THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

A Randomized Controlled Trial Evaluating the Use of G-CSF after Plerixafor-Mobilized Autologous Stem Cell Transplant (Auto HSCT)

Principal Investigator:	Dolores Grosso, DNP Medical Oncology 834 Chestnut St., Suite 320, Philadelphia, PA 19107 215-955-8874
Co-Investigator(s):	William J. O'Hara, PharmD Ubaldo Martinez Outschoorn, MD Joanne Filicko-O'Hara, MD Pierluigi Porcu, MD Matthew Carabasi, MD John Wagner, MD Usama Gergis, MD Margaret Kasner, MD S. Onder Alpdogan, MD Thomas Klumpp, MD Neil Palmisiano, MD Lindsay Wilde, MD Adam Binder, MD
Statistician:	Benjamin Leiby, PhD Division of Biostatistics 1015 Chestnut St. Suite 520, Philadelphia, PA 19107 215-503-3803
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CONFIDENTIAL

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Dolores Grosso, DNP

Title: Principal Investigator

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BMT	Bone Marrow Transplant
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTOC	Clinical Trials Oversight Committee
CXCR4	Chemokine Receptor 4
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ES	Engraftment Syndrome
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board

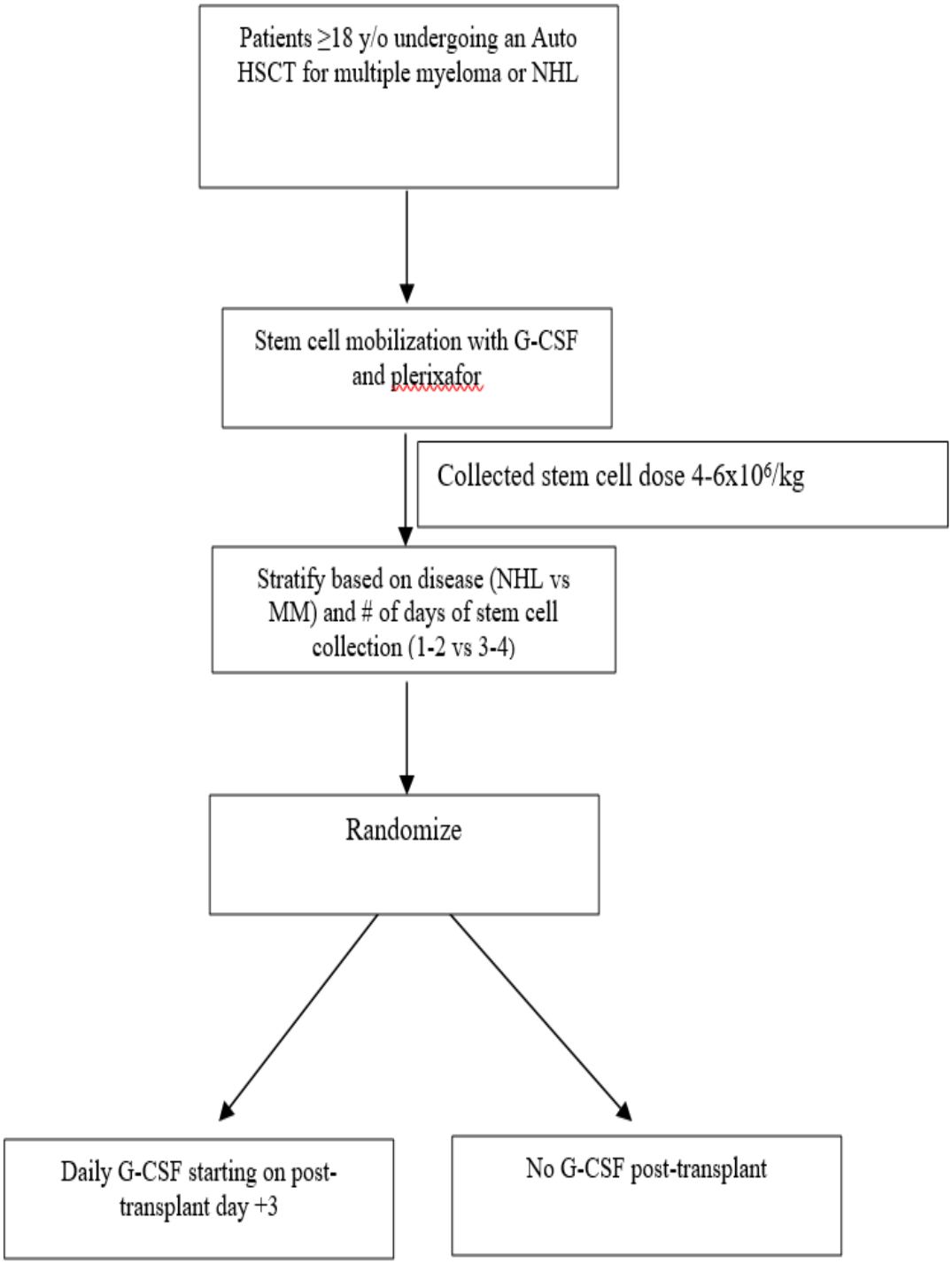
LVEF	Left Ventricular Ejection Fraction
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
Mcg	Microgram
MM	Multiple Myeloma
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PBSC	Plerixafor-Based Stem Cell Collection
PHI	Protected Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SKCC	Sidney Kimmel Cancer Center
SQ	Subcutaneously
SOP	Standard Operating Procedure
TJU	Thomas Jefferson University
TJUH	Thomas Jefferson University Hospital
UAP	Unanticipated Problem

Study Summary

Title:	A Randomized Controlled Trial Evaluating the Use of G-CSF after Plerixafor-Mobilized Autologous Stem Cell Transplant (Auto HSCT)
Précis:	Prior to admission for Auto HSCT, CD 34+ stem cells (also referred to as stem cells) are mobilized with growth colony stimulating factor (G-CSF) and collected from patients and stored to be used later during the Auto HSCT for blood count recovery after high dose chemotherapy. At Jefferson, and in many other transplant centers, plerixafor, a newer stem cell mobilizing agent, is combined with G-CSF resulting in the collection of significantly larger doses of stem cells. The infusion of high doses of stem cells during Auto HSCT accelerates blood cell count recovery after the procedure. In this clinical trial, all patients will undergo a G-CSF +plerixafor-based stem cell collection (PBSC) prior to Auto HSCT. During the Auto HSCT, G-CSF will be initiated 3 days after Auto HSCT in one-half of the study participants, which is the current practice, to accelerate blood count recovery. The other half of the study participants will not receive post Auto HSCT G-CSF with the hypothesis that the high dose of stem cells collected during G-CSF-plerixafor based PBSC collection will obviate the need for additional post Auto-HSCT growth factor.
Objectives:	Primary: To demonstrate non-inferiority in the number of days to discharge readiness after a G-CSF +plerixafor mobilized autologous stem cell transplant in patients not receiving post-transplant G-CSF support versus those receiving post-transplant G-CSF growth factor support. Secondary: To compare days to neutrophil engraftment, days to platelet engraftment, febrile days, days of febrile neutropenia, documented infections, number of antibiotic days, engraftment syndrome, and days on corticosteroids in patients receiving and not receiving post-transplant G-CSF growth support.
Population:	Individuals ≥18 years of age with multiple myeloma (MM) or non-Hodgkin lymphoma (NHL) undergoing plerixafor mobilized autologous stem cell transplant
Number of Sites:	1 (Thomas Jefferson University Hospital)
Description of Intervention:	Patients will be randomized to either receive G-CSF subcutaneously (SQ) daily starting on Day +3 after Auto HSCT and continuing for 3

	days after ANC > 500 x 10^9/L, or to not receive G-CSF post-transplant
Study Duration:	5 years
Participant Participation Duration:	90 days
Estimated Time to Complete Enrollment:	4 years

Schematic of Study Design:



1 Introduction

1.1 Background Information

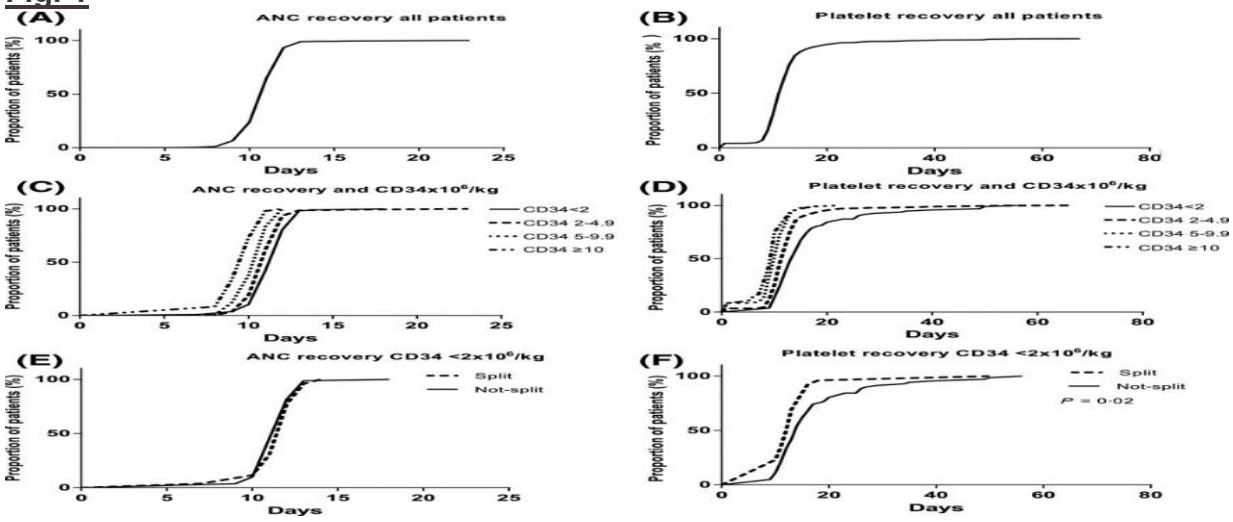
In 2006, the American Society of Clinical Oncology updated its guidelines for the use of white blood cell growth factors to include the recommendation that all patients undergoing Auto HSCT should be treated with growth factor support to reduce the duration of neutropenia and, in turn, decrease length of stay and cost[1]. This recommendation was made based on a small, randomized, placebo controlled study conducted by McQuaker et al. which showed that, in 38 patients with lymphoproliferative disorders undergoing autologous stem cell transplant, time to neutrophil recovery, antibiotic use, hospital stay, and cost were all significantly lower in patients who received daily post-transplant G-CSF[2].

Subsequent studies have replicated the finding that G-CSF administration decreases the window of time during which stem cell engraftment occurs, however, these same studies have not consistently shown an improvement in length of stay, hospital costs, or infection rates[2-7]. Furthermore, there have been numerous refinements in the transplant process since these studies were published, including the use of plerixafor for stem cell mobilization, which allows for the more consistent collection and infusion of large doses of hematopoietic stem and progenitor cells which should decrease the time to neutrophil engraftment.

Increased stem cell dose has been associated with decreased time to engraftment

Increased stem cell dose has been shown to correlate with decreased time to engraftment[8]. A recent retrospective review of 810 autologous stem cell transplants showed that patients had a statistically significantly shorter time to engraftment with stem cell doses of ≥ 5 × 10^6 cells/kg (Fig. 1). A prospective study by Olivieri also showed that patients given 5.0-7.8 x 10^6/kg stem cells had a significantly shorter duration of neutropenia, fewer platelet transfusions, and less time spent in hospital than patients receiving 2.5-4.9 x10^6/kg stem cells[9].

Fig. 1



Plerixafor mobilization leads to the collection of larger numbers of stem cells
For Auto HSCT, the minimum accepted dose of stem cells to obtain consistent and timely white cell and platelet recovery is 2 x 10^6/kg. However, the 2014 American Society for Blood and Marrow Transplantation guidelines for PBSC mobilization acknowledge that larger stem cell doses result in faster engraftment and, therefore, suggest that "a target CD34+ cell dose between 4 and 5 x10^6 CD34+ cells/kg seems most reasonable based on available data"[10]. Unfortunately, conventional stem cell mobilization, with G-CSF alone (ie without plerixafor) or chemotherapy followed by G-CSF, fails to result in an adequate number of cells in 10-40% of patients[9,11].
Plerixafor is a bicyclam molecule that reversibly binds the chemokine receptor-4 (CXCR4) which is present on CD34+ stem cells and blocks its interaction with SDF1α, which is present in the bone marrow stroma, ultimately resulting in the release of stem cells from their niche into the circulation. It is currently FDA approved for use in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent Auto HSCT in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).

Plerixafor significantly increases the number of stem cells collected both in patients undergoing first mobilization and patients who failed initial mobilization with G-CSF alone. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial comparing G-CSF plus placebo vs. G-CSF plus plerixafor for mobilization in multiple myeloma patients conducted by DiPersio et al. showed that a significantly higher proportion of patients receiving G-CSF plus plerixafor reached the target of 6 x 10^6 CD34+ stem cells/kg collected in ≤2 apheresis sessions (71.6% vs 34.4% (P < .001))[12]. A similar study in patients with non-Hodgkin lymphoma showed that 59.3% of patients in the plerixafor group vs. 19.6% in the placebo group reached the primary endpoint of ≥ 5 × 10^6 CD34+ stem cells/kg in ≤ 4 apheresis days (P < .001)[13].

At Jefferson, we have adopted the routine use of plerixafor in conjunction with G-CSF for PBSC mobilization and collection prior to Auto HSCT. With this technique, on average, we are able to collect 3 x 10^6 CD34+ stem cells in one pheresis session.

The use of post-Auto HSCT G-CSF has not been shown to improve clinical outcomes
In many transplant centers including Jefferson, G-CSF is also used after stem cell infusion in the Auto HSCT. The use of G-CSF after Auto HSCT has been shown to decrease time to neutrophil engraftment, although it has not consistently been shown to improve other clinical outcomes. In a review article published in 2009, Trivedi et al. concluded that, based on available data, the use of G-CSF conferred no significant improvement in days of febrile neutropenia or days of IV antibiotics[14]. Studies have also failed to show an acceleration in platelet recovery, and some have even shown a delay[4,15,16].

G-CSF use may be associated with an increased incidence of engraftment syndrome

Engraftment syndrome (ES), characterized primarily by non-infectious fever, skin rash, hepatic dysfunction, renal dysfunction, and pulmonary edema or infiltrates, is a well-described complication of Auto HSCT that contributes to post-transplant morbidity and mortality[16]. Given the variable presentation and severity of these symptoms, along with their association with a variety of other post-transplant complications (including sepsis), the exact incidence is difficult to measure. Regardless, an association between the development of ES and the use of post-transplant G-CSF has been described.
Lee et al. conducted a retrospective review of 248 patients who underwent Auto HSCT and found the incidence of ES to be 58.9 +/- 6.4%. Post-transplant granulocyte colony-stimulating factor increased the incidence of the syndrome from 48.3 +/- 8.2% without G-CSF to 79 +/- 4.6% with G-CSF ($P < 0.01$)[17]. Other studies have also suggested a correlation between G-CSF use and ES, but have failed to reach statistical significance[18, 19].

At our institution, we noted a significant increase in the incidence of ES with post-transplant use of granulocyte macrophage colony stimulating factor (GM-CSF-an alternate type white cell growth factor)[20]. Since then, we have switched to using G-CSF for post-transplant growth factor support, but have failed to see the expected drop in ES, suggesting that G-CSF may also predispose patients to the development of this transplant complication.

Use of post-transplant G-CSF may not significantly improve length of stay or cost of hospitalization
The utility of post-Auto HSCT G-CSF in the reduction of hospital length of stay (based on shortened time to neutrophil recovery) has been debated in the literature. No randomized studies have been published with length of stay as the primary outcome measure, however, many studies have looked at this metric as a secondary endpoint. While some studies have shown a significant reduction in post-transplant or overall length of stay with the use of G-CSF[4,5,7], others have failed to do so[21, 22]. At our institution, the average total length of hospital stay for Auto HSCT with growth factor support is 17 days. This is shorter than what is reported in the literature and may be related to the larger cell doses given with plerixafor mobilization.

Rigorous economic analyses of the use of post-Auto HSCT G-CSF are also lacking, however, cost reduction has been evaluated as a secondary endpoint in some small studies. Those studies report an overall decrease in length of stay with G-CSF with a decrease in cost of hospitalization[2]. However, a prospective, randomized study looking at the economic consequences of post-Auto HSCT G-CSF use in a pediatric population was published in 2004 and showed a trend toward higher overall hospital costs in the G-CSF group[23]. We reviewed our pharmacy records and determined the cost of administration of tbo-filgrastim, our standard G-CSF product, to be approximately $261 per dose. On average, our patients receive 9 days of treatment, therefore, the mean cost of G-CSF administration per hospitalization is $2356.

1.2 Rationale for the Proposed Study

Based on the above literature review, there is not clear evidence that the administration of post Auto HSCT G-CSF has a major beneficial impact on clinical outcomes other than more rapid recovery of neutrophils. In addition, the use of this agent has been associated with ES which can prolong length of stay and cause morbidity. With the addition of plerixafor to G-CSF for PBSC mobilization, higher doses of stem cells are collected for each patient potentially obviating the benefit of using post G-CSF for rapid neutrophil recovery. Therefore, the risk-benefit ratio of using post Auto HSCT G-CSF may shift toward more risk in the plerixafor era. The rational for this proposed trial is to assess if engraftment time is similar in patients whether post Auto HSCT G-CSF is used or not. If non-inferiority is proven in the no-G-CSF arm, we will discontinue use of the drug and avoid ES.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

Prospective subjects will be informed of all anticipated and possible unanticipated adverse effects of drug treatments. Anticipated adverse events related to G-CSF administration include fever, bone pain, splenic rupture, acute respiratory distress syndrome (ARDS), and allergic reaction. Possible adverse events related to the omission of G-CSF from the post-transplant period include prolonged myelosuppression, neutropenic fever, and infection. Prospective subjects will also be advised of issues related to confidentiality in accordance with HIPAA guidelines and will sign a separate consent to collection and appropriate disclosure of protected health information during the trial.

1.3.2 Benefits

Omission of treatment with G-CSF from the post-transplant period may provide substantial benefit for study participants, including decreased length of hospitalization, decreased pharmacy costs, and decreased incidence of engraftment syndrome. An additional and more certain benefit will be the scientific knowledge gained from this clinical trial. Although study participants cannot be guaranteed benefit, the information gained may benefit cancer patients in the future.

2 Study Objectives/Hypothesis

2.1 Hypothesis

We hypothesize that the number of days to discharge readiness after a GCS-F + plerixafor mobilized autologous stem cell transplant with a CD34 cell dose of 4-6x10^6/kg will be non-inferior (not more than 13.3% increase) in patients who do not receive G-CSF support in the post-transplant period compared with those who do receive G-CSF support.

2.2 Objectives

2.2.1 Primary

To demonstrate non-inferiority in the number of days to discharge readiness (defined in section 3.5) after a G-CSF + plerixafor-moblized autologous stem cell transplant in patients receiving versus not receiving post-transplant growth factor support.

2.2.2 **Secondary**

To compare days to ANC >500, days to platelet engraftment, febrile days, days of febrile neutropenia, documented infections, and number of antibiotic days in patients receiving versus not receiving post-transplant growth factor support.

2.2.3 **Exploratory**

To evaluate immunological recovery (lymphocyte number including CD 3/4 and CD3/8 T cell subsets) at Day + 60 in patients receiving versus not receiving post-transplant growth factor support. Rationale is that myeloid growth factor potentially has impacts on the quantity and quality of the recovering lymphocyte compartment.

2.3 **Endpoints/Outcome Measures**

2.3.1 **Primary**

The number of days to discharge, or discharge readiness, is a global reflection of how quickly counts recover, how rapidly toxicity and morbidity related to Auto HSCT resolves, and resolution of fever indicating discharge is safe. Therefore, discharge readiness is the primary method for assessing non-inferiority between the two arms in the study.

2.3.2 **Secondary**

Comparisons between the two study groups:

- Median days post Auto HSCT to neutrophil engraftment (defined as ANC >500 $x10^9$/L x 3 days); day of engraftment is the first of the 3 days of ANC >500 $x10^9$/L
- Median days post Auto HSCT to platelet engraftment (defined as date platelet greater than or equal to (≥) 20 x 10^9 /L without a platelet transfusion within the last 7 days). Platelet count of 20 x 10^9 /L must be sustained for 3 consecutive days
- Incidence of engraftment syndrome as defined by the Maiolino Criteria (Appendix B)
- Median number of febrile days during the Auto HSCT inpatient stay
- Median number of days of febrile neutropenia during the Auto HSCT inpatient stay (Fever defined as ≥100.4F)
- Median number of documented infections (defined as a positive blood culture not ultimately deemed to be due to a contaminant, a positive urine culture with ≥50,00 colony forming units per mL of urine, a positive cerebrospinal fluid culture, or imaging findings consistent with an infectious source) requiring treatment during the Auto HSCT inpatient stay
- Median number of antibiotic days during the Auto HSCT inpatient stay
- Median number of days on corticosteroids
- Number of post discharge G-CSF administrations through Day +60 post Auto HSCT
- Readmissions through Day +60 post Auto HSCT

2.3.3 **Exploratory**

Comparison of median actual lymphocyte count, CD3/4, and CD 3/8 counts between the groups at Day +28 and Day +60 post Auto HSCT. This objective is meant to form the basis of a potential successor study in which myeloid growth factor effects on lymphoid reconstitution and disease progression are studied. The actual lymphocyte counts may be obtained 10 days before or 10 days after Day +28 and 14 days before or after Day +60 to account for variability in patient scheduling and lab readiness on holidays/weekends

3 Study Design

After conditioning chemotherapy, all patients will receive equivalent cell doses of their G-CSF + plerixafor-mobilized stem cell product. One group will receive G-CSF after Auto HSCT (the current practice at Jefferson). The alternate group will not receive G-CSF after Auto HSCT. This design will allow for a high degree of homogeneity between the comparison groups in that patients in both groups will have similar diagnoses and disease statuses, identical stem cell mobilization procedures, and equivalent stem cell doses infused during the Auto HSCT.

3.1 Characteristics

This is a randomized controlled clinical trial evaluating differences in Auto HSCT outcomes between two similar groups of patients based on the administration of post Auto HSCT growth factor in one of the groups. Patients enrolled on this clinical trial will have a diagnosis of multiple myeloma or non-Hodgkin lymphoma. All patients will be adults and treated in an inpatient setting. All patients will have received therapy for their disease prior to undergoing Auto HSCT to consolidate previous therapy. As such, no patient will have rapidly evolving disease at the time of Auto HSCT admission.

3.2 Number of Participants

This is a 2-arm study in which 70 patients will be enrolled in each group, for a total of 140 patients enrolled in the study.

3.3 Duration of Therapy

The period of time during which G-CSF is administered after Auto HSCT is approximately 12-14 days. Therefore, the “therapy” versus “no therapy” part of the intervention will be approximately 14 days.

3.4 Duration of Follow Up

Patients will be followed for 60 days to meet objectives of this study. Patients will be followed for adverse events for 60 days post-Auto HSCT.

3.5 Discharge Readiness

Discharge readiness is defined by:

1. not-neutropenic,
2. not requiring transfusions more than twice weekly,

3. temperature ≤ 99.3° F x 24 hours without anti-pyretics,
4. not requiring IV fluids to maintain baseline creatinine,
5. no clinical issue related to Auto HSCT such as rash, uncontrolled pain.

Discharge readiness= medically appropriate for discharge except for social or placement issues that delay discharge.

3.6 Treatment Assignment Procedures

3.6.1 Randomization Procedures

The study statistician will generate the randomization schedule using the method of random permuted blocks within strata defined by disease type and days of stem cell collection. Randomization assignments will be loaded into a REDCap database prior to study initiation. Assignments will be accessed by the senior coordinator or his/her designee within the time frame of 2 weeks prior to Auto HSCT admission. Once the randomization assignment has been accessed in REDCap, the patient is considered randomized.

3.7 Study Timeline

3.7.1 Primary Completion

We anticipate that enrollment will be complete within 4 years.

3.7.2 Study Completion

We anticipate that the study will be complete within 5 years.

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

- Age ≥18 years
- Undergoing autologous stem cell transplant for one of the following diagnoses:
  - Multiple myeloma
  - Non-Hodgkin lymphoma
- Karnofsky performance status of ≥ 70%
- Patients must meet the TJUH BMT SOP guidelines for “Patient Criteria for Autologous HSCT.”
- Adequate organ function:
  - LVEF of ≥40%
  - Adj DLCO ≥45% of predicted corrected for hemoglobin
- Adequate liver function as defined by a serum bilirubin <1.8, AST or ALT < 2.5X upper limit of normal

- Serum creatinine ≤ 2.0 mg/dl and/or creatinine clearance of > 40 ml/min (excludes multiple myeloma patients receiving high dose Melphalan conditioning)
- Willingness to use contraception if childbearing potential
- Has the ability to give informed consent, or for cognitively or decisionally impaired individuals (vulnerable population), the availability of a family member or guardian to give consent and assist in the consent process
- Life expectancy of > 12 months (exclusive of the disease for which the Auto HSCT is being performed)
- Patients must have undergone stem cell mobilization with the combination of G-CSF and plerixafor as per TJUH BMT SOP guidelines
- Collection of an adequate number of CD34+ stem cells, i.e. ≥ 4-6 × 10^6/kg from apheresis

4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Uncontrolled HIV
- Uncontrolled bacterial infection
- Active CNS disease
- Pregnancy or lactation
- Evidence of another malignancy, exclusive of a skin cancer that requires only local treatment

4.2 Gender/Minority/Pediatric Inclusion for Research

Patients > 18 years will not be excluded based on gender, race, or economic status. Pediatric patients are not cared for in the TJU Medical Oncology and Blood and Marrow Transplant Programs which are all adult programs with no expertise in pediatrics.

4.3 Strategies for Recruitment and Retention

Patients will not actively be recruited for participation in this clinical trial. Patients who are being evaluated for Auto HSCT in the Thomas Jefferson Blood and Marrow Transplant Program and who meet eligibility criteria will be invited by their physician to participate in the study. All therapeutic options will be discussed with the patient and the patient's questions will be answered to their satisfaction. Patients will be asked to read, comment/ask questions about the study and then sign the informed consent form before study procedures take place.

4.4 Participant Withdrawal

4.4.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate a study participant's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.4.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

The reason for participant withdrawal or discontinuation will be documented in the clinical trial records of the participant. After this time, the patient's course will not be monitored for the purposes of this clinical trial. However, as a patient undergoing Auto HSCT in the Jefferson BMT program, the participant will be followed indefinitely for major outcomes.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 Study Intervention

5.1 Study Product

Granulocyte colony stimulating factor (G-CSF)

5.2 Study Product Description

Recombinant human granulocyte colony-stimulating factor

5.2.1 Acquisition

Tbo-filgrastim is the brand of G-CSF used at Thomas Jefferson University Hospital. It will be acquired through the Thomas Jefferson University Hospital inpatient pharmacy, and is expected to be available for the duration of the trial. A biologically-equivalent brand of G-CSF may be substituted for Tbo-filgrastim if market forces necessitate a brand change.

5.2.2 Formulation, Packaging, and Labeling

480 mcg/0.8 mL solution in single-use prefilled syringe.

5.2.3 Product Storage and Stability

G-CSF syringes should be stored in a refrigerator at 36° to 46° F (2° to 8° C). Protect from light. Within its shelf life, the product may be removed from 36° to 46° F (2° to 8° C) storage for a single period of up to 5 days between 73° to 81° F (23° to 27° C). If not used within 5 days, the product may be returned to 36° to 46° F (2° to 8° C) up to the expiration date. Avoid shaking. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Exposure to 23° to 30° F (-1° to -5 °C) for up to 72 hours and temperatures as low as 5° to -13° F (-15 to -25° C) for up to 24 hours do not adversely affect the stability of G-CSF.

5.3 Dosage, Preparation, and Administration

In patients in the G-CSF arm, 480 mcg of G-CSF will be administered to patients weighing > 60 kg subcutaneously as a once-daily subcutaneous injection beginning on d+3 after Auto HSCT and stopping after an ANC of >0.5 x 10^9/L x 3 days OR ANC>2 x 10^9/L, whichever comes first. For patients who weigh 60 kg or less, G-CSF is administered at a flat dose of 300 mcg from the 480 mcg syringe. This is the current practice. Recommended sites for subcutaneous G-CSF injections include the abdomen (except for the two-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily. G-CSF should not be injected into an area that is tender, red, bruised or hard, or that has scars or stretch marks.

5.4 Dose Modifications and Dosing Delays

Dose modifications will not be made.

6 Study Schedule

6.1 Enrollment/Baseline

(Visit 1, Day 0- Transplant Consent Conference)

- Obtain and document consent from participant on study consent form.
- Verify inclusion/exclusion criteria.
- Since patients will already have undergone assessment for Auto HSCT at Jefferson, demographic information, medical history, medication history, social history, and testing results will be part of the medical record at the time of the official consent conference. This information will be collected and maintained by the research coordinators assigned to this study. In addition, as with Auto HSCT, patient consent for this clinical trial is a process of education that occurs over several visits and culminates in a written consent conference which will occur at or around the time of the Auto HSCT. Consent for this trial will not be obtained after Day +0 after Auto HSCT.

6.2 Treatment Period

Post-transplant Day +3- Day of discharge

- Administer G-CSF (480 mcg for all patients weighing > 60 kg and flat dose of 300 mcg for all patients weighing 60 kg or less) starting on day +3 post HSCT and continuing until ANC is >0.5 x 10^9/L x 3 days OR ANC >2 x 10^9/L, whichever comes first, if the patient is in the treatment group. Patients in the non-treatment group will not receive growth factor.
- Red cell and platelet growth factors are prohibited through Day +60 of this trial
- Record adverse events as reported by participant or observed by investigator/clinical staff.
- There are no extra blood studies required by this protocol during the Auto HSCT admission.
- Assess for discharge readiness as defined in section 3.5.

6.3 Post-Treatment Period (Day of Discharge through Day +60)

Assess for any of the following unanticipated results of withholding of growth factor:

- Need for post discharge G-CSF administration
- Need for post discharge red cell or platelet growth factor administration
- Transfusion
- Fever (≥100.4)
- Infection
- Readmission

6.4 Withdrawal Visit/Discontinuation of Therapy

If a participant withdraws early or the investigator terminates a participant's participation the following should still be offered to the participant:

- Recording of adverse events
- Recording of physical examination

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

Participants will undergo standard evaluations per TJUH BMT SOP guidelines. There are no additional evaluations required for this protocol during the pre-transplant period, the Auto HSCT admission, or the post-transplant period.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Laboratory studies including CBC with differential, liver function tests, electrolytes, blood culture, urinalysis, urine culture, and cerebrospinal fluid culture will be performed during the Auto HSCT period when applicable, as determined by the treating physician. Pregnancy test will be performed prior to transplant, if applicable, in accordance with the TJUH BMT SOP. There are no extra blood studies required by this protocol during the Auto HSCT admission.

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

8.2 Safety Assessment and Follow-Up

The PI will follow adverse events from the first day of admission through day +60 after Auto HSCT. At that time, all of the effects of the administration versus non-administration of post HSCT G-CSF should be known.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 (Safety Assessment and Follow-Up).

8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.
The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

8.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

8.3.4 Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4 Safety Reporting

8.4.1 Reporting to IRB

8.4.1.1 *Unanticipated Problems*

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).
UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.
UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

8.4.1.2 *Adverse Events*

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

8.4.1.3 *Serious Adverse Events*

The following events are expected side effects of high-dose chemotherapy and transplant and will not be reported as SAEs:

- Alopecia
- Headache
- Dry skin
- Emesis from chemotherapy or other agents unless refractory to standard supportive care
- Nausea, anorexia
- Weight loss
- Cough
- Dry mouth
- Grades 1-3 fever
- Grades 1-3 infectious sequelae
- Grades 1-3 electrolyte imbalances
- Neutropenia/uncomplicated neutropenic fever
- Thrombocytopenia, petechiae, ecchymosis, minor vaginal bleeding, epistaxis, hemorrhoidal bleeding, or other similar bleeding events will not be reported. (Bleeding events requiring intervention such as endoscopy or radiologic evaluation will be reported)
- Anemia
- Grades 1-3 mucositis
- Grades 1-3 diarrhea
- Allergic or other reactions to drugs used for supportive care or GVHD prophylaxis unless grade 4-5

All grade 4-5 events occurring during the study period (Day of admission through d+60) will be reported.

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

8.4.2 Reporting to SKCC DSMC

All AEs and SAEs (that are reportable per the criteria noted in section 8.4.1.3), safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

For expedited reporting requirements, see table below:
DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

11 Statistical Considerations

11.1 Study Hypotheses

We hypothesize that the number of days to discharge readiness after a G-CSF + plerixafor mobilized autologous stem cell transplant with a CD34 cell dose of at least 4-6x10^6/kg will be non-inferior (not more than 13.3% increase) in patients who do not receive G-CSF support in the post-transplant period versus with those who do receive G-CSF support.

11.2 Analysis Plans

The primary outcome is measure by comparing days to discharge readiness between the two groups. The rationale for using discharge readiness as the primary outcome measure and the definition of discharge readiness is reviewed in section 3.5

The distribution of time to readiness will be estimated using the Kaplan-Meier method by treatment arm. Groups will be compared using a Weibull regression accelerated failure time model allowing for potential censoring of the outcome. The regression model will adjust for the stratification factors of disease type and number of days of stem cell collection. The acceleration factor for no G-CSF vs. G-CSF will be estimated along with a 90% confidence interval. The hypothesis of inferiority will be rejected if the upper bound is less than 1.133.

Time to neutrophil engraftment and platelet engraftment will be compared using Wilcoxon rank sum tests or, if some data are censored, log-rank tests.

Number of febrile days, number of days of febrile neutropenia, number of documented infections, number of antibiotic days, number of corticosteroid days, and number of post discharge G-CSF administrations through day +60 will be summarized by treatment arm and compared using Wilcoxon rank sum tests. Incidence of engraftment syndrome and readmission through Day +60 post Auto HSCT will be summarized by treatment arm and compared using a chi-square test or Fisher's exact test, as appropriate.

All primary and secondary outcome analyses will be performed on the intent-to-treat subset defined as all patients who are randomized with treatment group defined by randomization status regardless of treatment actually received.

Other events from discharge through Day +60 that are not formal objectives of the study but may represent unanticipated outcomes such as the need for platelet or red cell growth factors, post discharge fever and infection, and the need for transfusion will be reported for each group descriptively.

11.3 **Interim Analyses and Stopping Rules**

One interim analysis for futility will be performed when approximately 50% of the expected sample size has been randomized and followed for assessment of the primary outcome. Assuming the analysis is performed at 50% of expected information, using an O'Brien-Fleming spending function with a target type-II error rate of 20%, the study will stop for futility if the p-value for the test of the null hypothesis that the acceleration factor is greater than 1.133 has a p-value of 0.3784 or greater. Safety will be monitored continuously.

Stopping Rule
In the event that a patient in the non-G-CSF arm develops a serious infection during the Auto HSCT inpatient stay, G-CSF may be initiated by the attending physician in charge if in the judgment of that physician G-CSF would decrease the chance of significant morbidity or mortality. G-CSF will also be initiated if a patient in the non-G-CSF arm has prolonged neutropenia, defined as an ANC <500 on day +14 after transplant. If emergent initiation of G-CSF in the non-G-CSF arm occurs in > 10% of patients on that arm (first look after 20 patients), then the clinical trial will be closed.

11.4 **Sample Size Considerations**

Power was estimated via simulation. In the pilot data, median days to discharge were 15, with no patient ready for discharge before day 11. In order to mimic this distribution, the model for time to discharge (T) was assumed to be T=10+X where X was distributed as Weibull with shape parameter of 1.42 and scale parameter 6.47 in both groups. For a given sample size, 2000 data sets were simulated with random 5% censoring. Groups were compared using Weibull regression using rounded values of T as the outcome. Power was estimated as the percentage of datasets in which the upper bound of the 90% confidence interval for the acceleration factor was less than 17/15 (1.133). Power to accept the non-inferiority hypothesis when the two groups have the same median

time to discharge readiness is estimated to be at least 80% with a sample size of 140 (70 per arm).

11.4.1 Replacement Policy

Subjects who are randomized but do not undergo transplant may be replaced.

11.4.2 Accrual Estimates

The trial hopes to enroll 140 participants overall, with 70 participants in each of the two arms. We anticipate accrual of 140 patients per year over a period of 4 years.

11.4.3 Exploratory Analysis

Groups will be compared with respect to actual lymphocyte count, CD3/4, and CD 3/8 counts at Day +28 and Day +60 post Auto HSCT using Wilcoxon rank sum tests. The actual lymphocyte counts may be obtained 10 days before or 10 days after Day +28 and 14 days before or after Day +60 to account for variability in patient scheduling and lab readiness on holidays/weekends

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 Quality Control and Quality Assurance

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be

explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals age 18 years or older will not be excluded based on gender, race or economic status.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

15 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 Data Capture Methods

Data will be collected electronically through the Thomas Jefferson University Hospital electronic medical record system.

15.3 Study Records Retention

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations.

15.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

16 Study Finances

16.1 Funding Source

This study will be funded by the Thomas Jefferson University Hospital, Department of Medical Oncology.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

16.3 Participant Stipends or Payments

Participants will not receive payment for participation in this study.

17 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

18 Literature References

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Appendices

Appendix A: Schedule of Events

Appendix B: Maiolino Criteria for Engraftment Syndrome

APPENDIX A: SCHEDULE OF EVENTS

	Prior to Auto HSCT Admission	Auto HSCT Admission	Discharge through Day +60 post HSCT
Confirm G-CSF + plerixafor-mobilized stem cell product with adequate cell doses has been obtained	X		
Complete consent process	X		
Complete randomization process	X		
Confirm negative pregnancy test[1], if applicable	X		
Collect data[2]: • Days to discharge readiness • ANC >0.5 x10^9/L x 3 days or ANC >2 x10^9/L, whichever comes first • Platelet greater than or equal to (≥) 20 x 10^9 /L without a platelet transfusion within the last 7 days • Engraftment syndrome • Days of fever (≥100.4F) • Days of febrile neutropenia • Days preemptive or identified organism antibiotic treatment • Number of documented infections (excludes known colonizations) • Days on corticosteroids		X	
Post discharge assessments (section 6.3)[3]			X
Actual lymphocyte, CD3/4, and CD3/8 counts day +28 and day +60[2]			X

[1]Women of childbearing potential will have a pregnancy test performed prior to transplant per TJUH BMT SOP guidelines

[2]Laboratory studies will be done in accordance with TJUH BMT SOP guidelines at the discretion of the treating physician; no additional studies or tests are required for this protocol. The actual lymphocyte counts may be obtained 10 days before or 10 days after Day +28 and14 days before or after Day +60 to account for variability in patient scheduling and lab readiness on holidays/weekends.

[3]Post-discharge assessments will consist of a review of the patient's chart in order to determine whether they required post-discharge red cell or platelet growth factor administration, transfusions, or hospital readmission or if they developed fever or infection

APPENDIX B: MAIOLINO CRITERIA FOR ENGRAFTMENT SYNDROME

Non-infectious fever plus:

Skin rash or

Pulmonary infiltrates or

Diarrhea (at least two episodes of liquid stool/day without microbiological documentation of infection)

Commencing 24 h before or at any time after the first appearance of neutrophils.