BMT CTN #0903 Statistical Analysis Plan (SAP)

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Protocol:

BMTCTN #0903 Allo TX for HIV Participants v3.0

Protocol Synopsis:

The BMT CTN protocol #0903 titled "Allogeneic Hematopoietic Cell Transplant for Hematological Cancers and Myelodysplastic Syndromes in HIV-Infected Individuals" is a Phase II, multicenter trial. The primary objective is to assess the feasibility and safety of allogeneic hematopoietic cell transplantation (HCT) in HIV-infected participants. The primary endpoint is 100-Day Non-Relapse Mortality (NRM). Secondary endpoints include disease status at Day 100 post-HCT, time to hematopoietic recovery, hematologic function, chimerism, infections, overall survival, acute graft vs. host disease and chronic graft vs. host disease, immune reconstitution, and impact of HCT on the HIV reservoir. The target sample size was 15 participants and participants are being followed for 2 years post-HCT.

Study Status and Publication Plan:

The study opened to accrual in May 2012 and the last participant was enrolled in June 2016 with a total of 20 participants enrolled to the study. Seventeen participants proceeded to transplant as of July 14, 2016 and the last participant was pending transplantation due to donor issues. It is expected that all transplanted participants would have completed 100-day follow up by Dec 2016. And it is expected that all participants would complete 2-year follow up per protocol by August 2018. The Endpoint Review Committee (ERC) was formed in July 2016 and the ERC is planning to initiate the data review since September 2016 based on the ERC Charter developed by DCC statistician and approved by the protocol team. It is expected that ERC process including data QC for the primary endpoint will be completed by November 2016. Data lock is planned as soon as the ERC data compilation will be done to generate the preliminary analysis report. The analysis report will be provided to the team within 2 weeks of the data lock. The writing team will prepare a Tandem abstract (submission deadline in December 2016) and also work on the manuscript for publication.

Due to the ERC progress, primary endpoint review was completed in December 2016 and already passed the Tandem deadline, the team decided to target a ASCO abstract with deadline in Feb 2017. The Abstract was presented at the ASCO as oral presentation.

Primary Endpoint and Analysis:

The primary objective is to assess the feasibility and safety of allogeneic hematopoietic cell transplantation (HCT) in HIV-infected participants. The primary endpoint is 100-Day Non-Relapse Mortality (NRM) post transplant. The events for non-relapse mortality are death due to any cause other than relapse of the underlying malignancy. The primary analysis will consist of estimating the 100-day NRM probability along with a 95% confidence interval using the cumulative incidence function.

There are no interim analyses for this study. A stopping guideline using the futility boundary of a truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions for non-relapse mortality was implemented during the trial duration to guard against excessive mortality.

Sample Size Calculations and Stopping Guidelines

The sample size is 15 patients for this trial. Allogeneic transplant for patients with HIV is considered unacceptable if 100-day non-relapse mortality probability is 45% or higher. The objective of the study is to show that 100-day NRM is lower than 45%. In patients without HIV, non relapse mortality probability 100 days after allogeneic transplant is expected to be lower than 15%. Therefore, we framed this objective as a hypothesis test of the null hypothesis H0:p>=0.45, where p is the 100 day NRM probability, and this study is adequately powered against the alternative hypothesis H1:p=0.15. The stopping rule and study design described in detail below has a 8% chance of concluding that allogeneic transplant for patients with HIV has less than 45% NRM when in fact the 100 day NRM rate is 45% (type I error), and an 83% chance of concluding that the NRM rate is lower than 45% when the 100 day NRM rate is 15% (power).

To guard against excessive mortality, non-relapse mortality will be monitored up to 100 days post transplant and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

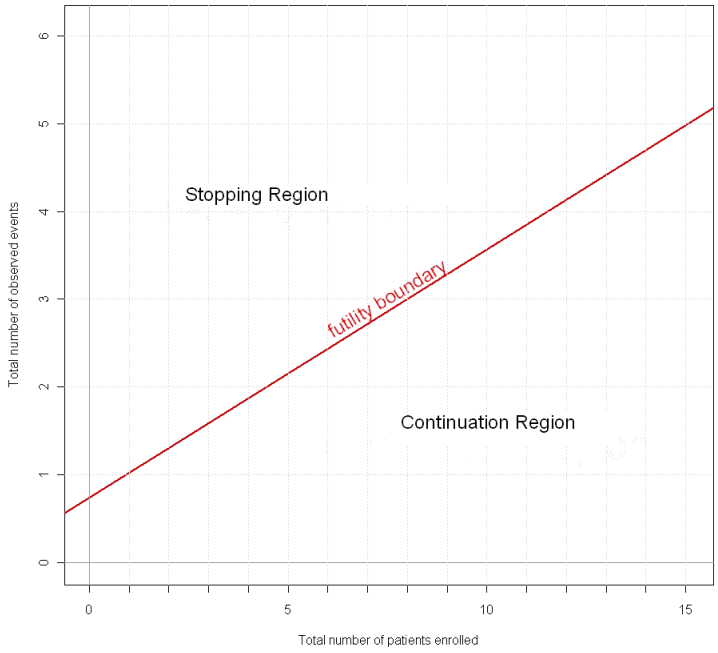
A truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions for non-relapse mortality will be used as described below. This sequential testing procedure conserves type I error across all of the monitoring looks for NRM. The SPRT can be represented graphically. At each interim analysis, the number of patients enrolled is plotted against the total number of patients who have experienced NRM. The continuation region of the SPRT is defined by two parallel lines. For a hypothesis test H_0: $\theta = \theta_0$ versus H_1: $\theta = \theta_1$ where $\theta_0 > \theta_1$, if the graph falls above the upper boundary, accept H_0 and if the graph falls below the lower boundary reject H_0 and conclude H_1. Only the upper boundary will be used to protect against excessive NRM which would make it unlikely that we could conclude that the NRM is less than 45% by the end of the study.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be slightly lower than the nominal level. The test to be used in this protocol was developed from the following SPRT:

- An SPRT testing H_0: p = 45% versus H_1: p = 15% NRM, with nominal type I and II errors of 7% and 30%, respectively.
- The slope of the parallel lines for monitoring NRM is 0.283 and the intercepts are –1.53 and 0.74.
- *Note that the stopping rule shown in Table 5.1 was constructed using the futility boundary of this SPRT test. The futility boundary was used to ensure that the DSMB will be notified if it is no longer likely that we will be able to demonstrate that 100-day NRM is lower than 45%, thus protecting against excessive NRM.*

The futility stopping boundary is shown in below Figure 5.1 for the SPRT test.

FIGURE 5.1 SPRT STOPPING BOUNDARY FOR 100-DAY NRM



The futility stopping rules are summarized in Below Table 5.1 for the SPRT test.

TABLE 5.1 STOPPING GUIDELINES FOR 100-DAY NRM AMONG PATIENTS ENROLLED

Number of patients enrolled (n)	SPRT stopping boundary (x)
2-4	2

5-7	3
8-11	4
12-15	5

* Stopping guideline is triggered if ≥ x patients out of n patients enrolled experience NRM.

Participants to Include:

The study enrolled a total of 20 participants. Only transplanted participants will be included to evaluate the post-transplant outcomes, which will be specified below for each. The participant's eligibility criteria will also be reviewed/adjudicated by the ERC.

Additional data source and data analysis:

Some data will be retrieved from CIBTMR data system including the platelet engraftment information and others as needed.

In a secondary analysis, a Cochran-Mantel-Haenszel test will be used to compare 100-day NRM probabilities between participants enrolled in this study to matched non-HIV-infected participants from the CIBMTR database. Closely matched controls will be identified at ratio 1:4 using the following criteria: age, gender, year of transplant, performance status, interval from diagnosis to transplant, diagnosis, disease status, preparative regimen/intensity, GVHD prophylaxis regimen, cytogenetics if available for acute leukemia.

Due to the CIBMTR decision, data was not extracted from CIBMTR database and the team decided to proceed the publication plan without addition the additional data analysis.

Software:

All analyses will be conducted using SAS 9.4 or higher software, or R version 3.1.0 or higher. Major procedures will include proc lifetest, proc means, proc freq in SAS and CUMINC in R.

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Data Summary

Exhibit 0903-1: Demographics and Baseline Characteristics.

Demographics and baseline characteristics will be described by median and range for continuous variables and by frequencies and percents for categorical variables. Characteristics to be examined inlcude: age, gender, race, ethnicity, performance status, disease stage, genotype, donor type, donor gender, donor-recipient CMV, HLA matching, graft type, conditioning regimen, HIV load, CD4 counts, number of prior chemotherapy regimens as treatment of primary malignancy and number of prior HIV regimens, bilirubin, creatinine clearance, ALT, AST. Data will be tabulated in a table as below:

Table 1: Demographics and Baseline Characteristics

Total Enrolled	
Total Transplanted	
Gender	
Male	
Female	
Ethnicity	
Hispanic or Latino	
Not Hispanic or Latino	
Unknown / not answered	
Race	
American Indian/Alaskan Native	
Black or African American	
White	
Multi-race	
Other (not specified)	
Unknown / not answered	
Age (yrs)	
Mean (Std. Dev.)	
Median (Range)	
Karnofsky Performance Score	
100	
90	
80	
70	

Participant Diagnosis	
Acute Myeloid Leukemia (AML)	
Acute Lymphocytic Leukemia (ALL)	
Myelodysplastic Syndromes (MDS)	
Hodgkin's Lymphoma	
Non-Hodgkin's Lymphoma	
Leukemia Stage	
First Complete Remission	
Second Complete Remission	
Lymphoma Stage	
Complete Remission	
Partial Remission	
HIV Load	
Undetectable	
Detectable	
Mean (copies/mL)	
Median (Range)	
Pre-transplant CMV Status	
Positive	
Negative	
Number of Induction Chemotherapy	
1	
2	
3	
4	

HLA Match Score	
7/8	
8/8	
Number of Salvage Chemotherapy	
0	
1	
3	
5	
Conditioning Regimen	
Myeloablative	
Reduced Intensity	
Bilirubin (mg/dL)	
Mean (Std. Dev.)	
Median (Range)	
Creatinine Clearance (mL/min)	
Mean (Std. Dev.)	
Median (Range)	
ALT (units/L)	
Mean (Std. Dev.)	
Median (Range)	
AST (units/L)	
Mean (Std. Dev.)	
Median (Range)	
Baseline CD4 Count (cells/µL)	
Mean (Std. Dev.)	
Median (Range)	

Exhibit 0903-2: Non-Relapse Mortality

The primary endpoint is 100-Day Non-Relapse Mortality (NRM) post transplant. The 100-day NRM along with a 95% confidence interval using the cumulative incidence function will be provided. A cumulative incidence curve will be generated.

Figure 1: Non-Relapse Mortality

Note: Outcomes post the Day 100 of transplant as described below will be provided when data becomes available, which is NOT the same time as the evaluation of the primary endpoint – Day 100 NRM.

Exhibit 0903-3: Overall Survival

The overall survival probability at 6 month, 1-year and 2-years with 95% confidence interval will be estimated using the Kaplan-Meier product limit estimator. A survival curve will be generated.

In an additional analysis, a Cochran-Mantel-Haenszel test will be used to compare 6-month overall survival probabilities between participants in the study to matched controls selected for the secondary analysis of 100-day NRM as described for the primary endpoint.

Figure 2: Overall Survival

Exhibit 0903-4: Relapse/Progression

The event is relapse/progression. Death without relapse/progression is considered a competing risk. Participants alive with no history of relapse/progression are censored at the time of the last observation. Time-to-relapse or progression will be measured from transplant. Relapse rate at 6 months, 1 year and 2 years will be computed with a 95% confidence interval. A cumulative incidence curve will be generated.

Figure 3: Relapse/Progression

Exhibit 0903-5: Primary Cause of Death

Table listing the primary causes of death (COD) and time of death post transplant. The ERC adjudicated COD will be used instead of the center-reported COD. Results will be shown in Table 2.

Table 2: Cause Of Death

Participant #	Primary COD	Time of Death
Total Deaths (N)		

Exhibit 0903-6: Cumulative Incidence of Neutrophil Recovery

Time to neutrophil recovery will be the first of two consecutive days of $\geq$ 500 neutrophils/μL following the expected nadir. It will be estimated using cumulative incidence function with death prior to engraftment as the competing risk. Time to neutrophil recovery will also be described separately in the myeloablative and reduced intensity groups. Estimates at Day 28 along with 95% confidence interval will be provided.

Figure 4 (A) Neutrophil Recovery for all transplanted participants

Figure 4 (B) Neutrophil Recovery by Conditioning Regimen

No need to create curves for by conditioning regimen due to the small sample size, just describe

Exhibit 0903-7: Cumulative Incidence of Platelet Recovery

Time to platelet recovery to $\geq$ 20,000/μL will be the date platelet count is $\geq$ 20,000/μL for the first of two consecutive labs with no platelet transfusions 7 days prior. Time to platelet recovery to $\geq$ 50,000/μL will be the date platelet count is $\geq$ 50,000/μL for the first of two consecutive labs with no platelet transfusions 7 days prior. Both will be estimated using cumulative incidence function with death prior to engraftment as the competing risk. Time platelet recovery will also be described separately in the myeloablative and reduced intensity groups. Estimates at Day 100 along with 95% confidence interval will be provided.

Figure 5 (A) Platelet Recovery to > 20,000/μL for all transplanted participants

Figure 5 (B) Platelet Recovery to > 20,000/μL by Conditioning Regimen

Figure 5 (C) Platelet Recovery to > 50,000/μL for all transplanted participants

Figure 5 (D) Platelet Recovery to > 50,000/μL by Conditioning Regimen

Due to the small patient number, agreed to remove platelet recovery by conditioning regimen and only do the overall.

Exhibit 0903-8: Hematologic function

Hematologic function was defined by ANC >1500, Hemoglobin >10g/dL without transfusion support, and platelets >100,000. Table 3 (A) will display the summary statistics for neutrophil counts, platelet counts and hemoglobin at Day 100 and 6 months.

The proportions of participants with hematologic function at Day 100 and 6 months will be described with confidence intervals in participants surviving to these time points in table (B).

Exploratory analysis to examine the relationship between hematologic function and cell dose may be conducted in an additional analysis.

Table 3 (A): Summary Statistics for ANC, platelets and hemoglobin

Table 3 (B): Summary of Hematologic Function

Hematologic Function at Day 100	
Yes	
No	
Have not reached Day 100 post transplant	
Hematologic Function at Day 180	
Yes	
No	
Died within 180 days post transplant	
Have not reached Day 180 post transplant	
Total Evaluable	
Total Transplanted	

Exhibit 0903-9: Disease response

The proportion of participants in complete remission (CR), partial remission (PR), stable disease, and relapse at 100 days post-transplant will be described. ERC adjudicated disease status will be used for the analysis.

Table 4: Disease Response at Baseline and Day 100

Exhibit 0903-10: Chimerism

Donor T-cell and myeloid chimerism at 4 weeks, 100 days, and 6 months will be described separately in the myeloablative and reduced intensity groups, according to proportions with mixed (5-95% donor cells), full (>95%), or graft rejection (<5%). Donor chimerism will be based on T-cell assays; If T-cell assay not done, marrow samples will be used. If marrow assay not done, blood samples will be used. Results will be summarized by conditioning group as in Table 4.

Table 4: Chimerism

Chimerism for **Myeloablative Group** Participants (n=)				
Assessment Time point post transplant	Full chimerism N (%)	Mixed chimerism N (%)	Graft rejection N (%)	Total # participants surviving/followed to the time point N (%)
@4 weeks				
@Day 100				
@6 months				
Chimerism for **Reduced Intensity Group** Participants (n=)				
Assessment Time point post transplant	Full chimerism N (%)	Mixed chimerism N (%)	Graft rejection N (%)	Total # participants surviving/followed to the time point N (%)
@4 weeks				
@Day 100				
@6 months				

Exhibit 0903-11: Unexpected Grades 3-5 Adverse Events

Table listing the unexpected grades 3-5 adverse events (AEs) including onset date, severity, relationship to protocol and medical monitor assessment.

Table 5: Unexpected Grades 3-5 Adverse Events

Patient ID	Center	AE Onset Date	Days Since Transplant	Adverse Event Description [Medical Monitor Description]	Event Severity	Relationship to Protocol	Effect on Therapy/ Intervention	DCC Expected?

Exhibit 0903-12: Grades 3-5 Core and Protocol-Specific Toxicities

Use bar graphs to show the toxicity frequency within 2 years post transplant for each assessment period and overall from transplant through 2 years. Toxicities as expected AEs were assessed at Day 28, Day 56, Day 100, Day 180, Day 365 and Day 730 using NCI CTCAE version 4.0. A summary table will be generated to show frequency with maximum toxicity of participants experiencing grade 3-5 toxicities and unexpected adverse events classified by system organ class. Results for this endpoint will be summarized in the below tables, besides the bar graphs.

Table 6: Grades 3-5 Adverse Events (Unexpected AEs and expected Toxicities) Within 2 Years of Transplant

Maximum Grades 3-5 AEs by System Organ Class		Total
System Organ Class	**Grade**	
Blood and lymphatic system disorders	3	
	4	
	5	
	Grades 3-5	
Cardiac disorders	3	
	4	
	5	
	Grades 3-5	
Eye disorders	3	
	4	
	5	
	Grades 3-5	
Gastrointestinal disorders	3	
	4	
	5	
	Grades 3-5	

Maximum Grades 3-5 AEs by System Organ Class		Total
……	3	
	4	
	5	
	Grades 3-5	
……	3	
	4	
	5	
	Grades 3-5	
……	3	
	4	
	5	
	Grades 3-5	
Any organs	3	
	4	
	5	
	Grades 3-5	

Figure 6: Toxicity Frequency Within 2 Years of Transplant

Exhibit 0903-13: Acute GVHD

Table to summarize the maximum acute GVHD post transplant. Plots of cumulative incidence of acute GVHD grade II-IV (Panel A) and acute GVHD grade III-IV (Panel B) from the time of transplant. Provide estimates of cumulative incidence of acute GVHD grade II-IV or III-IV at day 100 (as well as Day 180) post transplant, with 95% confidence intervals. Death prior to occurrence of acute GVHD will be considered as a competing risk.
Results for this endpoint will be summarized in the below table, besides the cumulative incidence curves.

Table 7: Acute GVHD

Maximum Acute GVHD Grade	Total	
	N	(%)
Grade 0, No aGVHD		
Grade I		
Grade II		
Grade III		
Grade IV		
Total Transplanted		

Maximum Acute GVHD Grade	Total	
	N	(%)
Day 100 Incidence Rate (95% CI) of Grade II-IV acute GVHD		
Day 100 Incidence Rate (95% CI) of Grade II-IV acute GVHD		

Figure 7: Acute GVHD

Exhibit 0903-14: Chronic GVHD

Table to summarize the maximum grade and overall maximum severity of chronic GVHD. Cumulative incidence of chronic GVHD post transplant will be plotted. Provide incidence rate of chronic GVHD at 1-year and 2 years post transplant with 95% confidence intervals. Death prior to occurrence of chronic GVHD will be considered as a competing risk.
Results for this endpoint will be summarized in the below table, besides the cumulative incidence curve.

Table 8: Chronic GVHD

	N (%)
1 year Incidence Rate (95% CI)	
2 year Incidence Rate (95% CI)	
Maximum Grade of chronic GVHD Limited Extensive	
Maximum Severity of chronic GVHD Mild Moderate Severe	

Figure 8: Chronic GVHD

Exhibit 0903-15: Infections

Table to summarize the site-reported infections. Number of infections per participant and maximum severity of infections per participant will be tabulated. Total number of infections by type of organism will also be tabulated. Results for this endpoint will be summarized in the below table.

Table 9: Infections

	Total N (%)
# Patients Transplanted	
# Patients with Infections	
# Patients with Infection Reports =1 =2 =3 =4 =5 >=6	
Total Infection Events	
Maximum Severity by Patient None Moderate Severe Life Threatening/Fatal	
Infection by Type (# of patients) Bacterial Viral Fungal Protozoal Other	

Exhibit 0903-16: Immune Reconstitution

Immune reconstitution assays on peripheral blood which include CD2, CD3, CD4, CD8, CD19, CD3+/CD25+, CD45 RA/RO, CD56+/CD3- and quantitative immunoglobulins (IgM, IgG and IgA) are measured in all patients prior to the conditioning, at 8 weeks, and 6 and 12 months (and possibly 2 years) post-transplant. These will be summarized at each time point using descriptive statistics.

Table of descriptive statistics as well as box plots across time point will be provided.

Table 10: Immune Reconsitution

		N	Mean	Std Dev	Median	Min	Max
CD2 (cells/µL)	**Baseline**						
	Day 56						

		N	Mean	Std Dev	Median	Min	Max
	6 Months						
	1 Year						
	2 Years						
CD3 (cells/µL)	**Baseline**						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
CD4 (cells/µL)	**Baseline**						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
CD8 (cells/µL)	**Baseline**						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
CD19 (cells/µL)	**Baseline**						
	Day 56						
	6 Months						
	1 Year						
	2 Years						

		N	Mean	Std Dev	Median	Min	Max
CD3+/CD25+ (cells/µL)	Baseline						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
CD45 RA/RO (cells/µL)	Baseline						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
CD56+/CD3- (cells/µL)	Baseline						
	Day 56						
	6 Months						
	1 Year						
	2 Years						
IgA (mg/dL)	Day 56						
	6 Months						
	1 Year						
	2 Years						
IgM (mg/dL)	Day 56						
	6 Months						
	1 Year						
	2 Years						
IgG (mg/dL)	Day 56						
	6 Months						
	1 Year						
	2 Years						

Figure 9: Immune Reconstitution

Exhibit 0903-17: Accrual Over Time By Center

Table showing accrual numbers for each participating center, actual accrual versus projected accrual number.

Table 11: Accrual

Exhibit 0903-18: Significant Protocol Deviations

Table listing the cumulative significant protocol violations/deviations occurred during the study, including transplant center, patient ID, description of the protocol deviations.

Table 12: Protocol Deviations

Protocol also defined the following two secondary endpoints. Data are needed from outside resource in order to proceed with the intended analysis. The protocol team decision is: The protocol team will closely follow up with NMDP repository for the lab results. If these can be made available prior to the submission of the primary manuscript, it will be included in the primary manuscript, otherwise it will be included in a follow up analysis to update the manuscript submission or in a secondary manuscript.

Maintenance of Antiretroviral Therapy

Maintenance of antiretroviral therapy will be monitored in all patients until time or death or two years post HCT whichever occurs first. Number and proportion of patients maintaining ARV will be summarized at 6, 12, and 24 months post-transplant.

Impact of Therapy on HIV-1 Reservoir

HIV RNA levels will be measured prior to initiation of ablative chemotherapy, and at Day 100, 12 months, 13 months (for some patients) and 24 months post-transplant. Standard assay will measure HIV RNA levels (viral load) and for patients with no detectable viral RNA using the standard assay, a single copy assay will be performed to assess persistent viremia. The proportion of patients with undetectable viral loads at Day 100, and 12 and 24 months will be examined and an exact binomial confidence interval will be calculated. Additionally, change in viral loads status between consecutive time points will be described by the proportion of patients whose viral loads changed from detectable to undetectable between assessment times.