recorded or estimated from chart review. Common activity scores will be pre-specified (eg, SLEDAI-2K for lupus, DAS28-CRP for RA, CDAI for CD).
- Activity/severity score immediately (within 1 mo) before conditioning.
- Was AID congenital and due to a monogenic mutation (eg, Crohn's disease with IL10R mutation)? (Y / N / Not determined)
- Was AID present in donor? (Y / N / Insufficient information)
- Was AID treated/prophylaxed after HCT? If yes, which drugs/modalities, from when till when?
- After HCT, did AID relapse (per pre-specified criteria)?
- If AID relapsed, what was the highest activity/severity score after HCT?
- If AID relapsed, did it respond to a drug to which it was unresponsive before HCT? Which drug?
- Date of last meaningful follow up (eg, a progress note or discharge summary by a health care provider who would likely note that the AID relapsed if it relapsed. Just knowing that the patient was alive is insufficient.). The date of the last meaningful follow up may be earlier than the date of the last follow up for survival.
- Date of last follow up for survival.

Sample Requirements:

If the study requires biologic samples from the NMDP Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology; 2) A summary of the investigator's previous experience with the proposed assay systems; 3) A biosketch or brief curriculum vitae documenting experience in the laboratory methods proposed.

There is the potential for evaluating the hypothesis that the likelihood of AID relapse is influenced by the non-HLA polygenic risk score (PRS) of the donor. This would require a sufficient number of specimens from NMDP/other repositories (pretransplant DNA from both donor and recipient) or from patients who are complete chimeras posttransplant and willing to donate buccal swab and blood specimens. In the latter case, the complete chimerism would be documented by comparing short tandem repeats (STRs) in the buccal swab and the blood (no buccal swab STRs present also in the blood). The PRS would be determine using an NGS panel developed by MyOme (submitted). The disadvantage of adding this goal would be that contacting the patients for an informed consent and the collection of specimens would be required. The advantage of adding this goal would be that MyOme would pay for the supplementary data collection as well as for the resources needed for obtaining the informed consent and the specimens.

Study Design:

Observational study identifying patients via CIBMTR/EBMT and collecting supplementary data using EMRs. The goal is to determine the outcomes (eg, PFS, curability) for each AID.

Non-CIBMTR Data Source:

If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question; 3) A list of the data elements available in both data sources that will be used to link the CIBMTR record with the external record; 4) The methodology used to link the datasets.

Supplementary data will be obtained from electronic or paper records (charts) at individual HCT centers. CIBMTR/EBMT database does not contain the supplementary data. The data elements used to link CIBMTR/EBMT record with the HCT center patient record will be the CRID (or analogous EBMT number) and the HCT date.

References:

1. Smith-Berdan S, Gille D, Weissman IL, Christensen JL. Reversal of autoimmune disease in lupus-prone New Zealand black/New Zealand white mice by nonmyeloablative transplantation of purified allogeneic hematopoietic stem cells. Blood 2007;110:1370-8.
2. Herrmann MM, Gaertner S, Stadelmann C, et al. Tolerance induction by bone marrow transplantation in a multiple sclerosis model. Blood 2005;106:1875-83.
3. Nash RA. Hematopoietic cell transplantation for autoimmune diseases. In: Forman S, Negrin R, Antin J, Appelbaum FR, eds. Thomas' Hematopoietic Cell Transplantation. West Sussex, UK: Wiley Blackwell; 2016:792-803.
4. Sherer Y, Shoenfeld Y. Stem cells transplantation--a cure for autoimmune diseases. Lupus 1998;7:137-40.
5. Daikeler T, Hugle T, Farge D, et al. Allogeneic hematopoietic SCT for patients with autoimmune diseases.[Erratum appears in Bone Marrow Transplant. 2009 Jul;44(1):67 Note: Urban, C [added]]. Bone Marrow Transplantation 2009;44:27-33.

6. Hinterberger W, Hinterberger-Fischer M, Marmont A. Clinically demonstrable anti-autoimmunity mediated by allogeneic immune cells favorably affects outcome after stem cell transplantation in human autoimmune diseases. Bone Marrow Transplant 2002;30:753-9.
7. Greco R, Labopin M, Badoglio M, et al. Allogeneic HSCT for Autoimmune Diseases: A Retrospective Study From the EBMT ADWP, IEWP, and PDWP Working Parties. Front Immunol 2019;10:1570.
8. Shifa I, Hazlewood GS, Durand C, et al. Efficacy of Allogeneic Hematopoietic Cell Transplantation for Autoimmune Diseases. Transplant Cell Ther 2021.
9. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv 2017;1:2742-55.
10. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. Anticancer research 2012;32:1119-36.
11. Anderson LA, Pfeiffer RM, Landgren O, Gadalla S, Berndt SI, Engels EA. Risks of myeloid malignancies in patients with autoimmune conditions. British journal of cancer 2009;100:822-8.

Conflicts of Interest:

Do you have any conflicts of interest pertinent to this proposal concerning:

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

☐ Yes

X No

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

Insert your text here.

Proposal submission: E-mail your observational study proposal to: proposals.cibmtr@mcw.edu

Autoimmune diseases undergoing first allogeneic HCT

Characteristic	TED	CRF
No. of patients	37	19
No. of centers	27	13
Age at transplant, years - no. (%)		
Median (min-max)	22 (1-62)	17 (2-53)
<10	5 (14)	5 (26)
10-17	9 (24)	5 (26)
18-29	9 (24)	3 (16)
30-39	4 (11)	1 (5)
40-49	5 (14)	3 (16)
50-59	3 (8)	2 (11)
60-64	2 (5)	0 (0)
Disease - no. (%)[1]		
Rheumatoid arthritis	2 (5)	1 (5)
Systemic lupus erythematosis (SLE)	7 (19)	2 (11)
System Scleroderma	10 (27)	9 (47)
Behcets Syndrome	1 (3)	0 (0)
ITP- Idiopathic thrombocytopenic purpura	4 (11)	1 (5)
Hemolytic anemia	8 (22)	2 (11)
Crohns disease	4 (11)	4 (21)
Ulcerative colitis	1 (3)	0 (0)
Donor type - no. (%)		
HLA-identical sibling	18 (49)	6 (32)
Twin	3 (8)	1 (5)
Other related	3 (8)	2 (11)
Well-matched unrelated (8/8)	7 (19)	3 (16)
Mis-matched unrelated (<= 6/8)	1 (3)	0 (0)
Unrelated (matching TBD)	2 (5)	0 (0)
Cord blood	2 (5)	7 (37)
Missing	1 (3)	0 (0)
Graft (Product) type - no. (%)		
Bone marrow	15 (41)	4 (21)
Peripheral blood	18 (49)	8 (42)
Umbilical cord blood	2 (5)	7 (37)
Missing	2 (5)	0 (0)
Year of Transplant - no. (%)		
1989-1999	2 (5)	1 (5)
2000-2004	12 (32)	5 (26)
2005-2009	5 (14)	8 (42)
2010-2014	6 (16)	4 (21)

Characteristic	TED	CRF
2015-2019	12 (32)	1 (5)
Follow-up, months - median (range)	47 (6-205)	72 (4-191)

[1] those with autoimmune disease as primary indication

Response Summary:

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

Q1. Study Title

Study Title: Outcomes After Second or Greater Allogeneic Stem Cell Transplants In Patients With Severe Aplastic Anemia: A Contemporary Analysis.

Q2. Key Words

Severe Aplastic Anemia, Second or greater transplant, Outcomes

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hemalatha G Rangarajan
Email address:	hemalatha.rangarajan@nationwidechildrens.org
Institution name:	Nationwide Children's Hospital
Academic rank:	Clinical Assistant Professor of Pediatrics

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

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Prakash Satwani, MD
Email address:	ps2087@columbia.edu
Institution name:	Columbia University Medical Center, NY.
Academic rank:	Associate Professor of Pediatrics

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

- No

Q8. Do you identify as an underrepresented/minority?

- Yes

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

Hemalatha Rangarajan

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

N/A

LETTER OF COMMITMENT:

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

Q12. 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 one of the co-principal investigators 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. Protocol development is in progress.
3. PC19-03: Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with AML and CNS involvement. February 2019. Data analysis is ongoing.

Q13. PROPOSED WORKING COMMITTEE:

- Non-Malignant Diseases

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

- No

Q15. RESEARCH QUESTION:

Has that advances in supportive care and increased use of alternative donors, led to improved outcomes after second allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA) when compared to historically treated patients?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that advances in supportive care and increased use of alternative donors, may have led to improved outcomes after second allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA) when compared to historically treated patients

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

Suggested word limit of 200 words:

Specific Aims
Determine the following outcomes of second allogeneic stem cell transplant in a contemporary cohort of patients with SAA
Primary Endpoint.
1. 2-year Overall Survival after a second allogeneic stem cell transplant for SAA
Secondary Endpoint
1. Neutrophil engraftment
2. Platelet engraftment
3. Incidence of second graft failure
4. Incidence of acute graft versus host disease (aGVHD) Grade II-IV
5. Incidence of chronic GVHD
6. Incidence of 100 day and 1-year Transplant related mortality (TRM)
7. 2-year Graft rejection free GVHD free Survival

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

With increasing use of alternative donors for patients with SAA, there is a critical need to review outcomes on second allogeneic transplants in patients with SAA with Graft failure (GF) post 1st HCT. While historical studies have included a greater proportion of patients who received matched sibling donor (MSD) donors for their 2nd HCT, our proposed study may capture a greater proportion of patients who have undergone alternative donor transplants. Outcomes of this study, therefore, will provide clinicians with practical information on how to approach and salvage these high-risk patients in this contemporary era.

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

Allogeneic matched sibling donor (MSD) donor HCT is the first line treatment for acquired SAA. Increasingly alternative donors such as matched unrelated donor (MUD), cord blood and most recently haploidentical donors are being considered in patients with fail upfront immunosuppressive therapy. GF however remains a major cause of transplant failure in patient with SAA . Historically, prevalence of GF ranged from 0-26% to as high as 46% in cord blood recipients[1]. In a recent CIBMTR study of transplants performed between 2000-2014 [2], based on conditioning regimen administered, the rate of GF was 8-16% in 955 MSD and 9-15% in recipients of 409 HLA matched or MMURD BM recipients. Notably, this study did not include recipients of haploidentical transplants. Autologous recovery with normalization of counts is rare and is seen only in 4.2% of patients [3]. GF can be primary or secondary and in rare instances can be seen along with full donor chimerism donor type aplasia[4]. In all these circumstances, patients often require a lifesaving second allogeneic HCT as a curative option. Second allogeneic HCT is a risky procedure and can itself be associated with lower probably of long-term survival due to high risk of GF, non-infectious organ toxicity and infectious complications. There is need for study outcomes after 2nd HCT for GF in patients with SAA in a contemporary era when alternative donors are increasingly being considered a reasonable salvage option.

A CIBMTR study [5]analyzed the outcomes of 166 patients with SAA who underwent a 2nd MSD (with same or different donor) HCT using bone marrow (BM) as graft source between 1986-2004. In this study inter transplant interval and performance status were associated with high mortality. The 8-year probability of OS for transplant ≤ 3 months vs > 3 months and with a with performance scores of 90-100% were 56% and 76% respectively. Corresponding probability in patients with lower performance scores were 33% and 61% respectively. GF was still seen in 72/166 (43%) patients and frequent in patients with primary or early secondary graft failure (51/72: 71%). With majority (146/166) of patients receiving transplants from the same donor the authors observed that there was no advantage to using a different sibling donor.

In a study by EBMT[6] of 162 SAA patients, 2nd allogeneic transplant (1998-2009) was found to be feasible and led to successful outcomes in 60% of patients. In this study 1/3 (52) of the recipients received graft from an unrelated donor and the remainder from a MSD. About 81% of the transplants was performed using the same donor. The graft source was BM in 31% and peripheral blood stem cells in 69% of patients. Grade II- IV aGVHD and cGVHD occurred in 21% and 37% of patients. GF occurred in 26% (n=42) of recipients. With a follow up of 3.5 years the 5-year OS was 61%. The only factor associated with better outcomes was a performance score of ≥ 80%. Graft source i.e. PBSC or BM did not influence outcomes.

In a large Japanese study[5] of 55 children with SAA, who a 2nd transplant between 1982-2012, the 5-year OS and failure free survival (FFS) was 82.9% and 81.2% respectively. 30 of the 55 patients received transplants from an alternative donor. Inter-transplant interval of > 60 days and use of fludarabine/melphalan based conditioning regimens were associated with better hemopoietic recovery and outcomes.

To summarize, in all the above studies longer inter transplant interval which allows for enough time to recovery from the toxicity and myelosuppressive effectors of conditioning and a better performance score were associated with improved outcomes after 2nd allogeneic HCT. Use of the same donor in these studies which contained predominantly MSD recipients was associated with good outcomes thereby pointing that use of different donor did not offer superior advantages[5, 7, 8]. It remains to be seen if these findings hold true in a contemporary cohort of patients many of whom may be recipients of alternative donor transplants.

Therefore, we propose utilizing data extracted from the CIBMTR database to not only interrogate the outcomes of second or greater allogeneic stem cell transplants in patients with SAA , but also to analyze factors associated with improved outcomes in this high-risk population.

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

N/A

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

Inclusion Criteria
1. All patients with acquired SAA reported to CIBMTR who underwent a second or greater allogeneic HCT from any donor with at least two years of follow up
2. Year of transplant 2000-2019
Exclusion criteria:
1. Patients with GF who did not undergo a second or greater allogeneic HCT
2. Non consented patients
3. Patients with < 2 years of follow up
4. Patients who received grafts from multiple donors

Q21. Does this study include pediatric patients?

- Yes

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

Data requirements
Patient related:
1. Age at 1st HCT
2. Sex
3. Race/Ethnicity
4. CMV status
5. ABO and Rh Typing
6. HCT CI index (prior to second transplant) 0-2 vs ≥ 3
7. Performance score prior to second transplant < 90 vs ≥ 90
Transplant details
1. First HCT details
a. Conditioning regimen
MA/RIC/NMA
Serotherapy used ATG/ Campath/ both/none
Regimen Fludarabine based± Cyclophosphamide (CY)/ busulfan based ± CY only/other
TBI used for conditioning regimen Y/N if Y dose TBI used Y/N if Y dose ≤ 800 vs > 800
b. Donor Age/Sex
c. Donor Related/Unrelated, if related sibling/others?
d. Donor HLA matching: matched, mismatched (1 antigen, 2 antigen or > 2 antigen)
e. Donor CMV status
f. Donor ABO and Rh Typing
g. GVHD prophylaxis: CNI± Methotrexate, CNI± MMF, PTCY± others, CNI only vs others
h. Graft Source: UCB, BM, PBSC

2. Graft failure details
a. Time of diagnosis of GF in relation to first HCT
3. Second HCT details
a. Inter transplant interval
b. Reason for 2nd HCT: primary or secondary graft failure
c. Conditioning regimen
MA/ RIC/ NMA
Serotherapy used ATG/ Campath/ both/none
Regimen Fludarabine based± CY/ busulfan based±CY/CY only/other
TBI used Y/N if Y dose ≤ 800 vs > 800
d. Donor Related/Unrelated: If related haploidentical?
e. Donor same as 1st HCT Y/ N
f. If Different 2nd Donor
i. 2nd HLA matching
ii. 2nd Donor Related/unrelated, if related sibling/others?
iii. 2nd Donor CMV
iv. 2nd Donor ABO
v. 2nd Donor Age /Sex
g. Graft Source: BM, PBSC, Cord blood
h. GVHD prophylaxis: CNI± Methotrexate, CNI± MMF, PTCY± others, CNI only vs others
i. aGVHD Y/N, Grade I-II vs Grade II-IV
j. cGVHD with severity (mild, moderate, severe or limited/extensive)
k. Year of transplant 2000-2009 vs 2010-2020
4. Complications post 2nd HCT
1. Infections in the first 100 days post 2nd HCT: viral , bacterial, fungal
2. Organ toxicities: VOD/ Renal failure/ Pulmonary toxicity/TMA/others
5. Follow up
1. Length of follow up
2. Was patient alive at last follow up?
3. If not, what was the cause of death?

If feasible, we will also capture outcomes after 3rd or greater transplant including Transplant details: conditioning regimen, donor and graft source, acute and chronic GVHD rates and OS

Study Design

This will be a retrospective CIBMTR led study. When appropriate, patient characteristics will be compared using Chi square or Fisher's exact test for categorical variables. The probabilities of neutrophil and platelet recovery and acute and chronic graft-versus-host disease (GVHD) will be calculated using the cumulative incidence estimator. The probabilities of 100-day TRM and OS will be calculated using Kaplan-Meier estimator . The 95% confidence interval (CI) will be calculated using log transformation. OS will be calculated from the date of second HCT to the date of any death due to any cause, or to the date of latest follow-up, respectively. Univariate and multivariate analyses will be performed to detect possible factors influencing survival. Variables to be considered are age, sex, performance score , reason for second transplant, inter transplant interval (< 3 months vs >/=3 months), conditioning regimen, GVHD prophylaxis, donor type (same as first, different related donor, different unrelated donor), donor matching, gender match, and graft source. Only variables with p-value ≤0.05 will be considered significant. If there are enough numbers an exploratory analysis of patients who underwent 3rd HCTs will be included.

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

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

Not applicable

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

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

Not applicable

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

Not applicable

Q26. REFERENCES:

References
1. Peinemann, F., et al., Unrelated donor stem cell transplantation in acquired severe aplastic anemia: a systematic review. Haematologica, 2009. 94(12): p. 1732-42.
2. Bejanyan, N., et al., Choice of conditioning regimens for bone marrow transplantation in severe aplastic anemia. Blood Adv, 2019. 3(20): p. 3123-3131.
3. Piccin, A., et al., Survival of patients with documented autologous recovery after SCT for severe aplastic anemia: a study by the WPSAA of the EBMT. Bone Marrow Transplant, 2010. 45(6): p. 1008-13.
4. Shaw, A., et al., Relapse of Aplastic Anemia with Majority Donor Chimerism (Donor-Type Aplasia) Occurring Late after Bone Marrow Transplantation. Biol Blood Marrow Transplant, 2020. 26(3): p. 480-485.
5. Horan, J.T., et al., Risk factors affecting outcome of second HLA-matched sibling donor transplantations for graft failure in severe acquired aplastic anemia. Biol Blood Marrow Transplant, 2009. 15(5): p. 626-31.
6. Cesaro, S., et al., Second allogeneic stem cell transplant for aplastic anaemia: a retrospective study by the Severe Aplastic Anaemia Working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol, 2015. 171(4): p. 606-14.
7. Kudo, K., et al., Second allogeneic hematopoietic stem cell transplantation in children with severe aplastic anemia. Bone Marrow Transplant, 2015. 50(10): p. 1312-5.
8. de Medeiros, C.R., et al., Second bone marrow transplantation for severe aplastic anemia: analysis of 34 cases. Bone Marrow Transplant, 2001. 28(10): p. 941-4.

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

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

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

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

N/A

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

Embedded Data:

N/A

Severe aplastic anemia undergoing second or greater allogeneic HCT, 2000-2019, among those with at least 2-years follow-up

Characteristic	TED	CRF
No. of patients	251	241
Age at transplant, years - no. (%)		
Median (min-max)	20 (2-71)	18 (2-76)
<10	57 (23)	59 (24)
10-17	57 (23)	63 (26)
18-29	56 (22)	62 (26)
30-39	42 (17)	23 (10)
40-49	23 (9)	15 (6)
50-59	12 (5)	10 (4)
60-64	3 (1)	5 (2)
65-69	0 (0)	3 (1)
>=70	1 (0)	1 (0)
Donor type - no. (%)[1]		
HLA-identical sibling	110 (44)	90 (37)
Twin	12 (5)	3 (1)
Other related	41 (16)	60 (25)
Well-matched unrelated (8/8)	36 (14)	35 (15)
Partially-matched unrelated (7/8)	20 (8)	13 (5)
Mis-matched unrelated (<= 6/8)	2 (1)	4 (2)
Unrelated (matching TBD)	21 (8)	15 (6)
Cord blood	8 (3)	19 (8)
Missing	1 (0)	2 (1)
Graft (Product) type - no. (%)		
Bone marrow	92 (37)	74 (31)
Peripheral blood	151 (60)	148 (61)
Umbilical cord blood	8 (3)	19 (8)
Year of Transplant - no. (%)		
2000-2004	48 (19)	64 (27)
2005-2009	38 (15)	67 (28)
2010-2014	98 (39)	31 (13)
2015-2019	67 (27)	79 (33)
Follow-up, months - median (range)	71 (24-223)	76 (24-241)

[1] excluding those with multiple donors

Response Summary:

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

Q1. Study Title

Pre-Transplant Factors Associated with Survival in Older Patients transplanted after 1st Line Treatment for Aplastic Anemia

Q2. Key Words

Aplastic Anemia
Adults
Survival

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Ashvind Prabahran MBBS
Email address:	ashvind.prabahran@mh.org.au
Institution name:	Royal Melbourne Hospital/Peter MacCallum Cancer Centre
Academic rank:	Fellow

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	David Ritchie MB ChB PhD
Email address:	david.ritchie@mh.org.au
Institution name:	Royal Melbourne Hospital/ Peter MacCallum Cancer Centre
Academic rank:	Professor

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

Nil

Q13. PROPOSED WORKING COMMITTEE:

- Non-Malignant Diseases

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

- No

Q15. RESEARCH QUESTION:

When is the right time to transplant an older patient with aplastic anemia?

Q16. RESEARCH HYPOTHESIS:

Older Patients with aplastic anemia who have had a prolonged time from diagnosis to allogeneic transplant due to multiple rounds of prior therapy, with an ineffective response or complications of bone marrow failure, have a poorer post-transplant survival.

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

Suggested word limit of 200 words:

Primary outcome
Overall survival
Secondary Outcomes
Cumulative incidence of graft failure at D40
Cumulative incidence of NRM at 6 months
Cumulative incidence of acute GVHD at D100
Cumulative incidence of chronic GVHD at 6 months

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

This study may encourage the use of earlier transplantation with alternate donor sources rather than engaging in further rounds of immunosuppressive or stem cell promoting therapies in older patients with aplastic anemia. This study also may provide further guidance on appropriate patient selection in applying allogeneic transplantation for aplastic anemia.

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

Allogeneic stem cell transplantation (alloSCT) is a curative procedure for the treatment of aplastic anemia (AA), giving the benefits of rapid neutrophil recovery as well as ameliorating the risk of clonal myeloid progression(1). However, there are significant risks associated with alloSCT especially in patients with increasing HLA disparity between their donors and the appropriate timing of alloSCT for patients without a matched sibling in AA remains an area of ongoing investigation. In general patients without a matched sibling donor are recommended to undergo 1st line immunosuppression prior to undertaken alloSCT due to the potential morbidity and mortality associated with complications of alloSCT such as graft failure, infection and graft versus host disease(2).

Although there is the potential for significant morbidity and mortality with alloSCT, multiple retrospective and prospective studies have demonstrated reasonable overall survival and low risks of complications in both the matched unrelated and haploidentical setting. A recent EBMT registry analysis of 1448 patients has demonstrated and overall survival (OS) of 78% in the entire population at 5 years with donor source not associated with any adverse impact on survival on univariate analysis(3). Similar survival rates seen in other studies involving transplantation with matched unrelated donors (4, 5). Patients without a matched unrelated donor are reliant on alternate donor sources such as haploidentical transplants. Like matched unrelated donor studies, both prospective and retrospective analyses of haploidentical transplantation utilizing the post-transplant cyclophosphamide have demonstrated reasonable OS of 60-100%(6-9). However, it should be noted that the median age of patients in these studies tends to be within the range of 19-25, which will have a positive impact on survival. Age is a frequent association with poorer survival in alloSCT in AA (3, 10) and the assumption is that older patients have a worse tolerance of transplantation and subsequent complication and therefore have poorer outcomes. However, there may be pre-treatment variables that need to be considered in addition to age which may influence outcome.

It has been noted on prior studies that and increased time from diagnosis to alloSCT has direct correlation on poorer transplant outcome in AA(3-5). Time from diagnosis to transplant is a surrogate measure for the development of complications due to bone marrow failure. However, it is a very coarse measurement that also encompasses both patients who may have had a significant PR or CR due to prior therapy and thus are protected from complications of bone marrow failure. There has not been an analysis of the relationship between best pre-alloSCT response to and post alloSCT outcomes. Another aspect of the pre-transplant journey includes the presence of infection (especially atypical or fungal infection) which may influence the decision to proceed straight to transplantation but similarly may negatively impact on eventual outcome. Pre transplant infection has been identified as a potential risk factor for poorer transplant outcome in retrospective single centre studies but needs further evaluation in a larger data set(11).

Furthermore, as most mortality related to transplantation in AA occurs early and is related primarily to factors attributed to non-relapse mortality such as acute GVHD and infection with or without graft failure (4, 10), this may be predicted by currently available risk scores such as the Endothelial Activation and Stress Index (EASIX)(12). This is an easily calculated score based on the following biomarkers: Lactate Dehydrogenase, Creatinine and Platelet count. The EASIX has been shown to predict overall mortality in acute GVHD following reduced intensity conditioning as well as overall survival following transplantation(13). The EASIX has recently been shown to predict early ICU admission in allogeneic transplantation(14). Relevant to AA, a persistently deranged immune microenvironment due to non-responsive disease, multiple rounds of infection or inflammation attributed to iron overload could be measured indirectly via the EASIX. The EASIX could provide a pretransplant measure of a high-risk alloSCT in AA and thus another pre-transplant factor that may provide caution to clinicians.

Essentially, the aim of this proposal is to dissect whether there are elements of patient's pre-transplantation therapy or clinical state that have a relationship on post-transplant outcome. These include complications of bone marrow failure such as infection (particularly atypical infection), best response to prior therapy and number of lines of prior therapy as well as EASIX. We especially want to examine these pre-transplant variables in an older patient group as these are patients susceptible to subsequent complications of allogeneic transplant. Evaluation of pre-transplant variables may lead to the optimization of patient selection as well as earlier consideration of alloSCT as a therapeutic modality in AA.

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

N/A

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

Inclusion Criteria
1. Patients with Aplastic Anaemia
2. Patients with age ≥40
Patients who have received at least one line of therapy prior to transplantation
3. Patients transplanted from 2009-2019
Exclusion criteria
1. Patients with confirmed constitutional bone marrow failure syndrome
2. Patients undergoing their second transplant for aplastic anemia.

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

The focus of the proposal is to assess pre-transplant prognostic factors in older adults with aplastic anemia. Older adults have been demonstrated to have poorer overall survival than pediatric and young adult cohorts following allogeneic transplant for aplastic anaemia.

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

Data Requirements
1. Patient related variables
a. Age, Sex
b. Presence of Fungal Infection
c. Pre-Transplant Platelet Count
d. Pre-Transplant LDH
e. Pre-Transplant Creatinine
f. Survival
i. Alive/Dead
ii. Cause of death
iii. Date of death
g. Initial ANC recovery yes/no
h. Graft versus Host Disease
i. Acute GVHD yes/no
ii. Grade of acute GVHD
iii. Date of acute GVHD onset
iv. Chronic GVHD yes/no
v. Grade of chronic GVHD
vi. Date of chronic GVHD onset
i. VOD
j. New malignancy/PTLD
2. Infusion Related Variables
a. Date of Infusion
b. Product Type
c. Related donor type
d. Intensity of transplant conditioning
e. Type of preparative regimen
f. Type of GVHD prophylaxis
3. Disease related variables
a. Date of diagnosis (measured by date of diagnostic bone marrow biopsy)
b. Lines of therapy
i. Date therapy started
ii. Date therapy stopped
iii. Therapy delivered
iv. ATG type
v. Best response (CR/PR/No response)
vi. Was there disease recurrence following therapy
4. Aplastic Anaemia post infusion data
c. Did Graft Failure Occur

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

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

Nil

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

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

Nil

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

N/A

Q26. REFERENCES:

1. Georges GE, Doney K, Storb R. Severe aplastic anemia: allogeneic bone marrow transplantation as first-line treatment. Blood Adv. 2018;2(15):2020-8.
2. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017;129(11):1428-36.
3. Bacigalupo A, Socié G, Hamladji RM, Aljurf M, Maschan A, Kyrcz-Krzemien S, et al. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. Haematologica. 2015;100(5):696-702.
4. Devillier R, Dalle JH, Kulasekararaj A, D'Aveni M, Clément L, Chybicka A, et al. Unrelated alternative donor transplantation for severe acquired aplastic anemia: a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the EBMT Severe Aplastic Anemia Working Party. Haematologica. 2016;101(7):884-90.
5. Rice C, Eikema DJ, Marsh JCW, Knol C, Hebert K, Putter H, et al. Allogeneic Hematopoietic Cell Transplantation in Patients Aged 50Years or Older with Severe Aplastic Anemia. Biol Blood Marrow Transplant. 2019;25(3):488-95.
6. Esteves I, Bonfim C, Pasquini R, Funke V, Pereira NF, Rocha V, et al. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. Bone Marrow Transplant. 2015;50(5):685-9.
7. Childs RW, Tian X, Vo P, Purev E, Kotecha RR, Carlsten M, et al. Combined haploidentical and cord blood transplantation for refractory severe aplastic anaemia and hypoplastic myelodysplastic syndrome. Br J Haematol. 2021;193(5):951-60.
8. Prata PH, Eikema DJ, Afansyev B, Bosman P, Smiers F, Diez-Martin JL, et al. Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party. Bone Marrow Transplant. 2020;55(6):1050-8.
9. DeZern AE, Zahurak ML, Symons HJ, Cooke KR, Rosner GL, Gladstone DE, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. Blood Advances. 2020;4(8):1770-9.
10. Marsh JC, Pearce RM, Koh MB, Lim Z, Pagliuca A, Mufti GJ, et al. Retrospective study of alemtuzumab vs ATG-based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anemia: a study from the British Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2014;49(1):42-8.
11. Sangiolo D, Storb R, Deeg HJ, Flowers ME, Martin PJ, Sandmaier BM, et al. Outcome of allogeneic hematopoietic cell transplantation from HLA-identical siblings for severe aplastic anemia in patients over 40 years of age. Biol Blood Marrow Transplant. 2010;16(10):1411-8.
12. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol. 2017;4(9):e414-e23.
13. Luft T, Benner A, Terzer T, Jodele S, Dandoy CE, Storb R, et al. EASIX and mortality after allogeneic stem cell transplantation. Bone Marrow Transplantation. 2020;55(3):553-61.
14. Peña M, Salas MQ, Mussetti A, Moreno-Gonzalez G, Bosch A, Patiño B, et al. Pretransplantation EASIX predicts intensive care unit admission in allogeneic hematopoietic cell transplantation. Blood Advances. 2021;5(17):3418-26.

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

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

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

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

N/A

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

Embedded Data:

N/A

First allogeneic HCT for aplastic anemia among adults age 40+, among those receiving a prior line of therapy, 2009-2019

Characteristic	N (%)
No. of patients	273
Age at transplant, years - no. (%)	
Median (min-max)	54 (40-74)
40-49	92 (34)
50-59	106 (39)
60-64	40 (15)
65-69	25 (9)
>=70	10 (4)
Time from diagnosis to transplant, months - median (min-max)	11 (-99-419)
Prior therapies - no./total no. (%)[1]	
Androgens	20/273 (7)
ATG, ALS, ATS, ALG	222/273 (81)
Chelation therapy for iron	14/273 (5)
Corticosteroids	157/273 (58)
Cyclosporine (CsA, Neoral, Sandimmune)	228/273 (84)
Cytokines	65/273 (24)
Other immune suppression	40/273 (15)
Other treatment	91/273 (33)
Donor type - no. (%)	
HLA-identical sibling	89 (33)
Twin	1 (0)
Other related	31 (11)
Well-matched unrelated (8/8)	120 (44)
Partially-matched unrelated (7/8)	18 (7)
Mis-matched unrelated (<= 6/8)	1 (0)
Multi-donor	2 (1)
Unrelated (matching TBD)	6 (2)
Cord blood	5 (2)
Graft type - no. (%)	
Bone marrow	181 (66)
Peripheral blood	85 (31)
Umbilical cord blood	4 (1)
BM + PB	2 (1)
PB + UCB	1 (0)
Year of Transplant - no. (%)	
2009-2014	80 (29)
2015-2019	193 (71)
Follow-up, months - median (range)	38 (3-145)

Characteristic	**N (%)**

[1] excluding those who received only cytokines for therapy

Response Summary:

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

Q1. Study Title

Allogeneic Hematopoietic Cell Transplantation for Acquired Pure Red Cell Aplasia

Q2. Key Words

Allogeneic Hematopoietic Cell Transplantation; Acquired Pure Red Cell Aplasia

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	John Vaughn, MD, MS
Email address:	vaughnj@mskcc.org
Institution name:	Memorial Sloan Kettering Cancer Center
Academic rank:	Adult Bone Marrow Transplant Fellow

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Brian Shaffer, MD, MS
Email address:	shaffeb1@mskcc.org
Institution name:	Memorial Sloan Kettering Cancer Center
Academic rank:	Assistant Attending

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

John Vaughn, MD, MS

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Non-Malignant Diseases

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

- No

Q15. RESEARCH QUESTION:

What are the outcomes of patients with acquired pure red cell aplasia (PRCA) who undergo allogeneic hematopoietic cell transplantation (HCT)?

Q16. RESEARCH HYPOTHESIS:

Allogeneic HCT results in 5-year overall survival (OS) greater than 50% for patients with acquired pure red cell aplasia. Recent improvements in allogeneic HCT supportive care and GVHD prophylaxis have led to improved outcomes in this patient population.

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

Suggested word limit of 200 words:

Primary:

1. To estimate the overall survival of patients receiving allogeneic HCT for acquired PRCA.

Secondary:

1. To estimate transplant outcomes in patients treated after 2015 versus earlier.
2. To estimate the cumulative incidence of transplant related mortality.
3. To estimate the cumulative incidence of primary engraftment failure.
4. To estimate the cumulative incidence of acute graft-versus-host disease (GVHD).
5. To estimate the cumulative incidence of chronic GVHD.

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

Acquired PRCA is a rare disorder that can be life-threatening without treatment. Treatment of PRCA is based on small case series, and few patients receive allogeneic HCT for this disorder each year. Recent published reports in allogeneic HCT for non-malignant conditions suggest improving outcomes in these patients. Given the rarity of the disorder, a registry based study is necessary to examine outcomes in this population. Improving OS after allogeneic HCT may suggest a new standard of care for management of this disorder.

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

Acquired PRCA is a rare disorder that is characterized by a loss of erythropoietic elements in the bone marrow with sparing of other hematopoietic progenitor lineages. Acquired PRCA may be primary or secondary. Primary acquired PRCA likely arises through autoimmune recognition of erythroid progenitors, whereas secondary acquired PRCA may be due to many different causes including drugs, infections, and malignancy (especially large granular lymphocyte leukemia and chronic lymphocytic leukemia). [1] Acquired PRCA is rare, so the exact incidence is unknown. The diagnosis of PRCA requires the following criteria to be met: normocytic, normochromic anemia, reticulocytopenia, normal white blood cell and platelet counts, normocellular bone marrow with erythroblasts totaling <1% or proerythroblasts plus basophilic erythroblasts totaling <5% percent of nucleated cells, and no significant abnormalities in the non-erythroid hematopoietic lineages.[1] In a large cohort study of acquired PRCA, a total of 185 patients were included. After a median follow-up of 87.6 months, the median OS had not yet been reached.[2]

Given the rarity of acquired PRCA, there are no high-quality data to guide management. Treatment generally involves supportive care with RBC transfusions. Initial disease modifying therapy includes immunosuppressive medications.[1,3-6] Immunosuppressive therapies that have been reported in small case series include glucocorticoids, cyclosporine, azathioprine, intravenous immunoglobulin, rituximab, and others. Allogeneic HCT has been used in a small number of cases and is curative, but may be complicated by a high risk for transplant related mortality.[7,8] The European Society for Blood and Marrow Transplantation published their experience transplanting acquired PRCA in 2019.8 A total of 33 adults received allogeneic transplants between 2000-2015. The median age at diagnosis was 34 years. The median time from diagnosis to transplant was 3.7 years. Approximately half of the transplants used bone marrow, and slightly less than half were myeloablative. The 5-year OS was 51%. Five patients required second transplants. Fifteen patients died. Causes of death included infection (8 patients), GVHD (5 patients), multiorgan failure (1 patient), and unknown (1 patient).

The feasibility of using alternative donors for acquired PRCA has not been reported. However, promising results have been reported for patients with severe aplastic anemia and hemoglobinopathies receiving haploidentical transplants.[9,10] In a recent study by DeZern and colleagues, outcomes of patients receiving haploidentical transplants for severe aplastic anemia were reported.[10] A total of 37 patients received haploidentical transplants. The conditioning regimen was rabbit antithymocyte globulin (2.5 mg/kg total), fludarabine (150 mg/m2 total), cyclophosphamide (29 mg/kg total), and total body irradiation (200-400 cGy). The GVHD prophylaxis was with posttransplant cyclophosphamide, mycophenolate mofetil, and tacrolimus. The OS for all patients was 94% (90% CI, 88-100) at 1 and 2 years. The cumulative incidence of grade II-IV acute GVHD at day 100 was 11%. The cumulative incidence of chronic GVHD at 2 years was 8%. It is unclear whether patients with acquired PRCA have similar outcomes when treated with haploidentical transplantation. These results are encouraging and suggest that allogeneic HCT is a viable therapy for patients with non-malignant bone marrow failure conditions regardless of donor source.

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

[Click here]

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

Any patient with a diagnosis of acquired PRCA who received allogeneic HCT between 2000 and the most recent year available.

Q21. Does this study include pediatric patients?

- Yes

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

Age at transplant
Sex
Performance status
HCT-Comorbidity Index
Donor type
Graft type
Conditioning intensity
Graft-versus-host disease prophylaxis
Year of transplant

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

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

None

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

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

None

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

None

Q26. REFERENCES:

1. Means RT, Jr. Pure red cell aplasia. Blood. 2016;128(21):2504-2509.
2. Hirokawa M, Sawada K, Fujishima N, et al. Long-term outcome of patients with acquired chronic pure red cell aplasia (PRCA) following immunosuppressive therapy: a final report of the nationwide cohort study in 2004/2006 by the Japan PRCA collaborative study group. Br J Haematol. 2015;169(6):879-886.
3. Clark DA, Dessypris EN, Krantz SB. Studies on pure red cell aplasia. XI. Results of immunosuppressive treatment of 37 patients. Blood. 1984;63(2):277-286.
4. Means RT, Jr., Dessypris EN, Krantz SB. Treatment of refractory pure red cell aplasia with cyclosporine A: disappearance of IgG inhibitor associated with clinical response. Br J Haematol. 1991;78(1):114-119.
5. Narra K, Borghaei H, Al-Saleem T, Hoglund M, Smith MR. Pure red cell aplasia in B-cell lymphoproliferative disorder treated with rituximab: report of two cases and review of the literature. Leuk Res. 2006;30(1):109-114.
6. Sawada K, Fujishima N, Hirokawa M. Acquired pure red cell aplasia: updated review of treatment. Br J Haematol. 2008;142(4):505-514.
7. Tseng SB, Lin SF, Chang CS, et al. Successful treatment of acquired pure red cell aplasia (PRCA) by allogeneic peripheral blood stem cell transplantation. Am J Hematol. 2003;74(4):273-275.
8. Halkes C, de Wreede LC, Knol C, et al. Allogeneic stem cell transplantation for acquired pure red cell aplasia. Am J Hematol. 2019;94(11):E294-E296.
9. Bolanos-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285-4291.
10. DeZern AE, Zahurak ML, Symons HJ, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. Blood Adv. 2020;4(8):1770-1779.

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

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

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

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

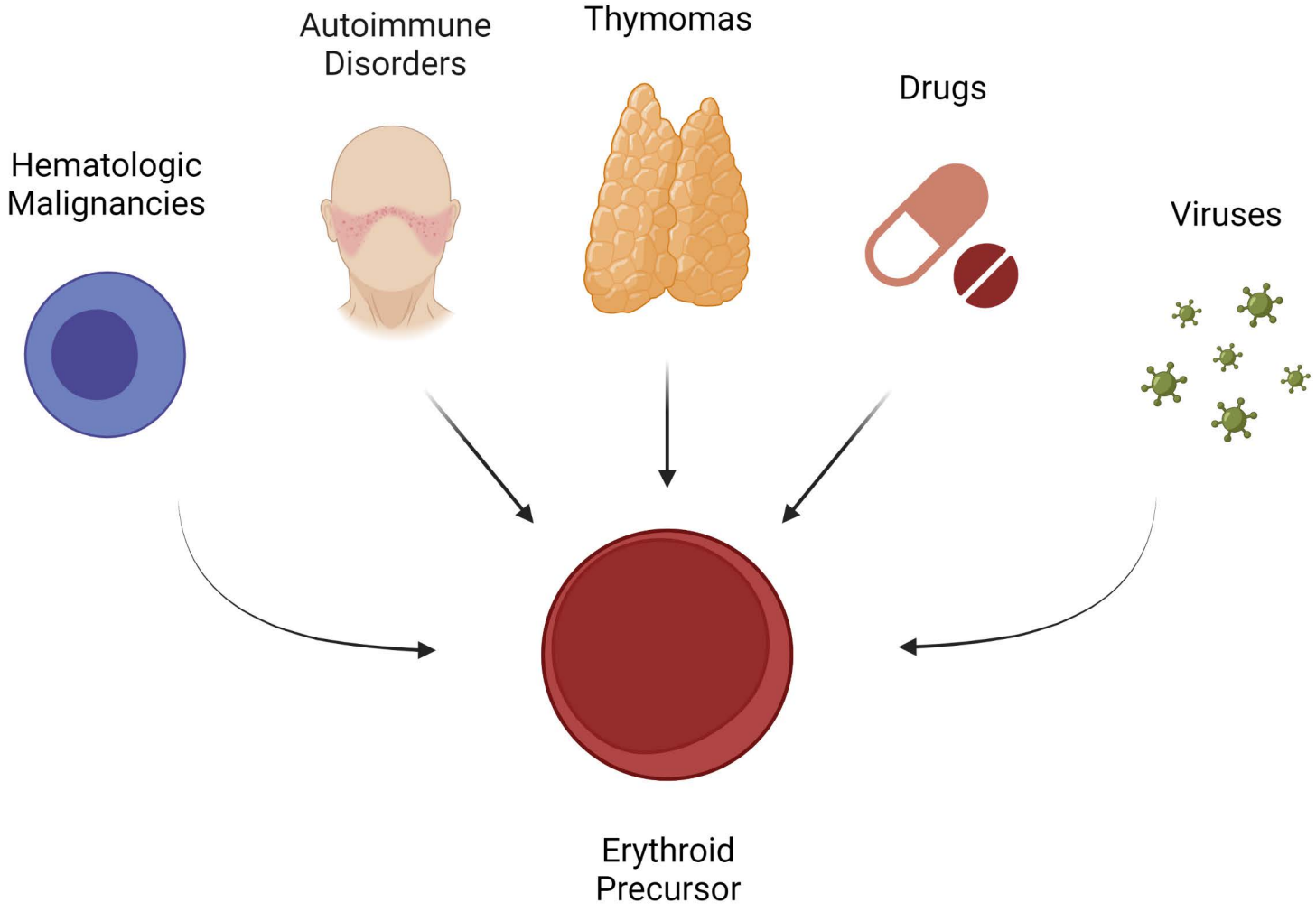
N/A

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

Embedded Data:

N/A

Acquired Pure Red Cell Aplasia



Diamond-Blackfan anemia and acquired pure red cell aplasia undergoing first allogeneic HCT, among those with at least 1-year follow-up, 2000-2019, US and Canada

Characteristic	TED	CRF
No. of patients	137	106
Age at transplant, years - no. (%)		
Median (min-max)	11 (1-71)	12 (1-74)
<10	64 (47)	47 (44)
10-17	28 (20)	23 (22)
18-29	19 (14)	15 (14)
30-39	12 (9)	7 (7)
40-49	4 (3)	8 (8)
50-59	7 (5)	4 (4)
60-64	1 (1)	0 (0)
65-69	1 (1)	0 (0)
>=70	1 (1)	2 (2)
Disease - no. (%)		
Acquired Pure Red Cell Aplasia	27 (20)	18 (17)
Diamond-Blackfan anemia (pure red cell aplasia)	110 (80)	88 (83)
Reported planned conditioning intensity - no. (%)		
RIC/NMA	49 (36)	34 (32)
MAC	86 (63)	63 (59)
Missing	2 (1)	9 (8)
Donor type - no. (%)		
HLA-identical sibling	65 (47)	25 (24)
Other related	11 (8)	8 (8)
Well-matched unrelated (8/8)	33 (24)	44 (42)
Partially-matched unrelated (7/8)	7 (5)	8 (8)
Mis-matched unrelated (<= 6/8)	1 (1)	2 (2)
Unrelated (matching TBD)	5 (4)	0 (0)
Cord blood	15 (11)	19 (18)
Graft (Product) type - no. (%)		
Bone marrow	95 (69)	65 (61)
Peripheral blood	26 (19)	22 (21)
Umbilical cord blood	10 (7)	16 (15)
BM + UCB	5 (4)	3 (3)
Missing	1 (1)	0 (0)
Year of Transplant - no. (%)		
2000-2004	15 (11)	19 (18)
2005-2009	24 (18)	28 (26)
2010-2014	60 (44)	17 (16)
2015-2019	38 (28)	42 (40)

Characteristic	TED	CRF
Follow-up, months - median (range)	74 (12-217)	61 (12-195)