**University of Minnesota**
**Masonic Cancer Center**
**Blood and Marrow Transplantation**
**Department of Pediatrics**

# Hematopoietic Stem Cell Transplant for Dyskeratosis Congenita or Severe Aplastic Anemia

**MT2013-34C**
**CPRC #2013OC127**

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**Revision History**

| Revision # | Version Date | Detail of Changes | Consent change? (Y/N) |
|---|---|---|---|
| | 02/05/2014 | Original to CPRC | |
| 1 | 01/08/2015 | Schema, sections 1, 2.11, 4.1, 5 – remove TBI from the DC treatment plan;<br>Insert a new section 5 for donor selection/cell requirements<br>Update protocol to current template | yes |
| 2 | 09/16/2016 | Clarify for SAA – second transplants will receive the unmatched donor preparative regimen regardless of donor type | yes SAA |
| 3 | 4/10/2017 | Revised per CPRC stipulations to include background and donor preferences for 2nd transplant; added link to CPRC DSMP | no |
| 3A | 4/12/2017 | Clarified section 5.2 per IRB stipulation | No |
| 4 | 3/22/2018 | Section 4.5.1 and Appendix II: changed GVHD Prophylaxis from CSA to tacrolimus | Yes (consent attachments) |
| 4A | 08/15/2018 | Sections 4.1, 4.2 & study summary, added fludarabine dose adjustments for pediatric patients < 10kg; Sections 4.5.1 & 4.5.2 edited the dosing guideline for tacrolimus and MMF per pharmacist recommendation | No |
| 5 | 03/19/20 | Change of PI to Dr. Christen Ebens; added Brian Betts and Kristina Nelson to study committee<br>Addition of haploidentical donor treatment arms for SAA and dyskeratosis congenita<br>Updated diagnostic criteria for dyskeratosis congenita | Yes (consents and new attachments for Haplo) |
| 6 | 05/21/2020 | Edited dosing instructions to current standard of care, per recommendations of inpatient pharmacist | No |
| 7 | 02/15/2021 | Section 6, minor edits to laboratory procedures to remove inconsistencies from SOC orders | No |

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# Synopsis

## Hematopoietic Stem Cell Transplant for Patients with Dyskeratosis Congenita or Severe Aplastic Anemia MT2013-34C

This study facilitates the collection and analysis of outcome data for patients with dyskeratosis congenita (DC) or severe aplastic anemia (SAA) undergoing a hematopoietic stem cell transplant (HSCT).

**Study Design:** This is a treatment study using a fludarabine-based preparative regimen followed by a related or unrelated allogeneic hematopoietic stem cell transplant. Five different preparative regimens are included based on disease and donor type.

**Patient Population:** Persons 0-70 years of age diagnosed with dyskeratosis congenita or severe aplastic anemia who have bone marrow failure chacaterized by a requirment for red blood cell and platelet transfusions, or require a second transplant due to graft failure.

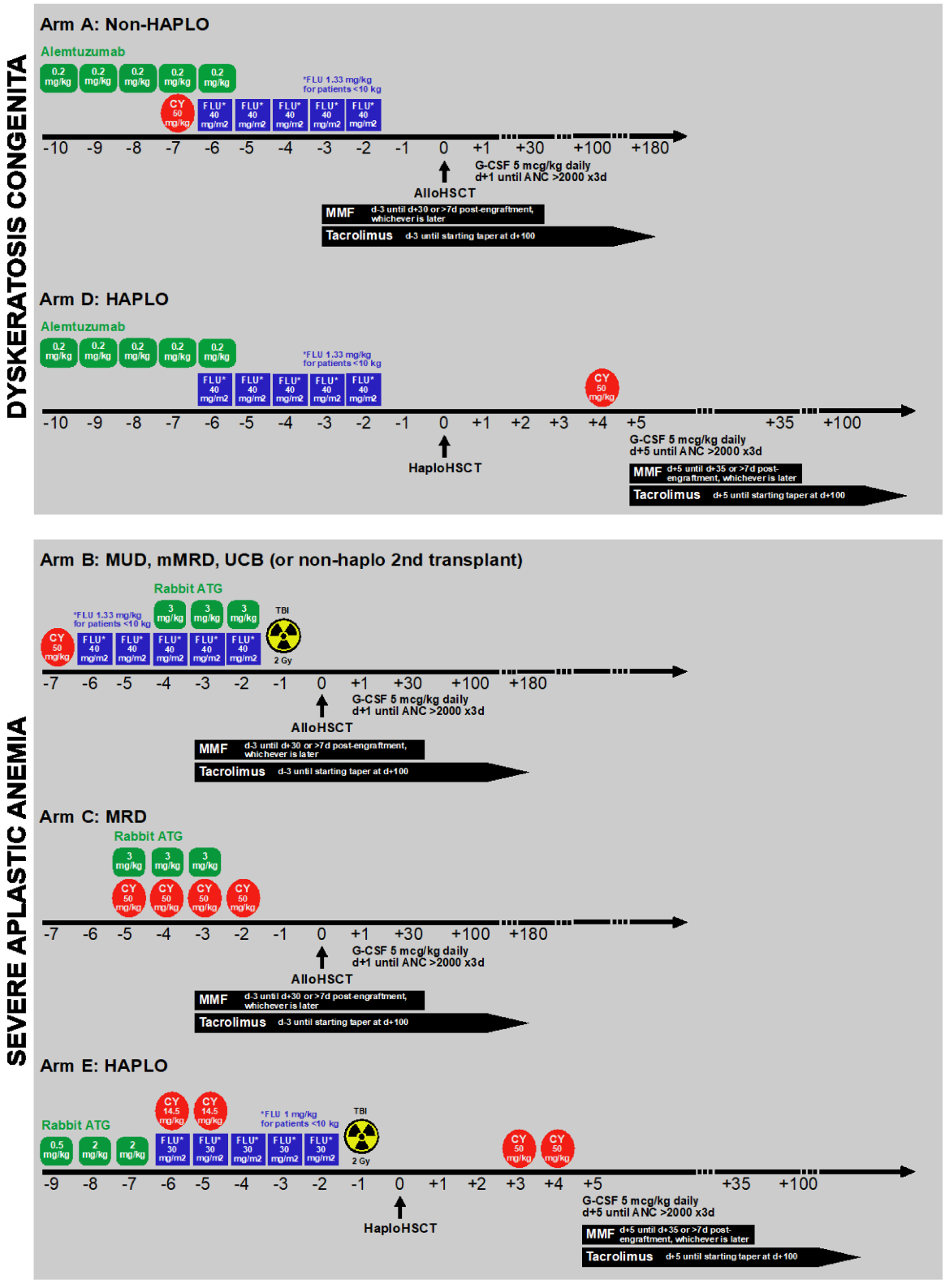
**Endpoints:** Specific transplant related endpoints include incidence of:

- neutrophil engraftment at day 42 and platelet engraftment at 1 year
- regimen related morality at 100 days
- acute GVHD at 100 days
- chronic GVHD at 6 months and 1 year
- secondary malignancies

All endpoint data will be recorded in the University Of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

**Enrollment** It is anticipated that 50 patients will be enrolled over 10 years

# Schema


DYSKERATOSIS CONGENITA
Arm A: Non-HAPLO
Alemtuzumab
0.2 mg/kg
CY 50 mg/kg
FLU* 40 mg/m2
*FLU 1.33 mg/kg for patients <10 kg
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +30 +100 +180
G-CSF 5 mcg/kg daily d+1 until ANC >2000 x3d
AlloHSCT
MMF d-3 until d+30 or >7d post-engraftment, whichever is later
Tacrolimus d-3 until starting taper at d+100
Arm D: HAPLO
Alemtuzumab
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +35 +100
HaploHSCT
G-CSF 5 mcg/kg daily d+5 until ANC >2000 x3d
MMF d+5 until d+35 or >7d post-engraftment, whichever is later
Tacrolimus d+5 until starting taper at d+100
SEVERE APLASTIC ANEMIA
Arm B: MUD, mMRD, UCB (or non-haplo 2nd transplant)
Rabbit ATG
3 mg/kg
TBI
2 Gy
-7 -6 -5 -4 -3 -2 -1 0 +1 +30 +100 +180
AlloHSCT
Arm C: MRD
Rabbit ATG
Arm E: HAPLO
CY 14.5 mg/kg
FLU* 30 mg/m2
*FLU 1 mg/kg for patients <10 kg
Rabbit ATG
0.5 mg/kg
2 mg/kg
-9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +35 +100
HaploHSCT

# 1.0 Introduction and Rationale

This is a treatment study for the use of hematopoietic stem cell transplant (HSCT) for dyskeratosis congenita (DC) and severe aplastic anemia (SAA). Based on the previous University of Minnesota study MT2006-06, this protocol offers a conditioning regimen that is less intensive but with adequate immunosuppressive activity to promote engraftment of HSC from related and unrelated donors. The modification eliminates the total body irradiation (TBI) from the DC preparative regimen only. It additionally expands donor options with haploidentical T-replete post-transplant cyclophosphamide based conditioning regimens.

Idiopathic severe aplastic anemia treatment focuses on disruption of an immune-mediated destruction of hematopoietic stem cells or the bone marrow niche, with either systemic immunosuppressive therapy (IST) or HSCT[1]. Historically, up-front HSCT was offered only for patients with an HLA-matched related donor. However, more recent compelling data supports equivalent overall survival (IST 82%, MUD HSCT 77%)[1] and equivalent, if not superior, event-free-survival with HLA-matched unrelated donor HSCT as compared to IST[2]. IST is limited by non-response in 30% of patients[3], relapse in 40%[4], clonal evolution of myelodysplastic or leukemia clones in 20%[5] and delayed recovery of cell counts (3-4 months). Additional improvements in HSCT outcomes have been recognized with decreased irradiation[6] and addition of fludarabine[7] in the conditioning regimen. Finally, the gap in outcomes between recipients of HLA-matched related donors and unrelated donors has been eliminated[8-11]. More recently, the donor pool has been expanded to include haploidentical donors, with results reviewed bu DeZern and Brodsky, 2018[12].

Literature on HSCT in DC continues to support non-myeloablative or reduced intensity conditioning regimens[13-15]. Evidence suggests that radiation-free conditioning does not compromise hematopoietic engraftment[16,17].It does however eliminate radiation related extra-medullary toxicity (especially to the lung and liver), a concern since pulmonary fibrosis and liver cirrhosis are a part of disease phenotype. While matched related donor HSCT has the best outcome in DC, success has been reported with alternative donor[18] and haploidentical HSCT[19-21]. With regard to haploidentical donor HSCT, use of post-transplant cyclophosphamide (PTCy) may be particularly detrimental to patients with DC, contributing to pulmonary and liver toxicity and increased risk for future carcinomas. Luznik et al. reported on comparison of 1 versus 2 days of PTCy, showing

equivalent outcomes with regard to acute graft-versus-host disease (GvHD)[22]. More recently, the Kanakry lab carefully examined exact timing of PTCy dosing in murine models, identifying day +4 as optimal in single PTCy dose regimen[23]. Consider the available data, should a DC patient require HSCT with a haploidentical donor, we will limit alkylator exposure by removing conditioning cyclophosphamide and adding single dose day +4 PTCy.

As bone marrow failure is the primary cause of premature deaths in DC and SAA patients, HSCT is an attractive option with proven potential for curing the BM failure associated with these diseases. This treatment will also be open to SAA patients who have experienced graft failure (GF) early after stem cell infusion. At the University of Minnesota, the incidence of graft failure by day 50 is 7 – 10%, creating a necessity for 2nd transplant treatment options for these patients.

Patients consent to allow the analysis of routine clinical data collected and maintained in OnCore, the Masonic Cancer Center's (MCC) clinical database, and specific transplant related endpoints in the University Of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

Endpoints include incidence of neutrophil engraftment at day 42 and platelet engraftment at 1 year, regimen related morality at 100 days, acute GVHD at 100 days, chronic GVHD at 6 and 12 months, and secondary malignancies.

# 2.0 Patient Selection

**Inclusion Criteria:**

## 2.1 Eligible Diseases:

### 2.1.1 Dyskeratosis Congenita (DC)

1) Diagnosis of DC:
   - short telomeres
   - pathogenic or suspected pathogenic variant(s) in a DC associated gene (e.g. *DKC1, TERT, TERC, NOP10, NHP2, TCAB1, TINF2, CTC1, ACD, PARN, RTEL1, WRAP53*)

2) With evidence of BM failure defined as:
   - requirement for red blood cell and/or platelet transfusions

<u>or</u>

- requirement for G-CSF or GM-CSF or erythropoietin

or

- refractory cytopenias having one of the following three
  - platelets <50,000/uL or transfusion dependent
  - absolute neutrophil count <500/uL without hematopoietic growth factor support
  - hemoglobin <9g/uL or transfusion dependent

2) OR early myelodysplastic features
3) With or without clonal cytogenetic abnormalities

**2.1.2 Severe Aplastic Anemia (SAA) primary transplant** with

1) Diagnosis of SAA:
   - Refractory cytopenias having one of the following three:
     - platelets <20,000/uL or transfusion dependent
     - absolute neutrophil count <500/uL without hematopoietic growth factor support
     - absolute reticulocyte count <20,000/uL
2) With evidence of BM failure:
   - Refractory cytopenia defined by bone marrow cellularity <50% (with < 30% residual hematopoietic cells)
3) OR early myelodysplastic features
4) With or without clonal cytogenetic abnormalities

**2.3.3 Severe Aplastic Anemia (SAA) requiring a 2nd transplant**

- Graft failure as defined by blood/marrow chimerism of < 5%

**2.2 Adequate organ function**

defined as:

Cardiac: left ventricular ejection fraction ≥ 35% with no evidence of decompensated heart failure

Pulmonary: DLCO ≥30% predicted, no supplemental oxygen requirement

Renal: Glomerular filtration rate (GFR) ≥30% predicted

**2.3 Age and consent**

**Age**: 0-70 years

**Consent:** Voluntary written consent (adult or parental/guardian)

## 2.4 Exclusion Criteria:

**2.4.1** Acute hepatitis or evidence of moderate or severe portal fibrosis or cirrhosis on biopsy

**2.4.2** Pregnant or lactating

**2.4.3** Uncontrolled infection

**2.4.4** Prior radiation therapy (applies to SAA patients only)

**2.4.5** Diagnosis of Fanconi anemia based on DEB

**2.4.6** Advanced MDS or acute myeloid leukemia with >30% blasts

## 2.5 Donor Selection:

**2.5.1 Donor-specific anti-HLA antibody testing requirement:** Testing for antibodies targeting donor specific HLA antigens at HLA-A, B, C, DRB1, DQ and DP will be completed as per institutional standards.

**2.5.2 Donor options**

- **Bone marrow or peripheral blood stem cells**
  - **Related donor: HLA matched, 1 antigen mismatched, or haploidentical** (matching at a minimum of one allele each of HLA-A, -B, -Cw, -DRB1 and -DQB1)
    - Related bone marrow or peripheral blood stem cell donors must meet donor criteria as outlined in the MT2012-14C: Procedure Guidelines for Related Hematopoietic Stem Cell Donors.
    - Related donors of patients with DC must have a telomere length within 2 standard deviations of normal
  - **Unrelated donor: HLA matched or 1 antigen mismatched**
- **UCB unit(s): Single or double UCB units** selected according to Minnesota BMT program guidelines

Refer to section 5 for additional donor selection preferences and cell doses based on source.

# 3.0 Registration in OnCore

Patients will be registered to this study in OnCore at the time of consent signing.

# 4.0 Treatment Plan

All drugs will be prepared and administered per institutional guidelines, with the drugs, doses and scheduled modified as clinically indicated. Dosing is based on actual body weight (ABW) and current institutional guidelines.

## 4.1 Dyskeratosis Congenita (DC)

| Day | ARM A: Non-haploidentical donor | ARM D: Haploidentical donor |
|---|---|---|
| **-10** | **Alemtuzumab** 0.2 mg/kg IV over 2 hours | **Alemtuzumab** 0.2 mg/kg IV over 2 hours |
| **-9** | **Alemtuzumab** 0.2 mg/kg IV over 2 hours | **Alemtuzumab** 0.2 mg/kg IV over 2 hours |
| **-8** | **Alemtuzumab** 0.2 mg/kg IV over 2 hours | **Alemtuzumab** 0.2 mg/kg IV over 2 hours |
| **-7** | **Alemtuzumab** 0.2 mg/kg IV over 2 hours<br>**Cyclophosphamide** 50 mg/kg IV over 2 hours | **Alemtuzumab** 0.2 mg/kg IV over 2 hours |
| **-6** | **Alemtuzumab** 0.2 mg/kg IV over 2 hours<br>**Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Alemtuzumab** 0.2 mg/kg IV over 2 hours<br>**Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour |
| **-5** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour |
| **-4** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour |
| **-3** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour |
| **-2** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour |
| **-1** | **rest** | **rest** |
| **0** | **stem cell transplant** | **stem cell transplant** |
| **+4** | | **Cyclophosphamide** 50 mg/kg IV over 2 hours |

Refer to appendix I for treatment related risks.

### 4.1.1 Conditioning Regimen for DC (Arms A and D)

#### 4.1.1.1 Alemtuzumab

Alemtuzumab will be administered at doses and days indicated for Arms A and D via central venous catheter as follows:

- Pre-medicate 30 minutes prior to Alemtuzumab infusion with methylprednisolone 1 mg/kg IV, (max dose = 125 mg), acetaminophen 15 mg/kg dose (max dose = 650 mg) enterally and diphenhydramine 1 mg/kg/dose (max dose = 50 mg) enterally or IV.
- Infuse Alemtuzumab over 2 hours.
- Hypersensitivity orders per standard guidelines during Alemtuzumab administration.

#### 4.1.1.2 Cyclophosphamide

Cyclophosphamide 50 mg/kg IV will be administered over 2 hours on day -7 (Arm A only). Cyclophosphamide dosing is calculated based on actual body weight (ABW). Refer to cyclophosphamide institutional standards regarding dosing for obese patients. Alterations to dosing should be discussed with the BMT pharmacist.

Uroprotection with MESNA and hyperhydration per cyclophosphamide institutional guidelines.

#### 4.1.1.3 Fludarabine

Fludarabine will be administered at a dose of 40 mg/m$^2$/day x 5 days, total dose 200 mg/m$^2$ (days –6 to –2). For children < 10 kg, fludarabine dosing will be 1.33 mg/kg/day x 5 days, total dose 6.65 mg/kg (days -6 to -2). Dosing is based on actual body weight. The fludarabine dose will be administered IV over one hour at a constant rate. If the normalized GFR is <70 ml/min, a 20% dose-reduction of fludarabine may be considered after discussion between the protocol PI, patient's primary BMT physician and BMT pharmacist.

### 4.2 Severe Aplastic Anemia (SAA)

| Day | ARM C: Matched related donor |
|---|---|
| **-5** | **Cyclophosphamide** 50 mg/kg IV over 2 hours<br>**Rabbit ATG** 3 mg/kg IV over 4-6 hours |
| **-4** | **Cyclophosphamide** 50 mg/kg IV over 2 hours<br>**Rabbit ATG** 3 mg/kg IV over 4-6 hours |
| **-3** | **Cyclophosphamide** 50 mg/kg IV over 2 hours<br>**Rabbit ATG** 3 mg/kg IV over 4-6 hours |
| **-2** | **Cyclophosphamide** 50 mg/kg IV over 2 hours |
| **-1** | **rest** |
| **0** | **stem cell transplant** |

| Day | ARM B: MUD, mMRD, UCB donor OR Non-Haplo 2nd transplant) | ARM E: Haploidentical donor |
|---|---|---|
| **-9** | | **Rabbit ATG** 0.5 mg/kg IV over 4-6 hours |
| **-8** | | **Rabbit ATG** 2 mg/kg IV over 4-6 hours |
| **-7** | **Cyclophosphamide** 50 mg/kg IV over 2 hours | **Rabbit ATG** 2 mg/kg IV over 4-6 hours |
| **-6** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Cyclophosphamide** 14.5 mg/kg IV over 2 hours<br>**Fludarabine** 30 mg/m$^2$ IV (1 mg/kg if <10 kg) over 1 hour |
| **-5** | **Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Cyclophosphamide** 14.5 mg/kg IV over 2 hours<br>**Fludarabine** 30 mg/m$^2$ IV (1 mg/kg if <10 kg) over 1 hour |
| **-4** | **Rabbit ATG** 3 mg/kg IV over 4-6 hours<br>**Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 30 mg/m$^2$ IV (1 mg/kg if <10 kg) over 1 hour |
| **-3** | **Rabbit ATG** 3 mg/kg IV over 4-6 hours<br>**Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 30 mg/m$^2$ IV (1 mg/kg if <10 kg) over 1 hour |
| **-2** | **Rabbit ATG** 3 mg/kg IV over 4-6 hours<br>**Fludarabine** 40 mg/m$^2$ IV (1.33 mg/kg if <10 kg) over 1 hour | **Fludarabine** 30 mg/m$^2$ IV (1 mg/kg if <10 kg) over 1 hour |
| **-1** | **TBI** 2 Gy | **TBI** 2 Gy |
| **0** | **stem cell transplant** | **stem cell transplant** |
| **+3** | | **Cyclophosphamide** 50 mg/kg IV over 2 hours |
| **+4** | | **Cyclophosphamide** 50 mg/kg IV over 2 hours |

Refer to Appendix II (Arms B, E) and Appendix III (Arm C) for treatment related risks.

### 4.2.1 Conditioning regimen for SAA (Arms B, C and E)

#### 4.2.1.1 Rabbit ATG (Thymoglobulin®)

Rabbit ATG will be administered at doses and days indicated for Arms C, D, and E above via central venous catheter as follows:

- Pre-medicate 30 minutes prior to ATG infusion with methylprednisolone 1 mg/kg IV, (max dose = 125 mg), acetaminophen 15 mg/kg dose (max dose = 650 mg) enterally and diphenhydramine 1 mg/kg/dose (max dose = 50 mg) enterally or IV.
- Infuse ATG through a 0.22 micrometer filter over 4-6 hours.
- Hypersensitivity orders per standard guidelines during ATG administration.

#### 4.2.1.2 Cyclophosphamide

Cyclophosphamide will be administered over 2 hours at the doses and days indicated above for Arms B, C, and E. Refer to cyclophosphamide institutional standards regarding dosing for obese patients. Alterations to dosing should be discussed with the BMT pharmacist.

Uroprotection with MESNA and hyperhydration per cyclophosphamide institutional guidelines. Hyperhydration is not required for 14.5 mg/kg cyclophosphamide doses.

#### 4.2.1.3 Fludarabine (Arms B and E only)

For Arm B, Fludarabine will be administered at a dose of 40 $mg/m^2$/day x 5 days, total dose 200 $mg/m^2$ (days –6 to –2). For children < 10 kg, fludarabine dosing will be 1.33 mg/kg/day x 5 days, total dose 6.65 mg/kg (days -6 to -2).

For Arm E, fludarabine will be administered at a dose of 30 $mg/m^2$/day x 5 days, total dose of 150 $mg/m^2$ (days -6 to -2). For children <10 kg, fludarabine dosing will be 1 mg/kg/day x 5 days, total dose 5 mg/kg (days -6 to -2).

The fludarabine dose will be administered IV over one hour at a constant rate. If the normalized GFR is <70 ml/min, a 20% dose-reduction of fludarabine may be considered after discussion between the protocol PI, patient's primary BMT physician and BMT pharmacist.

#### 4.2.1.4 Total Body Irradiation (Arms B and E only)

2 Gy administered in a single fraction will be given at a dose rate between 1 and 1.9 Gy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The total body irradiation will be delivered with right and left lateral fields, with the patient supine on a specially designed couch.

Total body irradiation will be delivered with a linear accelerator using 6, 18, or 24 MV X-rays.

Based on measurements of transverse thicknesses, aluminum compensators may be used to ensure that the dose homogeneity across the field is within 10% of the prescribed dose. Usually head/neck, leg and lung compensators are used (although based on calculated mid-mediastinal doses, lung compensators are often not needed).

A beam “spoiler” will be used to ensure a full skin dose. Half value layer lung and kidney blocks will not be utilized. Testicular boosts are not given.

### 4.3 Cell Infusion (day 0)

Refer to section 2.2 for cell source options and section 5 for selection considerations.

On day 0 the cells will be infused per cell source specific institutional guidelines.

Recommended Pre-medication: acetaminophen 15 mg/kg (max dose = 650 mg) PO and diphenhydramine 1 mg/kg (max dose 50 mg) PO/IV with adjusted dosing for pediatric patients.

Vital signs will be checked before and after the infusion, and one hour post infusion per University Of Minnesota transplant guidelines. More frequent vital signs may be required depending on reactions to the product infusion.

Refer to appendix IV for transplant related risks.

### 4.4 Post-Transplant G-CSF (filgrastim)

Beginning on day +1 (Arms A, B, C) or day +5 (Arms D, E), patients will receive G-CSF SQ or IV 5 micrograms/kg once daily until post-nadir ANC > 2000/μL for 3 consecutive days.

Refer to appendix IV for G-CSF related risks.

## 4.5 GVHD Prophylaxis

Standard acute GVHD prophylaxis and immune suppression will be used; however, an alternative regimen may also be used as clinically appropriate.

Refer to appendix IV for GVHD prophylaxis related risks.

### 4.5.1 Post-transplant Cyclophosphamide (Arms D, E only)

Cyclophosphamide will be administered over 2 hours at the 50 mg/kg on day +4 (Arm D) or on days +3 and +4 (Arm E). Refer to cyclophosphamide institutional standards regarding dosing for obese patients. Alterations to dosing should be discussed with the BMT pharmacist.

Uroprotection with MESNA and hyperhydration per cyclophosphamide institutional guidelines.

### 4.5.2 Tacrolimus (All Arms)

Tacrolimus therapy will begin on day -3 (Arms A, B, C) or day +5 (Arms D, E). Initial dosing of tacrolimus will be 0.03 mg/kg/day IV via continuous infusion. Goal trough levels will be 10-15 ug/mL for the first 14 days post-transplant and then decreased to a goal of 5-10 ng/mL thereafter. Dose adjustments will be made on the basis of toxicity and/or tacrolimus levels outside of goal range. Conversion from IV to oral tacrolimus will be done as the patient tolerates and prior to discharge. Potential toxicities are detailed in Appendix II.

The timing of the tacrolimus taper will be at the discretion of the treating physician, but in general:

- Taper begins at day +100 +/- 10 days, if the patient is stably engrafted and has no active GVHD.

Taper to zero by reducing dose by approximately 10% a week (rounded to nearest pill size), with a goal to discontinue by month 6 post-HCT.

In the presence of severe tacrolimus toxicities, other alternative agents may be used after review and approval by the PI.

### 4.5.3 Mycophenylate Mofetil (MMF)

Mycophenylate mofetil (MMF) therapy will begin on day -3 (Arms A, B, C) or day +5 (Arms D, E). Dosing of MMF will be 15 mg/kg/dose three

times daily up to a max of 1gm per dose. The same dosage is used orally or intravenously. Consider dose modification if renal and/or hepatic impairment (GFR<25 mL/minute corrected). The first MMF pharmacokinetic time point will be obtained at day +3 (Arms A, B, C) or day +11 (Arms D, E). An attempt will be made to maintain an MMF AUC of 200 - 250 ng*hr/mL for q8h dosing and an AUC of 300-350 ng*hr/ml for q12h dosing. Should dose adjustments be made, repeat AUC monitoring at steady-state should be considered.

Stop MMF at Day +30 (Arms A, B, and C), Day +35 (Arms D and E) or 7 days after engraftment achieved (ANC>500 x $10^6$ neutrophils/L x 3 days) if later than day +30 (Arms A, B, and C) or day +35 (Arms D and E). If sufficient acute GvHD is observed to require systemic therapy, MMF should be continued for 7 days after initiation of systemic therapy. Afterward, use of MMF is at the discretion of the treating physician.

Refer to appendix II for risks associated with MMF.

### 4.6 Follow-Up

Follow-up will be according to the current University Of Minnesota BMT follow-up guidelines as outlined in section 6.

### 4.7 Supportive Care

Patients will receive standard supportive transplant care, including antibacterial/antifungal/antiviral prophylaxis according to institutional guidelines or as modified based on clinical parameters.
Patients will be eligible for any supportive care studies regarding infectious disease prophylaxis and management, immunoglobulin support, etc. as appropriate.

## 5.0 Donor Selection and Cell Dose Requirements

### 5.1 Donor specific HLA antibodies:

Absence of donor-specific HLA antibodies is preferred [negative flow cytometric cross-match assay or the mean fluorescence intensity (MFI) of any anti-donor HLA antibody by solid phase immunoassay <1000]. If donor-specific anti-HLA antibodies cannot be avoided, the risks will be discussed with the patient and consenting parent/guardian and options including debulking or deferring transplant will be considered

## 5.2 Donor Considerations When More Than 1 Potential Donor

- Bone marrow is preferred over peripheral blood. Peripheral blood is preferred over cord blood.
- HLA-matched related donor bone marrow is optimal, followed by HLA-matched unrelated donor cell sources. If HLA-matched sources are not available, the lowest number of mismatches in the host-versus-graft direction is prioritized to minimize graft rejection.
- If more than one donor with the same degree of HLA match, absent or equivalent donor-specific anti-HLA antibodies, and equivalent host-versus-graft allele mismatches, the following prioritization will be used:
  a. Homozygous normal donor is preferable to heterozygote (carrier)
  b. ABO-compatible donor is preferable to ABO-incompatible donor
  c. CMV status
     1) For a CMV seronegative patient, prefer a CMV seronegative donor
     2) For a CMV seropositive patient, prefer a CMV seropositive donor
  d. Younger donor is preferable to older, avoiding those >55 years of age if possible
  e. Male donor preferred over nulliparous female donor over multiparous female donor

## 5.3 Donor Considerations for 2nd Transplant

- In the case of 2$^{nd}$ transplant, the original donor source, if willing and available, is preferred
- If original donor not available, any readily available graft source as per section 2.2 will be considered

## 5.4 Cell Dose Requirements Based on Cell Source

### 5.4.1 Bone Marrow (BM)

BM will be collected with a goal of >5.0 x $10^8$ nucleated cells/kg recipient body weight per MT2012-14C (for related donor) or NMDP guidelines (for unrelated donor).

### 5.4.2 Peripheral Blood (PB)

CD34+ cell dose goal to infuse will be >10.0 x $10^6$ CD34+ cells/kg recipient body weight.

Related donor: If donor is > 12 years and > 40 kg, PB will be collected after G-CSF mobilization per MT2012-14C.

Unrelated donor: The PB product will be collected, processed and shipped according to the existing protocols of the National Marrow Donor Program to obtain GCSF mobilized PB for primary allogeneic HSC transplant with unrelated donors.

### 5.4.3 Umbilical Cord Blood (UCB)

For umbilical cord blood, a minimum cell dose of ≥ 3.5 x $10^7$ nucleated cells/kg is required with an optimal cell dose ≥ 5 x $10^7$ nucleated cells/kg recipient body weight. The unit(s) will not be manipulated.

Unrelated unlicensed UCB unit(s) will require the recipient's co-enrollment on MT2011-13R (Infusion of Cell Populations from Unlicensed Umbilical Cord Blood Units – C Brunstein sponsor/investigator).

# 6.0 Clinical Evaluations

All clinical evaluations are standard of care and will be done according to current institutional guidelines. Post-transplant and some pre-transplant monitoring are suggested guidelines and should be tailored for each patient's clinical case.

| | Pre-transplant work-up | Days in Reference to the transplant | | |
|---|---|---|---|---|
| | | Day 1 to engraftment | Follow-up Days 31-100 | 6 months, 1 and 2 years |
| Informed consent | X | | | |
| Medical history including prior transfusions, alloantibodies and allergies | X | | | |
| DEB and cytogenetics (unless previously documented negative) | X | | | |
| Physical exam | X | daily | weekly | X |
| Radiation Therapy consult (SAA only) | X | | | |
| Neuropsych testing and QOL | X | As clinically indicated | | 1 and 2 years |
| Any other subspecialty consultations as clinically indicated | X | As clinically indicated | | X |
| Height/Weight | X | | | X |
| GVHD evaluation | | daily | weekly | X |
| CMV Surveillance | X | weekly | weekly | prn |
| EBV assessment (ATG and Alemtuzumab patients only) | | | every 2 weeks | every 2 weeks until day 180 |
| Laboratory | | | | |
| CBC, diff , platelet | X | daily | weekly | X |
| Anti-HLA antibody testing | X | | | |
| PT/PTT | X | As clinically indicated | | |
| Serum chemistries | X | As clinically indicated | | |
| Creatinine, Na, K, HCO3 | X | daily | weekly | X |
| LH, FSH and Estradiol levels for females ≥10 years; LH, FSH and testosterone levels for males ≥11 years | X | | Day 100 | 1 and 2 years |
| Free T4 and TSH | X | | Day 100 | X |
| Chimerism – PB | X | Day 28 | Day 60 | X |
| Quantitative immunoglobulins | X | | Day 60, 100 | X |
| T cell subsets, extended profile | X | | Day 60,100 | X |
| Urinalysis | X | | | X |
| Urine or serum pregnancy test - females of childbearing potential only | X | | | |
| Procedures | | | | |
| EKG | X | | | |
| MUGA or echo as age appropriate | X | | | 1 year |
| PFTs if age appropriate/ pulse oximetry | X | | Day 100 | 1 and 2 years |
| Chest CT | X | | | |
| Bone Marrow Biopsy/Aspirate (with chimerism) | X | | Day100 | X |

# 7.0 Event Reporting

The only research element is the collection and analysis of routine clinical data in association with study milestones. Therefore, the only events reportable to the University Of Minnesota Institutional Review Board in an expedited manner (5 business days from discovery) will be those in association with data collection. Primarily these risks would be:

- Any breach in confidentiality that may involve risk to the subject or others *in association with the data collection*
- Any complaint *in association with the data collection* of a subject that cannot be resolved by the research staff

Any report should be made using the Report form found on the IRB's website (http://www.research.umn.edu/irb/).

# 8.0 Data Collection and Statistical Plan

Specific transplant related endpoints include incidence of:

- neutrophil engraftment at day 42 and platelet engraftment at 1 year
- regimen related morality at 100 days
- acute GVHD at 100 days
- chronic GVHD at 6 months and 1 year
- secondary malignancies

All endpoint data will be recorded in the University Of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

## 8.1 Trial Size Justification

Since this treatment plan among these patients has been studied over the last 8 years, this is now a standard of care protocol. No trial size justification is needed.

## 8.2 Analysis of Primary and Secondary Endpoints

Cumulative incidence will be used to estimate TRM, neutrophil engraftment, GVHD and graft failure treating non-events as competing risks. Kaplan-Meier curves will be used to estimate disease-free survival and overall survival. Chimerism will be plotted with box-plots and described over time.

## 8.3 Safety Monitoring

We have studied this regimen for patients with these diagnoses for the past 8 years and it has been shown to be safe. Continuous stopping rules are no longer needed. Safety parameters will be monitored on a yearly basis through the DSMC.

The Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp

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# Appendix I – Treatment Related Risks Dyskeratosis Congenita (Arms A and D)

| **Alemtuzumab (Campath, Campath 1-H)** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • mild allergic reaction with first few infusions (may include fever, headache, chills, itching, hives, nausea)<br>• low white blood cell count with increased risk of infection<br>• low platelet count with increased risk of bleeding<br>• low red blood cell count<br>• fever<br>• nausea<br>• vomiting | • allergic reaction with later infusions (same symptoms as under common)<br>• abdominal pain, back pain, or chest pain<br>• headache<br>• feeling tired<br>• infections, which can be serious*<br>• diarrhea<br>• mouth sores<br>• loss of appetite<br>• shortness of breath<br>• trouble sleeping<br>• anxiety<br>• cough<br>• itching<br>• rash<br>• blood pressure changes<br>• swelling in the hands or feet<br>• abnormal blood test results which suggest that the drug is affecting the liver or kidneys | • serious allergic reaction, with trouble breathing, swelling of the mouth or face, tightness in the throat, faintness, heart attack, shock, cardiac arrest<br>• serious damage to the bone marrow, so that it stops making blood cells<br>• feeling dizzy<br>• rapid heart rate<br>• upset stomach<br>• constipation<br>• muscle aches<br>• sore throat<br>• deaths due to allergic reactions, severe bone marrow damage, infections, or other causes |

| **Cyclophosphamide** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • low white blood cell count with increased risk of infection<br>• hair loss or thinning, including face and body hair (usually grows back after treatment)<br>• nausea<br>• vomiting<br>• loss of appetite<br>• sores in mouth or on lips<br>• bleeding from bladder, with blood in urine<br>• diarrhea<br>• long-term or short-term infertility in women and men | • low platelet count (mild) with increased risk of bleeding<br>• darkening of nail beds<br>• acne<br>• tiredness<br>• infection<br>• fetal changes if pregnancy occurs while taking cyclophosphamide | • heart problems with high doses, with chest pain, shortness of breath, or swollen feet<br>• severe allergic reactions<br>• skin rash<br>• scarring of bladder<br>• kidney damage (renal tubular necrosis) which can lead to kidney failure<br>• heart damage, with trouble getting your breath, swelling of feet, rapid weight gain<br>• scarring of lung tissue, with cough and shortness of breath<br>• second cancer, which can happen years after taking this drug<br>• death from infection, bleeding, heart failure, allergic reaction, or other causes |

| **Fludarabine** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • low white blood cell count with increased risk of infection<br>• low platelet count with increased risk of bleeding<br>• low red blood cell count (anemia) with tiredness and weakness<br>• tiredness (fatigue)<br>• nausea<br>• vomiting<br>• fever and chills<br>• infection | • pneumonia<br>• diarrhea<br>• loss of appetite<br>• weakness<br>• pain | • numbness and tingling in hands and/or feet related to irritation of nerves<br>• changes in vision<br>• agitation<br>• confusion<br>• clumsiness<br>• seizures<br>• coma<br>• cough<br>• trouble breathing<br>• intestinal bleeding<br>• weakness<br>• death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes |

# Appendix II – Treatment Related Risks Severe Aplastic Anemia (Arms B and E)

| **Cyclophosphamide** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • low white blood cell count with increased risk of infection<br>• hair loss or thinning, including face and body hair (usually grows back after treatment)<br>• nausea<br>• vomiting<br>• loss of appetite<br>• sores in mouth or on lips<br>• bleeding from bladder, with blood in urine<br>• diarrhea<br>• long-term or short-term infertility in women and men | • low platelet count (mild) with increased risk of bleeding<br>• darkening of nail beds<br>• acne<br>• tiredness<br>• infection<br>• fetal changes if pregnancy occurs while taking cyclophosphamide | • heart problems with high doses, with chest pain, shortness of breath, or swollen feet<br>• severe allergic reactions<br>• skin rash<br>• scarring of bladder<br>• kidney damage (renal tubular necrosis) which can lead to kidney failure<br>• heart damage, with trouble getting your breath, swelling of feet, rapid weight gain<br>• scarring of lung tissue, with cough and shortness of breath<br>• second cancer, which can happen years after taking this drug<br>• death from infection, bleeding, heart failure, allergic reaction, or other causes |

| **Fludarabine** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • low white blood cell count with increased risk of infection<br>• low platelet count with increased risk of bleeding<br>• low red blood cell count (anemia) with tiredness and weakness<br>• tiredness (fatigue)<br>• nausea<br>• vomiting<br>• fever and chills<br>• infection | • pneumonia<br>• diarrhea<br>• loss of appetite<br>• weakness<br>• pain | • numbness and tingling in hands and/or feet related to irritation of nerves<br>• changes in vision<br>• agitation<br>• confusion<br>• clumsiness<br>• seizures<br>• coma<br>• cough<br>• trouble breathing<br>• intestinal bleeding<br>• weakness<br>• death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes |

| **Anti-Thymocyte Globulin (ATG)** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • fever<br>• chills<br>• leukopenia<br>• pain<br>• headache<br>• abdominal pain<br>• diarrhea<br>• hypertension<br>• nausea<br>• thrombocytopenia | • malaise<br>• dizziness | • severe allergic reaction (anaphylaxis) |

| **Anti-Thymocyte Globulin (ATG)** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • peripheral edema<br>• dyspnea<br>• asthenia<br>• hyperkalemia<br>• tachycardia | | |

| **Total Body Irradiation (TBI)** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • nausea and vomiting<br>• diarrhea<br>• cataracts<br>• sterility<br>• endocrinopathies<br>• growth failure<br>• intestinal cramps<br>• mucositis | • parotitis<br>• interstitial pneumonitis<br>• generalized mild erythema<br>• veno-occlusive disease | • dysphagia<br>• vertebral deformities<br>• nephropathy<br>• risk of 2nd malignancy years later (when given along with chemotherapy) |

# Appendix III – Treatment Related Risks Severe Aplastic Anemia (Arm C)

| **Cyclophosphamide** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • low white blood cell count with increased risk of infection<br>• hair loss or thinning, including face and body hair (usually grows back after treatment)<br>• nausea<br>• vomiting<br>• loss of appetite<br>• sores in mouth or on lips<br>• bleeding from bladder, with blood in urine<br>• diarrhea<br>• long-term or short-term infertility in women and men | • low platelet count (mild) with increased risk of bleeding<br>• darkening of nail beds<br>• acne<br>• tiredness<br>• infection<br>• fetal changes if pregnancy occurs while taking cyclophosphamide | • heart problems with high doses, with chest pain, shortness of breath, or swollen feet<br>• severe allergic reactions<br>• skin rash<br>• scarring of bladder<br>• kidney damage (renal tubular necrosis) which can lead to kidney failure<br>• heart damage, with trouble getting your breath, swelling of feet, rapid weight gain<br>• scarring of lung tissue, with cough and shortness of breath<br>• second cancer, which can happen years after taking this drug<br>• death from infection, bleeding, heart failure, allergic reaction, or other causes |

| **Anti-Thymocyte Globulin (ATG)** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • fever<br>• chills<br>• leukopenia<br>• pain<br>• headache<br>• abdominal pain<br>• diarrhea<br>• hypertension<br>• nausea<br>• thrombocytopenia<br>• peripheral edema<br>• dyspnea<br>• asthenia<br>• hyperkalemia<br>• tachycardia | • malaise<br>• dizziness | • severe allergic reaction (anaphylaxis) |

# Appendix IV – Transplant Related Risks – General, Regardless of Diagnosis

**Hematopoietic Stem Cell Transplantation – regardless of stem cell source**

- nausea and vomiting
- possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)
- graft-versus-host-disease (GVHD)
- veno-occlusive disease,
- mucositis,
- infections (sepsis)

**Risks associated with the use of Umbilical Cord Blood**

- **DMSO Toxicity** is a possible complication of UCB infusion and occurs due to the presence of DMSO in the thawed product. The risk of toxicity increases with the number of units (total volume per kg body weight) infused. Symptoms are due to histamine release and include:
  - cough
  - flushing
  - rash
  - chest tightness
  - nausea and vomiting
  - bradycardia and tachycardia
  - hypertension

- **Bacterial/Endotoxin Contamination** of cellular therapy products may occur, but rarely cause acute, severe or life threatening effects. However, the onset of high fever (>2ºC or >3.5ºF rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after infusion should suggest the possibility of bacterial contamination and/or the presence of endotoxin in the product.

- **Transmission of Infectious Disease** may occur because cellular therapy products are collected from human body and/or tissues. The donor selection criteria do not totally eliminate the risk of transmitting the agents currently tested such as HIV, HTLV, HBV, HCV, CMV, T. pallidum (Syphilis), West Nile Virus, and Trypanosome (Chagas). For some other infectious disease there are no routine tests to prevent disease transmission including Parvovirus spp., Plasmodium spp. (Malaria), the coronavirus associated with severe acute respiratory syndrome (SARS), and the agents of human transmissible spongiform encephalopathies (TSEs).

| **G-CSF given to help the blood counts recover more quickly** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare** |
| • none | • bone and muscle pain<br>• abnormal blood tests which suggest that the drug is affecting the liver | • fast heartbeat<br>• low blood pressure<br>• allergic reaction (may include shortness of breath, wheezing, swelling in the mouth or throat, hives, itching, flushing, or fever) |

| **Tacrolimus** | | |
|---|---|---|
| **Common** | **Less Common** | **Rare, but may be serious** |
| ▪ kidney problems<br>▪ loss of magnesium, calcium, potassium<br>▪ high blood pressure<br>▪ tremors<br>▪ increases in cholesterol and triglyceride | ▪ nausea<br>▪ vomiting<br>▪ liver problems<br>▪ changes in how clearly one can think<br>▪ insomnia<br>▪ unwanted hair growth<br>▪ confusion | ▪ seizures<br>▪ changes in vision<br>▪ dizziness<br>▪ red blood cell destruction |

**It is very important that grapefruit or drinks with grapefruit juice are not consumed while taking Tacrolimus**. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study**.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

| **Mycophenolate Mofetile (MMF)** | |
|---|---|
| **Common** | **Rare, but may be serious** |
| • constipation<br>• stomach pain or swelling<br>• nausea<br>• vomiting<br>• difficulty falling asleep or staying asleep<br>• pain, especially in the back, muscles, or joints<br>• uncontrollable shaking of a part of the body<br>• headache<br>• rash | • diarrhea<br>• swelling of the hands, arms, feet, ankles, or lower legs<br>• difficulty breathing<br>• chest pain<br>• fast heartbeat<br>• dizziness<br>• fainting<br>• lack of energy<br>• pale skin<br>• black and tarry stools<br>• red blood in stools<br>• bloody vomit<br>• vomit that looks like coffee grounds<br>• yellowing of the skin or eyes |

Arms D and E only: Post-transplant cyclophosphamide (Risks as documented in treatment related risks, Appendix I and II)