BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN PROTOCOL #0903/AMC-080

Allogeneic Hematopoietic Cell Transplant for Hematological Cancers and Myelodysplastic Syndromes in HIV-Infected Individuals

Deletions to the protocol are indicated in strike-out text. Additions are noted in underlined text.

Major Changes to the Protocol

- *Synopsis:*
  - Primary objective: The primary objective is to assess the feasibility and safety of allogeneic hematopoietic cell transplantation (HCT) in HIV-infected patients. The primary endpoint is 100-Day Non-Relapse Mortality (NRM).
  - *Eligibility Criteria:* Patients ~~>~~≥ 15 years old, HIV-infected and diagnosed with acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL) in first or second complete remission (CR); Int-2 or high-risk myelodysplastic syndrome (MDS) with < 10% marrow blasts and no circulating myeloblasts after their most recent therapy; or Hodgkin or non-Hodgkin lymphoma beyond first CR with at least a partial response to last treatment. Patients must have either an 8/8 matched ~~(HLA-A, -B, -C, -DR)~~ related donor at HLA-A, -B, -C, (serologic typing or higher resolution) and –DRB1 (at high resolution using DNA based typing) or at least a 7/8 ~~high resolution~~ matched unrelated donor at HLA-A, -B, -C and DRB1 (at high resolution using DNA based typing). A 7/8 matched related donor match is permitted only if an 8/8 unrelated donor cannot be identified. A secondary matching criterion is the presence of homozygosity for the CCR5 delta32 mutation. Allogeneic transplantation using cord blood, T-cell depletion or ~~and~~ prior allogeneic HCT are not allowed for this study.

    Patients must have adequate organ function defined as 1) left ventricular ejection fraction at rest ≥40%; 2) DLCO, FEV_1, FVC ≥ 45% predicted; 3) total bilirubin ≤ 2.0 mg/dL, and ALT and AST≤ 5 x upper limit of normal (ULN); 4) ~~serum~~ creatinine clearance > 40mL/min (measured or calculated). Karnofsky/Lansky performance status≥ 70%.

- *§2.3.1 Patient Inclusion Criteria #3:* Patients must be ≥ 15 years of age.
- *§2.3.1 Patient Inclusion Criteria #4b:* Patients with advanced myelodysplastic syndromes (MDS), including those with International Prognostic Scoring System (IPSS) Int-2 and high-risk disease with less than 10% marrow blasts and no circulating myeloblasts after most recent therapy. Patients with acute leukemia that develops from a pre-existing MDS must meet the inclusion criteria for patients with AML detailed above.

- *§2.3.1 Patient Inclusion Criteria #5:* Donor/Recipient HLA Matching:
  a) Related donor: must be an 8/8 match at HLA-A, -B, -C, (serologic typing or higher resolution) and –DRB1 (at high resolution using DNA based typing). A 7/8 related donor match is permitted only if an 8/8 unrelated donor cannot be identified.
  b) Unrelated donor: must be a 7/8 or 8/8 match at HLA-A, -B, -C, and -DRB1 (at high resolution using DNA based typing).
- *§2.3.2 Patient Exclusion Criteria #2:* ~~<15 years of age.~~
- *§2.3.2 Patient Exclusion Criteria #11:* T-cell depletion (including ATG or alemtuzumab) is not allowed.
- *§2.3.2 Patient Exclusion Criteria #12:* Use of cord blood as the source of hematopoietic cells is not allowed.
- *§2.4 Donor Inclusion Criteria:* ~~Donor/Recipient HLA Matching:~~
  ~~a) Related donor: must be an 8/8 match (HLA-A, -B, -C, and -DR). A 7/8 related donor match is permitted only if an 8/8 unrelated donor cannot be identified.~~
  ~~b) Unrelated donor: The donor must have no more than a single antigenic or allelic mismatch at HLA-A, -B, -C, and -DRB1 compared to the recipient; the remaining 7 loci must be matched at the allelic level. Both recipient and unrelated donor must be HLA-typed at high resolution.~~

TABLE 2.5A- DIAGNOSES, PREPARATIVE REGIMENS, AND GVHD PROPHYLAXIS REGIMENS

Diagnosis	RIC	MAC	GVHD
AML in morphologic CR1/2 **MDS**: IPSS int-2/high with <10% marrow blasts **HL** beyond CR1 in PR/CR **ALL** in morphologic CR1/2 **NHL** beyond CR1 in PR/CR	Flu/Bu		Tac/MTX or Tac/Sirolimus or Post-Tx Cy with Tac/MMF
		Bu/Flu	Tac/MTX or ~~Tac/Sirolimus or~~ Post-Tx CY with Tac/MMF (Tac/MMF not required with post-tx CY for 8/8 matches)
	Flu/Mel	~~Bu/Cy~~ Cy/TBI	Tac/MTX or Tac/Sirolimus

Table 2.5B GVHD PROPHYLAXIS REGIMENS

Conditioning Regimen/Match	GVHD Prophylaxis
Fludarabine/Busulfan (Flu/Bu) – RIC / 7/8 or 8/8 Match	**Tacrolimus** • Blood trough levels 5-15 ng/mL • Tacrolimus initiation tapering and discontinuation is per institutional guidelines **Methotrexate** • 15 mg/m^2 Day 1 • 5-10 mg/m^2 Days 3, 6 and 11
	Tacrolimus • Blood trough levels 5-10 ng/mL • Tacrolimus initiation tapering and discontinuation is per institutional guidelines **Sirolimus** • ~~10-15 mg/m^2 Day 1~~ • ~~5-10 mg/m2 Days 3, 6 and 11~~ • 12 mg loading dose on Day -3 • 4 mg daily starting on Day -2 adjusted to maintain a trough level between 3-12 ng/ml • Sirolimus tapering and discontinuation is per institutional guidelines
	Post-transplant ~~Cytoxan~~Cyclophosphamide • 50 mg/kg Days 3 and 4 (with MESNA) **Tacrolimus** • Beginning on Day 5, administer tacrolimus to achieve ~~Blood~~ trough levels 5-10~~0~~5 ng/mL for 6 months • 1 mg Day 5 and dose adjusted weekly after Day 7 and continued for 6 months post-transplantation • Tacrolimus tapering and discontinuation is per institutional guidelines **MMF** • 15 mg/kg ~~– 1 gram/kg~~ po TID (max dose 1 gm po TID)Day 5 to Day 35
Busulfan/Fludarabine (Bu/Flu) - MAC/ 7/8 or 8/8 Match	**Tacrolimus** • Blood trough levels 5-15 ng/mL • Tacrolimus initiation tapering and discontinuation is per institutional guidelines **Methotrexate** • 15 mg/m^2 Day 1 • 5-10 mg/m^2 Days 3, 6 and 11
	~~**Tacrolimus**~~ • ~~Blood trough levels 5-10 ng/mL~~ • ~~Tacrolimus initiation tapering and discontinuation is per institutional guidelines~~ ~~**Sirolimus**~~ • ~~10-15 mg/m^2 Day 1~~

	• ~~5-10 mg/m2 Days 3, 6 and 11~~
Busulfan/Fludarabine (Bu/Flu) – MAC 8/8 Match	**Post-transplant ~~Cytoxan~~ Cyclophosphamide (8/8 match)** • 50 mg/kg Days 3 and 4(with MESNA) • Note that tacrolimus/MMF is not required in this setting
Busulfan/Fludarabine (Bu/Flu) – MAC 7/8 Match	**Post-transplant Cyclophosphamide** • 50 mg/kg Days 3 and 4 (with MESNA) **Tacrolimus** • Beginning on Day 5, administer tacrolimus to achieve trough levels 5-15 ng/mL for 6 months • 1 mg Day 5 and dose adjusted weekly after Day 7 and continued for 6 months post-transplantation • Tacrolimus tapering, and discontinuation is per institutional guidelines **MMF** 15 mg/kg po TID (max dose 1 gm po TID) Day 5 to Day 35
Fludarabine/Melphalan (Flu/Mel) - RIC ~~Busulfan/~~Cyclophosphamide/ Total Body Irradiation(~~Bu/~~Cy/TBI) **– MAC** / **7/8 or 8/8 Match**	**Tacrolimus** • Blood trough levels 5-15 ng/mL • Tacrolimus initiation tapering and discontinuation is per institutional guidelines **Methotrexate** • 15 mg/m^2 Day 1 • 5-10 mg/m^2 Days 3, 6 and 11
	Tacrolimus • Blood trough levels 5-10 ng/mL • Tacrolimus initiation tapering and discontinuation is per institutional guidelines **Sirolimus** • ~~10-15 mg/m^2 Day 1~~ • ~~5-10 mg/m2 Days 3, 6 and 11~~ • 12 mg loading dose on Day -3 • 4 mg daily starting on Day -2 adjusted to maintain a trough level between 3-12 ng/ml • Sirolimus tapering and discontinuation is per institutional guidelines

- *§2.8.7 Sirolimus:* ~~However, the incidence of veno-occlusive disease of the liver was not noted to be higher than expected in trials of unrelated transplantation.~~
- *§2.8.9 Mycophenolate Mofetil:* The most frequent reported adverse reactions associated with MMF include infection, upset stomach and nausea. Less common reported adverse effects are low blood counts, vomiting and diarrhea. Some rare but serious reported adverse

reactions include serious injury to the gut including bloody stools and vomit, secondary cancers such as lymphoproliferative disease or lymphoma, serious infections of the brain, risks to a baby in pregnancy and progressive multifocal leukoencephalopathy (PML).

- *Table F-1:* Removed ~~Cy/Bu~~ and replaced it with Cy/TBI. The recommendations regarding drug-drug interactions were updated to reflect the drug changes.

Changes to the Consent Form (Appendix B)

- *Table B-2 – Adverse Events:* Abbreviations for drug names were added
- *§7C Risks Related to the Medication Used to Help Prevent Graft-versus-Host Disease (GVHD)*:
    - GVHD may be bad enough to cause death added as a risk for GVHD.
    - **Mycophenolate Mofetil:** MMF is a potent immunosuppressive drug that blocks the growth of the immune cells that can cause GVHD. Side-effects you might experience include nausea and vomiting, diarrhea, infection, low blood counts, serious injury to your gut (digestive tract) including bloody stools and vomit, secondary cancers, such as lymphoproliferative disease or lymphoma, serious infections of the brain, risk to an unborn child, or Progressive Multifocal Leukoencephalopathy (PML).
- *§7F Infections:* Infections may be bad enough to cause death added as a risk for infections.
- *§18. CCR5 Donor Screening*

    Human Immunodeficiency Virus (HIV) uses a protein called CCR5 as a way to get inside of cells. A few people are naturally able to block HIV infection because their body does not make the CCR5 protein. As a result, HIV does not have a way to enter their cells and cause an infection.

    Proteins are in every cell in our body and help keep the blood, skin and other parts of our bodies healthy. Every protein is made by a specific kind of gene. Every person has 2 copies of the gene that makes the CCR5 protein. One copy is from their mother and the other copy is from their father. Some people have changes to their genes that make the CCR5 protein. Another word for changes to a gene is mutation. Changes to the CCR5 gene means the body can't make the CCR5 protein. People who have 2 copies of the CCR5 gene mutation are called CCR5delta32homozygotes and they are naturally able to block HIV infection.

    Very few people in the world have mutations to both copies of their CCR5 gene. If you are Caucasian with a family background from northern Europe, the chance is about 1 out of 100 people in finding a matched donor with 2 copies of the CCR5 gene mutation. If you do not have a northern European background, the chance is very, very small that you would find a donor who has 2 copies of the CCR5 gene mutation.

    In one case, a person with 2 copies of the CCR5 gene mutation donated their blood-making cells for a transplant in a patient who had HIV and a blood cancer. Now the patient does not have any signs of HIV and does not need drugs to treat his HIV. We do not know if this will happen again, even if a donor has the CCR5 gene mutation

Besides the possible benefit of blocking HIV infection, some risks may come with a donor who has the CCR5 mutations. Research has shown that people with 2 copies of the CCR5 gene mutation may not fight off infections from West Nile virus (WNV) very well. WNV spreads through mosquito bites. Serious cases of WNV can cause a brain infection.

In addition to doing the standard tests to make sure a donor is a good match for you, we will also test possible donors to see if they have the CCR5 gene mutations. This testing will not slow down our search for your donor. We will let you know if we find a donor and if that donor has the CCR5 mutations. At that point, you and your doctor will need to decide if you want to use a donor with or without the CCR5 mutations.

- *Blood Samples for Research (optional):* We would like to have one small (4 teaspoons or 17 mL) blood sample for future research. If you agree, this sample will be obtained pre-transplant. ~~They~~It will be kept and may be used in research to learn more about HIV, cancer and other diseases
    - I do agree to ~~allow my~~ give a blood sample~~s to be stored~~ for research
- *Pediatric Assent to Participate in Research:*
    - Your doctor will check to see if you have a type matched ~~bone marrow~~ donor for your transplant.
    - Also, 1~~2~~3 months after your transplant, we will ask to take more blood from you (about 36 teaspoons) only if the HIV in your body still does not show up in a standard test.
    - I do agree to ~~allow my~~ give a blood sample ~~to be stored~~ for research

Minor Changes to the Protocol

- The clinicaltrials.gov study identifying number was added to the cover page.
- ~~Hematopoietic Stem Cell Transplantation (HSCT)~~ was changed to Hematopoietic Cell Transplantation (HCT) throughout the protocol for consistency.
- ~~Ablative therapy~~ changed to conditioning throughout the protocol for consistency.
- *Synopsis:*
    - Secondary Objectives:
        1. Disease status at Day 100 post-HCT
        2. Time to hematopoietic recovery
        3. Chimerism at ~~30 days~~ 4 weeks, 100 days, and ~~180 days~~ 6 months
        4. Hematologic function at 100 days and ~~180 days~~ 6 months
        5. Infections
        6. Six-month overall survival
        7. Acute graft-vs-host disease
        8. Chronic graft-vs-host disease
        9. Immunologic reconstitution at 8 weeks, ~~180 days~~ 6, 12 and ~~365 days~~ 24 months

10. Impact of HCT on the HIV reservoir at Day 100, 6 ~~months~~, 12 ~~year~~ and 24 ~~years~~ months post-HCT

- *§2.1 Study Overview:* The study is designed to evaluate the feasibility and safety of reduced-intensity and fully-ablative allogeneic hematopoietic cell transplantation (HCT) for patients with hematological malignancies or myelodysplastic syndromes (MDS) who have HIV infection
- *§2.2.1 Primary Objective:* The primary objective of this multicenter study is to assess the feasibility and safety of allogeneic hematopoietic stem cell transplantation (HCT) in HIV-infected patients. The primary endpoint is 100-Day Non-Relapse Mortality (NRM). ~~The primary objective of this multi-center study is to assess 100-day non-relapse mortality after allogeneic HCT in patients with HIV infection and hematological malignancies or MDS.~~
- *§2.2.2 Secondary Objectives:*
  - Disease status at Day 100 post-HCT
  - Time to hematopoietic recovery
  - Chimerism at ~~30, 100, and 180 days~~ 4 weeks, 100 days and 6 months post-HCT
  - Hematologic function at ~~100 and 180 days~~ 100 days and 6 months post-HCT
  - Infections
  - Six-month overall survival
  - Acute graft-vs.-host disease
  - Chronic graft-vs.-host disease
  - Immunologic reconstitution at 8 weeks ~~(or 6 months and 1 year), 180 days, 365 days~~ and 6, 12 and 24 months post-HCT
  - The impact of HCT on the HIV reservoir at Day 100, 6 ~~months~~,12 ~~year~~ and 24 ~~years~~ months post-HCT
- *§2.4 Donor Selection Criteria #3:* CCR5-delta32 mutation: An additional matching criterion for this study will be the presence of homozygosity for the CCR5-delta32 mutation. When ~~approximately 20 or more well-matched donors are identified via predictive HLA matching software (HapLogic 2® or its successor)~~ feasible based on donor likelihood of CCR5delta32 homozygosity and timeliness, potential donors will be assessed for CCR5—delta32 homozygosity. Among equivalently desirable donors as determined by transplant center donor selection criteria, a donor who is found to be a homozygote for CCR5-delta32 will be favored as long as such a selection does not compromise the optimal timing of HCT. HLA matching as a selection criterion will always take precedence over CCR5—delta32 homozygosity (see Appendix E for details).
- *§2.4.1 Donor Exclusion Criteria #4:* ~~Cord blood units.~~
- *§2.5 Study Treatments:* Table 2.5A outlines the diseases, conditioning regimens and GVHD prophylaxis regimens allowed for this study.
- *§2.5.1.1 Fludarabine and busulfan (Flu/Bu):* Days -5 to -4: Busulfan (4mg/kg/day PO or 3.2 mg/kg/day IV, 130 mg/m^2/day IV, total dose of 8 mg/kg PO or 6.4 mg/kg IV, or 260 mg/m^2 IV, respectively)
- Intraveneous busulfan may be administered in divided doses or once daily. Oral busulfan must be administered in divided doses. Busulfan dose adjustments for obesity are listed in

Section 2.5.2.4. Fludarabine dose adjustments for renal impairment are listed in Section 2.5.2.3.

See Section 2.5.4 and Table 2.6.1.4 for critical information about antiretroviral management in the setting of a busulfan-containing reduced intensity conditioning regimen when the antiretroviral regimen includes ritonavir.

- *§2.5.1.2 Fludarabine and melphalin(Flu/Mel)*
- *§2.5.2 Myeloablative Conditioning Regimens:* Myeloablative regimens permitted in this protocol are detailed below. See Section 2.5.4 and Table 2.6.1.4 for critical information about antiretroviral management in the setting of a myeloablative regimen when the antiretroviral regimen includes ritonavir.
- *§2.5.2.1 Busulfan and fludarabine (Bu/Flu):* Busulfan may be administered intravenously in divided doses or once daily
- *§2.5.2.2 Cyclophosphamide and total body irradiation (Cy/TBI):* Days -7 to -4: TBI (total dose of 1200-1420 cGy)

  MESNA will be given to reduce the risk of cyclophosphamide-associated hemorrhagic cystitis. MESNA will be dosed based on cyclophosphamide dose and may be administered per institutional guidelines.
- *§2.5.2.3 Conditioning agent dose adjustments for renal impairment:* Fludarabine: Patients with a creatinine clearance of ~~30~~40-70 ml/min (measured or calculated) should have a 20% dose reduction
- *§2.5.2.4 Conditioning agent dose adjustment for obesity:* Added Adjusted Ideal Body Weight (AIBW) formula and removed MESNA section.
- *§2.5.3 GVHD Prophylaxis Regimen: ~~Ex vivo~~* ~~T-cell depletion, *in vivo* T-cell depletion with ATG or alemtuzumab and prednisone-based prophylactic regimens are not allowed.~~ Transplant centers must use the GVHD prophylaxis regimens that are listed below in Table 2.5B. Guidelines for continuing ARV therapy with various prophylaxis regimens are detailed below in Table 2.5C.
- *§2.5.3.1 Tacrolimus:* Tacrolimus doses are adjusted to target whole blood levels between 5 and 15 ng/mL, except when the patient is receiving both tacrolimus and sirolimus, in which case it is recommended that serum trough levels of tacrolimus do not exceed 10 ng/mL. ~~Refer to Appendix F-4 for dosing.~~

  ~~For patients who are taking both tacrolimus and sirolimus it is recommended that serum trough levels of tacrolimus do not exceed 10 ng/mL.~~
- *§2.5.3.2 Methotrexate:* Dose reductions per institutional guidelines should be made for renal, hepatic and mucosal toxicity
- *§2.5.3.4 Post-transplant Cyclophosphamide with MESNA:* Post-transplantation cyclophosphamide with ~~MENSA~~ MESNA may only be used with fludarabine/busulfan for non-myeloablative and busulfan/fludarabine for myeloablative conditioning regimens

MESNA will be given to reduce the risk of cyclophosphamide-associated hemorrhagic cystitis. MESNA will be dosed based on cyclophosphamide dose and may be administered per institutional guidelines.

~~Hydration prior to cyclophosphamide may be given according to institutional standards. A recommended approach is as follows: Patients are instructed to increase fluids overnight before cyclophosphamide administration. Hydration with normal saline at 3 ml/kg/hr IV will be started 2 hours prior to cyclophosphamide, then the rate will be reduced to 2 ml/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 ml/kg/hr for 8 hours post-cyclophosphamide.~~

~~MESNA will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide or administered per institutional standards. MESNA dose will be based on the cyclophosphamide dose being given. The total daily dose of MESNA is equal to 80% of the total daily dose of cyclophosphamide.~~

~~Cyclophosphamide [50mg/kg IBW] will be given on Day 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).~~

It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids ~~as anti-emetics~~ for any reason.

Tacrolimus and MMF should not be used with post-transplant cyclophosphamide if the patient received a myeloablative conditioning regimen and the donor/recipient match is 8/8.

Additional immunosuppression for patients receiving post-transplant cyclophosphamide:

- Full myeloablative regimen and donor/recipient match is 8/8: no additional prophylaxis is given
- Full myeloablative regimen with a 7/8 match and for Flu/Bu non-myeloablative regimen:
  - On Day 5, patients will begin prophylaxis with Tacrolimus and Mycophenolic Acid Mofetil (MMF). Tacrolimus will be given at a dose of 1 mg IV ~~q day~~ daily then will be changed to a PO dosing schedule once a therapeutic level is achieved or as per institutional standards.
  - ~~Serum levels of Tacrolimus will be measured around Day 7 and then should be checked weekly thereafter and the dose adjusted accordingly to maintain a level of 5-15 ng/mL.~~
  - MMF will be given at a dose of 15 mg/kg PO TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID).
  - MMF prophylaxis will be discontinued after the last dose on Day 35 and Tacrolimus prophylaxis will be discontinued ~~after the last dose~~ per institutional standards, typically around Day 180.

- *§2.5.4 Ritonavir-Based Antiretroviral Therapy Dosing Considerations:* For patients receiving post-transplant cyclophosphamide for GVHD prophylaxis, antiretroviral therapy will be restarted on Day +5 as tolerated
- *§2.6.1.4 Antiretroviral Therapy:* Table 2.6.1.4 outlines continuation guidelines for ARV regimens based on the conditioning regimen used.
- *§3.2 Secondary Endpoints:* Removed all visit numbers from section headers.
- *§3.2.3 Chimerism:* Blood samples will be evaluated for T cell and myeloid chimerism at ~~Days 30, 100 and 180~~ 4 weeks, day 100, and 6 months post-transplant.
- *§3.2.4 Hematologic Function:* Hematologic function will be defined by ANC >1500, Hemoglobin >10g/dL without transfusion support, and platelets >100,000 and measured at day 100 and ~~180 days~~ 6 months. Use of growth factors will be noted
- *§3.2.7 Acute Graft-versus-Host Disease (GVHD):* Acute GVHD will be graded according to the BMT CTN MOP. The time to onset of acute grades II-IV GVHD and grades III-IV GVHD will be recorded, as well as the maximum grade ~~achieved~~ experienced.
- *§3.2.9 Immunologic reconstitution:* This will be measured in all patients at ~~8 weeks, 6 months and 12 months~~ 8 weeks, 6, 12 and 24 months.
- *§3.2.10 Impact of Therapy on the HIV Reservoir:* HIV-1 RNA levels will be measured in plasma prior to the initiation of ablative chemotherapy, and at Day 100, 6, 12 and 24 ~~years~~ months post-transplant in all patients. The latent HIV reservoir measurement assay at approximately 13 months will only occur in those patients who have no measurable viral load by single copy HIV assay at 12 months. (Appendix C).
- *§4.1.1 Screening and Eligibility Procedures #1:* An authorized user at the transplant center completes the Segment 0 Screening Form (patient demographic data~~, designation of donor type, high resolution HLA typing,~~ and the date that informed consent was signed). A study number will be generated for the patient with the submission of the Segment 0 Screening Form.

  Note: There are two reasons for completing the screening enrollment phase early. First, blood specimens are collected at baseline to address important research questions in this study. Secondly, for patients ~~receiving~~ requiring an unrelated donor, ~~transplant appropriate~~ sufficient time is needed ~~to search~~ for ~~a potential CCR5 delta32 homozygote donor~~ the unrelated donor search.

- *§4.2.1 Follow-up Schedule:*

  Follow-up Visits: Follow-up visits will begin as soon as patients are enrolled onto the study. The follow-up period is 24 ~~years~~ months.

  Reporting Patient Deaths: Recipient Death Information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death on the Death Form. If the cause of death is unknown at that time, ~~it need not be recorded at that time~~ the cause of death field may be left blank. However, once the cause of death is determined, the form must be updated in AdvantageEDC. In addition, all deaths must be reported via the Unexpected Grade 3-5 Adverse Event Forms in AdvantageEDC for this study.

Weekly GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day ~~100~~ 56 post-transplant for GVHD. After Day ~~100~~ 56 patients will be assessed at each follow-up visit (Day 100, and 6, 12 and 24 months~~180, 365 and 730~~) for the presence of GVHD. For scheduling, a target day range has been provided in Table 4.2.1.

- *§4.2.3 Patient Evaluations prior to the HCT conditioning therapy (within 3 months) #6:* ~~Bone marrow biopsy/aspirate for pathology~~ (This was already in the within 4 week window)
- *§4.2.3 Patient Evaluations prior to the HCT conditioning therapy:*

  The following observations need to be performed within 3 months of initiation of conditioning:

  6. HIV-1 RNA level (HIV viral load by standard assay).

  The following tests and observations will be performed within 4 weeks prior to initiation of conditioning:

  ~~1. Blood for HIV single copy measurements (see Appendix C).~~

  2. For lymphoma patients: CT scans of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease. PET scan should be performed.

  3. Bone marrow aspiration and biopsy, including cytogenetics

  ~~4. Future research sample collection for consenting patients (See Appendix C).~~

  The following tests and observations will be performed within 1-3 weeks prior to initiation of conditioning:

  1. Blood for HIV single copy measurements (see Appendix C).
  2. Optional future research sample collection for consenting patients (see Appendix C).
- *§4.2.4 Patient Post-HCT Evaluations:* Visits were corrected to be consistent with the rest of the protocol.
- *§4.2.4 Patient Post-HCT Evaluations #1:* Physical examination and weight weekly until 4 weeks then at 8 weeks, 100 days, 6, 12 and 24 months post-HCT.
- *Table 4.2.2A Pre-HCT Evaluations:* Table was corrected to be consistent with the text in §4.2.3.
- *Table 4.2.2B Post-HCT Evaluations:* Table was corrected to be consistent with the text in §4.2.4.
- *§5.4.2 Analysis of Secondary Endpoints:* Visits were corrected to be consistent with the rest of the protocol.
- For consistency throughout all BMT CTN studies, in this protocol 'pausing guidelines' or 'pausing rule' has been changed to 'stopping guidelines' or 'stopping rule.'
- *Appendix C:* Updated section headers and visits to be consistent with the rest of the protocol.
- *Appendix I Identification of CCR5delta32 Mutation Homozygous Donors:* Added to the protocol.