Amendment

Protocol Number: 12C0074-H **Reference Number:** 373683

Principal Investigator: Jen Kanakry NCI ETIB 301.451.3787 jennifer.kanakry@nih.gov

(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: Mobilization and Collection of Autologous Hematopoietic Progenitor Cell (HPC) for Transplantation (AHCT) for Plasma Cell Myeloma (PCM)

SIGNATURES

Principal Investigator (*):
Daniel Fowler - applied signature on 09/22/2017 2:16 PM EDT
Jen Kanakry - applied signature on 09/22/2017 11:39 AM EDT

Accountable Investigator:
Ronald Gress - applied signature on 09/22/2017 12:17 PM EDT

Branch Chief/CC Department Head (**):
Ronald Gress - applied signature on 09/22/2017 12:18 PM EDT

Medical Advisory Investigator (if applicable):
N/A

Lead Associate Investigator signature:
N/A

Referral Contact signatures:
Jen Kanakry - applied signature on 09/22/2017 11:39 AM EDT

Associate Investigators signatures:
N/A

For Institute/Center Scientific Review Committee:
N/A

Other IC Clinical Director signatures:
N/A

APPROVALS

IRB Chair:
Michael Hamilton - applied signature on 09/23/2017 1:18 PM EDT

Clinical Director:
N/A

CONCURRENCE

OPS Protocol Specialist:

Lemuel Clayborn	AM H	10/04/2017
Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: 09/22/2017

Protocol Version Date: 09/14/2017

Abbreviated Title: HPC for AHCT in PCM
CC Protocol Number: 12-C-0074
NCT#: NCT01547806

Version Date: September 14, 2017

Amendment: H

Protocol Title: Mobilization and Collection of Autologous Hematopoietic Progenitor Cell (HPC) for Transplantation (AHCT) for Plasma Cell Myeloma (PCM)

NCI Principal Investigator: Jennifer A. Kanakry, M.D [A-F]
Experimental Transplantation and Immunology Branch
Center for Cancer Research, NCI
10 Center Drive, Building 10, Rm 4-3132
Bethesda, MD 20892
Phone: 240-760-6172
Fax: (301) 451-5667
Email: jennifer.kanakry@nih.gov

NIH Associate Investigators:

Daniele Avila, C.R.N.P., ETIB, CCR [A-E]	Dennis Hickstein, MD.,ETIB, CCR [A-F]
Bazetta Blacklock Schuver, R.N., OCD, CCR [A-C]	Ellen Carroll, R.N., OCD, CCR [A-C]
Tracey Chinn, R.N., ETIB, CCR [A-C]	Jeremy Rose, M.S, ETIB, CCR [E-F]
Constance Yuan, M.D., Ph.D, CCR E-F	Jennifer Mann, C.R.N.P., ETIB, CCR [A-E]
Ronald E. Gress, M.D., ETIB, CCR [A-F]	Steven Pavletic, M.D., ETIB, CCR [A-F]
Fran Hakim, Ph.D, ETIB, CCR [E-F]	Seth Steinberg Ph.D., OCD, CCR [B, E]
Brenna Hansen, R.N., OCD, CCR [A-C]	Maryalice Stetler-Stevenson, M.D., PhD., CCR [B, E-F 4]
Stephanie Cotton, R.N., OCD, CCR[A-C]	David Stroncek, M.D.,DTM, CCR[E-F]

Referral contact: Jennifer Kanakry, M.D.

Telephone: 240-760-6172
Email: jennifer.kanakry@nih.gov

Study Coordinator: Bazetta Blacklock Schuver, RN

Phone number: 240-760-6156

Email: bblacklock@mail.nih.gov

For each person listed above, roles are identified with the appropriate letter

A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals

C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

Investigational Agents: None
Commercial Agents: Filgrastim and Plerixafor

PRÉCIS

Background:

- High-dose chemotherapy followed by autologous hematopoietic cell transplant (AHCT) remains a critical part of the Plasma Cell Myeloma (PCM) treatment in subjects eligible for the procedure. The timing of the procedure however, has become more controversial recently. This protocol will allow collection of Hematopoietic Progenitor Cells by Apheresis (HPC, Apheresis) in potential candidates for various PCM protocols at the Clinical Center.
- The mobilizing agent plerixafor (Mozobil®, Genzyme) has been recently approved by the FDA for mobilization in PCM. However, the best and most cost effective strategy for its use remains to be defined.

Objectives:

- Evaluate the overall validity of an HPC mobilization strategy (with G-CSF alone or in combination with plerixafor) using a formula calculating the likelihood of collecting $\geq 5 \times 10^6$ $CD34^+$ cells/kg in a single mobilization cycle.
- Collect mobilized Hematopoietic Progenitor Cells by Apheresis (HPC, Apheresis) prior to AHCT for PCM

Eligibility:

- Subjects with a possible indication for AHCT for the treatment of newly diagnosed PCM.
- Subjects with recurrent or persistent evaluable disease who have not undergone AHCT for the treatment of the PCM.

***Design*:**

- Subjects will undergo mobilization and collection of HPC, Apheresis for subsequent use in various clinical protocols.
- Mobilization will be provided by a 5-daily administration of filgrastim according to standard procedure.
- The need for an additional mobilizing agent (plerixafor) to be given on day 4 of mobilization will be evaluated in real time in each patient, based on the peripheral blood CD34 count on the morning of day 4 of filgrastim administration.
- Study accrual over a 3-year period: 70 subjects

TABLE OF CONTENTS

PRÉCIS **3**

TABLE OF CONTENTS **4**

1 INTRODUCTION **7**

1.1 STUDY OBJECTIVES 7
1.1.1 Primary Objectives *7*
1.1.2 Secondary Objectives *7*
1.2 BACKGROUND AND RATIONALE 7
1.2.1 Overview of Treatment of MM *7*
1.2.2 AMD3100 (Plerixafor, Mozobil™, Genzyme) *8*
1.2.3 Evaluate the need for systematic use of Plerixafor on day 4 ..... *9*
1.2.4 Evaluation of minimal residual disease *10*
1.2.5 Lack of need for purging of HPC, Apheresis product *11*
1.2.6 Utilization of HPC products in NCI protocols *11*

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT **12**

2.1 ELIGIBILITY CRITERIA 12
2.1.1 Inclusion Criteria *12*
2.1.2 Exclusion Criteria *12*
2.1.3 Recruitment strategy *13*
2.2 SCREENING EVALUATION 13
2.2.1 History and Physical examination *13*
2.2.2 Laboratory evaluation *13*
2.3 REGISTRATION PROCEDURES 13

3 STUDY IMPLEMENTATION **13**

3.1 STUDY OVERVIEW 13
3.2 TREATMENT SCHEMA 14
3.3 DRUG ADMINISTRATION 15
3.3.1 Filgrastim administration *15*
3.3.2 Plerixafor Administration *16*
3.3.3 Apheresis *16*
3.3.4 Inadequate collection *17*
3.3.5 Salvage collection regimen *17*
3.4 DOSE MODIFICATIONS 17
3.5 STUDY CALENDAR 18
3.6 OFF STUDY CRITERIA 18
3.6.1 Criteria for removal from protocol therapy *18*
3.6.2 Off-Study Criteria *18*
3.6.3 Off Protocol Therapy and Off Study Procedure *19*

4 CONCOMITANT MEDICATIONS/MEASURES **19**

5 BIOSPECIMEN COLLECTION **19**

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES 19
5.1.1 Clinical end points 19
5.1.2 Biologic end points 19
5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION 20
5.2.1 Clinical HPC, Apheresis Products 20
5.2.2 Storage/Tracking 20
5.2.3 Protocol Completion/Sample Destruction 21

6 DATA COLLECTION AND EVALUATION 22

6.1 DATA COLLECTION 22
6.2 TOXICITY CRITERIA 23

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN 23

7.1 DATA REPORTING & RECORDS TO BE KEPT 23
7.2 DEFINITIONS 23
7.2.1 Adverse Event 23
7.2.2 Suspected adverse reaction 24
7.2.3 Unexpected adverse reaction 24
7.2.4 Serious 24
7.2.5 Serious Adverse Event 24
7.2.6 Disability 25
7.2.7 Life-threatening adverse drug experience 25
7.2.8 Protocol Deviation (NIH Definition) 25
7.2.9 Non-compliance (NIH Definition) 25
7.2.10 Unanticipated Problem 25
7.3 NCI-IRB AND CLINICAL DIRECTOR REPORTING 25
7.3.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths 25
7.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review 26
7.3.3 Exceptions to reporting: 26
7.4 DATA AND SAFETY MONITORING PLAN 26
7.4.1 Principal Investigator/Research Team 26

8 STATISTICAL CONSIDERATIONS 27

9 HUMAN SUBJECTS PROTECTIONS 28

9.1 RATIONALE FOR SUBJECT SELECTION 28
9.2 PARTICIPATION OF CHILDREN 28
9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT 28
9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS 28
9.5 RISKS/BENEFITS ANALYSIS 28
9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION 29
9.6.1 Telephone re-consent procedure 29
9.6.2 Short form consent process for non-English speaking patients 29
9.7 SUBJECT INFORMATION AND CONFIDENTIALITY 30

10 PHARMACEUTICAL INFORMATION 30

10.1 FILGRASTIM (NEUPOGEN®, G-CSF) 30
10.1.1 Source *30*
10.1.2 Adverse effects *30*
10.1.3 Formulation, Storage, and Stability *30*
10.1.4 Administration *30*
10.2 PLERIXAFOR (MOZOBIL®) 31
10.2.1 Source *31*
10.2.2 Adverse effects *31*
10.2.3 Formulation, Storage, and Stability *31*
10.2.4 Administration *31*
10.2.5 Pharmacokinetics *31*

11 REFERENCES 32

12 APPENDIX 1: ON-STUDY CHECK LIST 36

13 APPENDIX 2: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL 37

13.1 PATIENT ENROLLMENT 37
13.2 STUDY DRUG ADMINISTRATION 37
13.3 LABORATORY AND DIAGNOSTIC TEST DATA 37
13.4 ADVERSE EVENTS 37
13.5 CONCOMITANT MEASURES 37
13.6 OFF STUDY 38

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- Evaluate the overall validity of an HPC mobilization strategy (with G-CSF alone or in combination with plerixafor) using a formula calculating the likelihood of collecting ≥ 5 x 10^6 $CD34^+$ cells/kg in a single mobilization cycle.
- Collect and cryopreserve "HPC Apheresis" products for subsequent use in AHCT in subjects with Plasma Cell Myeloma (PCM).

1.1.2 Secondary Objectives

- Determine the proportion of subjects requiring addition of plerixafor to the G-CSF mobilization regimen.
- Determine the proportion of subjects achieving the target or optimum goal of ≥ 5 x 10^6 $CD34^+$ cells/kg in a single mobilization cycle with or without Plerixafor.
- Determine the proportion of subjects achieving the minimum goal of ≥ 2 but <5 x 10^6 $CD34^+$ cells/kg in a single mobilization cycle with or without Plerixafor.
- Determine the degree of tumor cell contamination in the final product.
- Determine the impact of plerixafor in the degree of tumor cell contamination in the final product.

1.2 BACKGROUND AND RATIONALE

1.2.1 Overview of Treatment of MM

Approximately 20,000 new cases of Plasma Cell Myeloma (PCM) are diagnosed each year in the United States. In the general population, the incidence of PCM is 5 per 100,000 with an average age of onset around 70 years. Rates are higher in African Americans and in men. It is the second most common hematologic malignancy in the United States. There are an estimated 45,000 people living with PCM in this country and it is estimated that there were 19,900 new diagnoses and 10,790 deaths due to MM in 2007[1]. The median survival of patients with MM was less than one year before introduction of alkylating agents (melphalan) in the 1960s which resulted in improved survival but still in a very limited number of complete responses and in no curative effect.

For many years dexamethasone (Dex) alone or in combination with oral melphalan (MP) or with vincristine and doxorubicin (VAD)[2] has been the mainstay of induction therapy for newly diagnosed PCM. Recently, several agents with novel mechanisms of action have shown superior activity in PCM. Thalidomide in combination with Dex was found to be superior to Dexalone as well as superior to VAD in randomized trials[3, 4]. Additionally, bortezomib, a proteosome inhibitor, has been shown to be superior to VAD as induction therapy in randomized trial[5]. Two phase III studies show an increased overall survival with oral lenalidomide plus Dex

compared to Dex plus placebo in previously treated PCM patients[6, 7]. Phase II studies in newly diagnosed patients corroborate these findings. Therefore, significant progress has been made in the last decade in the management of PCM with the advent of therapy with thalidomide, bortezomib and more recently lenalidomide[8] and their combination in strategies including high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation(AHCT). In patients not exposed to this new generation of drugs, the median survival following relapse after AHCT is about 18 months while in patients exposed to these drugs following relapse after AHCT, the median survival has almost doubled to 36 months. Overall, in a recent study from Mayo Clinic, the median overall survival for subjects diagnosed in the last decade was 44.8 months (95% CI; 39.6,50) compared with 29.9 months (95% CI; 28.3, 31.6) $p< .001$,for those diagnosed earlier[9]. These successes have allowed moving these agents to front line therapy in newly diagnosed subjects with significant improvement in response rates and EFS[10-12]. The multiple improved therapeutic options now available as induction therapy for MM were recently reviewed[13]and are available as standard of care for newly diagnosed MM. Guidelines are described and regularly up-dated by the National Comprehensive Cancer Network (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

Prior to the present era of novel therapeutic agents for PCM, AHCT has been shown to significantly increase the complete remissions (CR) rate to almost 50% in selected patients (*versus* 1–13% CR with conventional dose therapy), but the disease recurs almost without exception[14-16]. AHCT increases the CR rate and time-to-progression and has shown a survival improvement[17, 18] though not consistently[19, 20]. In a meta-analysis of 2411 subjects on 9 randomized trials, Koreth et al. showed progression free survival (PFS) benefit but not overall survival (OS) benefit for AHCT with single autologous transplantation performed early in multiple myeloma over chemotherapy alone[18].

Of note, prior to the present era of novel agents, there was no advantage in delaying AHCT until disease progression. The treatment duration was overall shorter in patients transplanted upfront following induction chemotherapy[21]. In the present era of more effective induction therapy though, this assertion needs to be revisited and at least two randomized trials are presently ongoing to address the question of upfront versus delayed AHCT following induction with novel agents.

Of significance, to the present day, achievement of a CR continues to be the single most predictive factor for EFS and OS for PCM[22]. Better responses lead to better response durations. Outcomes of 4,990 AHCT patients according to their best tumor response were reported in two meta-analyses of 21 studies (10 prospective and 11 retrospective). Both meta-analyses indicated highly significant association between maximal response (CR/VGPR) during or after AHCT and long-term outcomes (OS and EFS) as well as a highly significant associations between maximal response following induction therapy and EFS/OS[23]. Therefore, improvement of the initial CR rate continues to be at the forefront of clinical research in PCM.

1.2.2 AMD3100 (Plerixafor, Mozobil™, Genzyme)

Plerixafor is a small molecule reversible inhibitor of the binding of SDF-1 α to its cognate receptor CXCR4 and mobilizes hematopoietic stem cells from the marrow to the blood[24, 25]. Plerixafor clinical experience and toxicity have been recently reviewed[26, 27].

Maximal mobilization of CD34+ cells occurs 8-10 h after dosing[26]. There is a highly synergistic interaction of G-CSF and AMD3100 on mobilization[28].The combination plerixafor/ G-CSF is more effective than G-CSF alone for $CD34^+$ cell mobilization. In a study of stem cell mobilization for AHCT for PCM, the percentage of patients who collected $\geq 6 \times 10^6$ $CD34^+$ cells/kg in ≤ 2 aphereses was 71.6% (106 of 148 patients) in the G-CSF + plerixafor group and 34.4% (53 of 154) in the G-CSF + placebo group ($p < .001$). 54% of G-CSF + plerixafor-treated patients reached target after one apheresis, whereas 56% of the G-CSF + placebo-treated patients required 4 aphereses to reach target[29]. Similar results were found in a phase III randomized placebo controlled study in non-Hodgkin's lymphoma[30].

Plerixafor (Mozobil™) received FDA approval in December 2008 for use in stem-cell mobilization in NHL and PCM. This was based on the results of two placebo-controlled clinical trials. In both studies, the subjects were randomized to receive either plerixafor 0.24 mg/kg or placebo on each evening prior to apheresis. They received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of plerixafor or placebo and on each morning prior to apheresis. Study 1[30] enrolled 298 NHL subjects. Fifty nine percent of the subjects mobilized with plerixafor and G-CSF collected $\geq 5 \times 10^6$ $CD34^+$ cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 20% of subjects mobilized with placebo and G-CSF ($p < 0.001$). The median number of apheresis days to collect $\geq 5 \times 10^6$ $CD34^+$ cells/kg was 3 days for the plerixafor group and not evaluable for the placebo group. Study 2[29] enrolled 302 MM subjects. Seventy two percent of patients mobilized with plerixafor and G-CSF collected $\geq 6 \times 10^6$ $CD34^+$ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% of patients mobilized with placebo and G-CSF ($p < 0.001$). The median number of apheresis days to collect $\geq 6 \times 10^6$ $CD34^+$ cells/kg was 1 day for the plerixafor group and 4 days for the placebo group.

More recent experience has now also been acquired in using plerixafor alone as a mobilization agent prior to AHCT for PCM[31]and prior to allo BMT[32].

1.2.2.1 Plerixafor pharmacokinetics

Peak plasma concentrations occur about 30 to 60 minutes after a subcutaneous dose. It is about 58% bound to plasma proteins and largely confined to the extravascular fluid space. About 70% of a dose is eliminated in the urine within 24 hours after a dose, and the terminal half-life is about 3 to 5 hours.

In moderate and severe renal impairment (creatinine clearance 50 ml/min or less) the dose of plerixafor should be reduced to 160 micrograms/kg, given by subcutaneous injection about 10 hours before apheresis, for up to 4 consecutive days. The daily dose should not exceed 27 mg. complete information is available at the following web site:

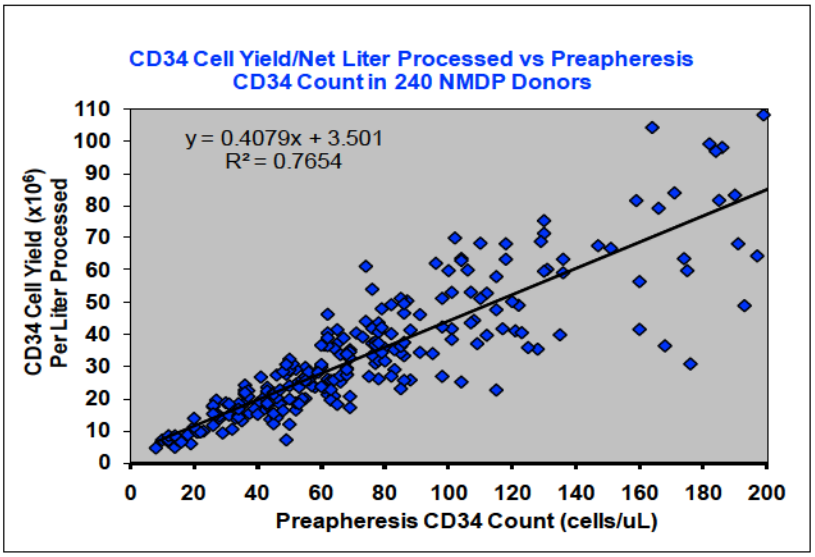
http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/C8B255/DUPLICATIONSHIELDSYNC/257110/ND_PG/PRIH/ND_B/HCS/SBK/1/ND_P/Main/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/20551-p/ContentSetId/30/SearchTerm/mozobil/SearchOption/BeginWith

1.2.3 Evaluate the need for systematic use of Plerixafor on day 4

Based on recent work from the Department of Transfusion Medicine of the Clinical Center, the yield of an apheresis procedure could be accurately predicted on the basis of a pre-procedure

peripheral blood CD34+ cells content determination[33]. However, this work was done prior to the use of plerixafor in mobilization and in a population of healthy donors for allogeneic transplantation.

This study will seek to validate the formula developed by DTM that calculates the likelihood of collecting ≥ 5 million $CD34^+$ cells/kg in a single apheresis after 5 days of G-CSF alone (without plerixafor). The equation is based on the circulating blood $CD34^+$cell concentration in healthy subjects on the morning of day 5 (after 4 evening doses of G-CSF); see Figure and Table.



Therefore, with the knowledge of the pre-procedure peripheral blood $CD34^+$ cell count after 4 doses of G-CSF, the patient's weight and the blood volume that can be processed during a single apheresis procedure, it should be possible to predict which subjects would most likely achieve a collection of 5 x 10^6 $CD34^+$ cells/kg with a single apheresis. These subjects would not need to receive plerixafor on day 4 of mobilization but would receive day 5 of G-CSF as planned.

Table 1

Prediction of Need for Plerixafor based on Pre-Apheresis CD34 Count

Pt Kg Wgt	Target CD34 x 10^6	Minimum CD34 x10^6/L processed yield in 25 L procedure	Minimum required pre-apheresis CD34/uL	Minimum acceptable D4 CD34 count (predicted) w/o plerixafor
≤60	300	12	21	24
61-65	325	13	23	26
66-70	350	14	26	28
71-75	375	15	28	31
76-80	400	16	31	33
81-85	425	17	33	35
86-90	450	18	36	38
91-95	475	19	38	40
≥96	500	20	40	42

1.2.4 Evaluation of minimal residual disease

- Residual disease evaluation will be performed using high resolution detection methods:
- Multicolor Flow cytometry[34-38]

- Molecular Pathology
- Idiotype-specific PCR[39-42].

High sensitivity detection methods may be used for the determination of the degree of tumor cell contamination in the HPC, Apheresis product and/or as a surrogate marker for treatment efficacy comparing pre-treatment values with those of best response. Furthermore, clinical relapse may be anticipated. In a study using IgH PCR with patient-specific probes, increase of clonotypic cells in PB was detectable a median of 3 months before clinical relapse[43].

1.2.5 Lack of need for purging of HPC, Apheresis product

Multiple studies have been performed in an attempt to improve the EFS post-transplant by purging the "HPC, Apheresis" product from myeloma cells. Results have been conflicting at best, but mostly disappointing [44].

Two phase 3 randomized trials compared patients with PCM who received autografts purged of tumor cells ($CD34^+$-selected PBSC) with those with unselected PBSCs[45, 46]. Both studies used a highly sensitive, tumor-specific PCR technique to identify the Ig heavy chain sequence of the myeloma clone and determine the level of tumor cell contamination. Both studies achieved a large reduction in tumor burden (approximately 1 to 6 log tumor load reduction), but no significant differences were observed between the 2 groups in terms of response, EFS/PFS, or OS.

These disappointing results clearly demonstrate that the residual tumor burden in the patient and the inability to eradicate it at the time of the High-Dose chemotherapy are the primary cause for treatment failure post-AHCT and should remain the primary focus for improving transplant outcome. There is much hope, however, that the combination of novel agents and AHCT will achieve much greater disease burden reduction than previously achieved in the randomized studies cited above. Therefore, tumor cell contamination of HPC products may then become an impediment to prolonged disease free survival. It will be important then to have knowledge of the potential contribution of each mobilization strategy to HPC tumor cell contamination. This protocol offers a great opportunity to compare the contribution of G-CSF and plerixafor to HPC product tumor cell contamination.

1.2.6 Utilization of HPC products in NCI protocols

The cellular products collected on this protocol are extremely likely to be subsequently used in a CCR protocol. HPC collection for subsequent AHCT is a recommendation of the International Myeloma Working Group for all patients treated for PCM. This position is echoed in several recent reviews[47-49].

ETIB has presently one protocol open which includes AHCT for PCM (11-C-0016).

The Myeloma Program is presently accruing 2 to 3 patients per week, the majority of whom are either already eligible for protocol11-C-0016 at the time of their enrollment on the Lymphoid Malignancies Branch (LYMB) studies or are likely to become eligible. The ETIB protocol in preparation is also likely to capture a large number LYMB recruited subjects as AHCT continues to play a large role in PCM therapy in spite of the recent therapeutic advances with the use of novel agents. At this point it is expected that more than 80% of subjects who would undergo HPC collection under this protocol would undergo AHCT as part of a CCR study.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Multiple Myeloma criteria

- Subjects with an indication for AHCT for the treatment of PCM as determined by the PI or LAI.
  - Subjects following induction treatment for PCM
  - Subjects with recurrent or persistent evaluable disease who have not undergone AHCT for the treatment of the PCM.

2.1.1.2 Other eligibility criteria

- Age ≥18 years and less than or equal to 75 years. In subjects between 65 and 75 years of age, physiologic age and co-morbidity will be thoroughly evaluated before enrolling.
- Karnofsky performance status of 70% or greater (ECOG 0 or 1)
- Ejection fraction (EF) by MUGA or 2-D echocardiogram within institution normal limits. In case of low EF, the subject may remain eligible after a stress echocardiogram is performed if the EF is more than 35% and if the increase in EF with stress is estimated at 10% or more.
- Hgb ≥ 8g/dl (transfusion acceptable)
- No history of abnormal bleeding tendency.
- Patients must be able to give informed consent

2.1.2 Exclusion Criteria

- Prior allogeneic stem cell transplantation
- Hypertension not adequately controlled by 3 or less medications.
- Clinically significant cardiac pathology: myocardial infarction within 6 months prior to enrollment, Class III or IV heart failure according to NYHY, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or acute conduction system abnormalities. Specifically, any history of cardio-vascular pathology or symptoms, not clearly fitting this exclusion criterion will prompt an evaluation by a Clinical Center Cardiologist and eligibility will be considered on a case-by-case basis. Should the cardiologist deem the patient's findings on work-up to be not clinically significant pathology, the patient will have met this exclusion criterion.
- Patients with a history of coronary artery bypass grafting or angioplasty will receive a cardiology evaluation and be considered on a case-by-case basis.
- Active hepatitis B or C infection
- HIV seropositive, with positive confirmatory nucleic acid test
- Patients known or found to be pregnant.
- Patients of childbearing age who are unwilling to practice contraception.
- Patients may be excluded at the discretion of the PI/LAI if it is deemed that allowing participation would represent an unacceptable medical or psychiatric risk.

2.1.3 Recruitment strategy

It is anticipated that internal recruitment from CCR subjects will be likely sufficient for the expected accrual.

2.2 SCREENING EVALUATION

2.2.1 History and Physical examination

All patients must have a complete history, review of systems and physical examination within 4 weeks of study entry date. Appropriate consultations may also be obtained as indicated for best clinical care.

2.2.2 Laboratory evaluation

The following laboratory studies must be performed within the specified period prior to study entry date:

- Studies performed at diagnosis to establish the diagnosis of PCM (or subsequent studies demonstrating the presence of disease) must be available for review and diagnostic confirmation at the NCI.
- CBC with differential and platelet count (1 week),
- Acute, Hepatic and Mineral panels (1 week),
- PT/PTT, fibrinogen (1 week),
- ABO typing (4 weeks),
- Serology for hepatitis B and C virus, HIV-1/2, HTLV I/II, T. Cruzi (4 weeks), Nucleic acid testing (NAT) for transmissible disease agents, per DTM policy (4 weeks),
- β-HCG or urine pregnancy test in non-menopausal women only (1 week),
- ECG (4 weeks)

2.3 REGISTRATION PROCEDURES

All patients must be registered on study once study consent has been obtained. This is typically done after eligibility has been confirmed. Authorized staff must register an eligible candidate with Central Registration within 24 hours after the candidate signing informed consent. A registration checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. The Central Registration Office will send a confirmation of eligibility and will call Pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. For questions regarding registration, authorized individuals should call the Central Registration Office between the hours of 8:30AM and 5:00PM, Monday – Friday: phone (301) 402-1732. Voicemail is available during non-business hours.

3 STUDY IMPLEMENTATION

3.1 STUDY OVERVIEW

- Subjects will undergo mobilization and collection of peripheral blood stem cells for subsequent use in various clinical protocols.

- The need for an additional mobilizing agent (plerixafor) to be given on day 4 of mobilization will be evaluated in real time in each patient, based on the peripheral blood CD34 count on the morning of day 4 of G-CSF administration.
  - Patients with a peripheral CD 34^+ cells count of greater than or equal to 42 cells/µl performed on the morning of day 4, a minimum of 3 hours after the 4^{th} G-CSF administration will not receive plerixafor but will receive a fifth dose of filgrastim in the morning of day 5. The apheresis will start that morning, day 5 of mobilization, a minimum of 3 hours after the 5^{th} G-CSF administration.
  - Patients with a peripheral CD 34^+ cells count of less than 42 cells/µl on the morning of day 4 of G-CSF administration may receive either filgrastim alone on day 5 of mobilization or both plerixafor in evening of day 4 and filgrastim in the morning of day 5 of mobilization, depending on their weight and their circulating CD34 count, as described in **Table 1**. The apheresis will start that morning, day 5 of mobilization, a minimum of 3 hours after the administration of the 5^{th} G-CSF dose (and plerixafor, if indicated).
- The collection target dose is 5 x 10^6 $CD34^+$ cells/kg, to be sufficient for a double AHCT if clinically indicated (or for a rescue procedure as required on some transplant protocols) (minimum dose is 4 x 10^6 $CD34^+$ cells/kg for a double transplant and 2 x 10^6 $CD34^+$ cells/kg for a single autologous transplant).

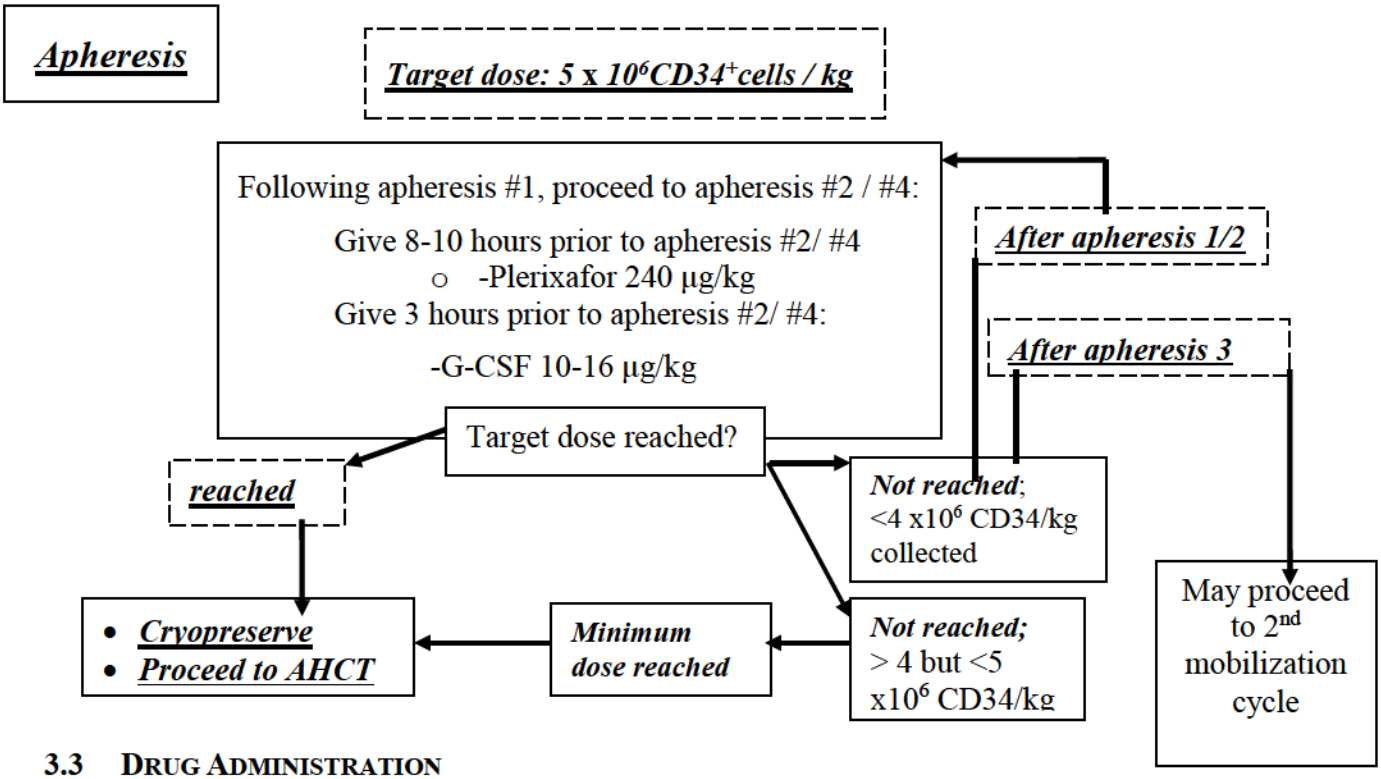
3.2 TREATMENT SCHEMA

Mobilization

Day 1:	- G-CSF 10-16 µg/kg/dose *(at 9 am +/- 1 h)
Day 2:	- G-CSF 10-16 µg/kg/dose *(at 9 am +/- 1 h)
Day 3:	- G-CSF 10-16 µg/kg/dose *(at 9 am +/- 1 h)
Day 4:	- G-CSF 10-16 µg/kg/dose *(at 6 am +/- 1 h)
Day 4:	- circulating blood CD 34 cell count, drawn a minimum of 3 hours after the G-CSF dose - if Day 4 CD 34 < 42 cells/µl, **refer to Table 1 for decision**: -Plerixafor**as indicated in **Table 1 to be given at 10pm on day 4**
Day 5:	- G-CSF 10-16 µg/kg/dose * 3 hours prior to apheresis (at 6 am) - *start apheresis #1 the same day*

* G-CSF 10-16µg/kg/dose (according to DTM algorithm in section **3.3.1)** subcutaneously

** Plerixafor240 mcg/kg, not to exceed 24,000 mcg total



3.3 DRUG ADMINISTRATION

- Filgrastim will be administered as a single daily dose in a dose range of 10-16ug/kg/day subcutaneously for 5-7days (see Table below for sliding-scale filgrastim dose schedule).
- The filgrastim doses for days 1-3 are to be given at approximately 9:00 a.m.(+/- 1 h). On day 4, the filgrastim dose is to be given at 6:00 a.m. (+/- 1h).
- The filgrastim dose to be administered on day 5 (and if necessary days 6 and 7) may be combined with a concurrent day 4 dose of plerixafor 240 mcg/kg subcutaneously based on the peripheral blood $CD34^+$ cell count (see Table 1 for prediction of need for plerixafor based on patient weight and circulating $CD34^+$ cell count).
- On days 5, 6 or 7, filgrastim (or both drugs) must be given approximately 3 hours prior to starting apheresis.
- It is not anticipated that a fourth consecutive apheresis procedure will be required; however, there may be circumstances, such as technical problems during apheresis or damage to a product during processing that require an additional procedure. In this case, the same mobilization regimen given prior to the previous apheresis procedures will be given again. The maximum number of consecutive apheresis procedures performed in any patient will be 4.

3.3.1 Filgrastim administration

Filgrastim will be administered according to a vial-based algorithm to reduce wastage and increase the total filgrastim dose given to lighter weight donors in order to improve CD34 yields[33]. The weight on day 1 will be used for all calculations

Subject Weight	Total Filgrastim Dose	Dose /kg (range)
38 - <49 kg	600 mcg	(12.5 to 15.8 mcg/kg)
49 - < 57 kg	780 mcg	(13.9 to 15.9 mcg/kg)
57 - <61 kg	900 mcg	(15.0 to 15.8 mcg/kg)
61 - <68 kg	960 mcg	(14.3 to 15.7 mcg/kg)
68 - <109 kg	1080 mcg	(10.0 to 15.9 mcg/kg)
≥ 109 kg	1200 mcg	(11.0 or less)

3.3.2 Plerixafor Administration

If plerixafor is necessary, it will be given on day 4, 8-10 hours before the day 5 apheresis

Subject Weight	Total Plerixafor Dose
≤ 90 kg	calculate dose at 240 mcg/kg
> 90 kg	24,000 mcg (flat dose, equal to one full 1.2-mL vial)

3.3.3 Apheresis

HPC, Apheresis collection will be performed in the Dowling Apheresis Clinic of the Department of Transfusion Medicine (DTM). A DTM physician is within the immediate vicinity of the procedure or available within one minute by pager. The minimum $CD34^+$ cell dose that must be collected in order to proceed with a single autologous transplantation is 2 x 10^6 $CD34^+$ cells/kg. As standard of care not infrequently calls for tandem transplants in multiple myeloma and as some NCI protocols require that a backup product be collected in cases of single transplants , a higher dose of ≥ 5 x10^6 $CD34^+$ cells/kg will be targeted, to permit more than one cycle of high dose chemotherapy with autologous stem cell rescue. Based on the mobilization response of individual subjects, this may require additional collections even if the minimum required for a single transplant (2x10^6 CD34 cells/kg) has been collected in a single apheresis procedure.

The volume processed per apheresis procedure will be determined by DTM medical staff on the day of apheresis, based on peak $CD34^+$ cell mobilization response to filgrastim and optimum and minimum CD34 cell dose needed. In general, volume processed will range from 12 to 30 liters per procedure for 1 to3 consecutive daily procedures, not to exceed a total of 60 liters over 3days. If the minimal cell dose necessary to proceed with a single autologous transplant (≥2 x10^6 CD34+ cells/kg) is not achieved with 3 daily large volume leukapheresis procedures, then it is exceedingly unlike that a fourth consecutive apheresis procedure will reach this goal. The patient in such cases is likely to have minimal marrow reserve and not mobilize progenitor cells in response to pharmacologic agents. In contrast, if a technical mishap occurs during apheresis, or product contamination occurs during processing, resulting in inadvertent product loss, then a fourth daily procedure may be considered.

All decisions about the need for a third day of collection will be made in concert between PI/LAI and DTM physicians.

Collections will be performed with use of a dual-access continuous-flow apheresis device (Spectra Apheresis System, Caridian). Many subjects will require a central double lumen apheresis catheter. Subjects will receive continuous intravenous calcium prophylaxis to prevent citrate toxicity during apheresis, in accordance with standard DTM policies.

The products will be cryopreserved in the Cell Processing Section, DTM, CC and will be stored in the vapor phase of liquid nitrogen.

3.3.4 Inadequate collection

If, after 3 or 4 consecutive daily procedures, the total number of CD34+ cells collected is:

- Greater or equal to $4x10^6$/kg; the subject will not be offered a 2nd collection cycle and will come off study.
- Less than $4x10^6$/kg; on a case by case basis, the subject may be offered a 2nd collection cycle on study.

All decision about the need for an additional cycle of collection will be made in concert between PI/LAI and DTM physicians.

3.3.5 Salvage collection regimen

Subjects with an inadequate collection as defined above may be offered a 2nd mobilization and collection cycle. The following regimen is suggested;

Day 1: - G-CSF 10-16 µg/kg/dose *(approximately at 9am, +/- 1h)
Day 2: - G-CSF 10-16 µg/kg/dose *(approximately at 9 am, +/- 1h)
Day 3: - G-CSF 10-16 µg/kg/dose *(approximately at 9 am, +/- 1h)
Day 4: - G-CSF 10-16 µg/kg/dose *(approximately at 6 am, +/- 1h)
- Plerixafor** (at 8-10 pm)
Day 5: - 3 hours prior to apheresis (approximately at 6 am)
- G-CSF 10-16 µg/kg/dose* - Plerixafor** (at 8-10 pm)
Day 6: - 3 hours prior to apheresis (approximately at 6 am)
- G-CSF 10-16 µg/kg/dose*
- Plerixafor** (at 8-10 pm)

Day 7: - 3 hours prior to apheresis (approximately at 6 am)
- G-CSF 10-16 µg/kg/dose*

The salvage regimen may start no sooner than 4 weeks after the last apheresis procedure.

If, after a second collection, the cumulative $CD34^+$cell number collected during the two collections is less than $2x10^6$ cells / kg, the product may be discarded since no transplant will be performed.

3.4 Dose Modifications

See dosage algorithm above in sections **3.3.1**and **3.3.2**

There are no planned dose modifications.

3.5 STUDY CALENDAR

	ON STUDY	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day post last apheresis
History & Physical (2 week)	X								X
CBC, diff, plts (1 week)	X								X
Chemistries (1 week)	X								X
PT/PTT, fibrinogen (1 week)	X								
Serology: HBV, HCV, HIV, HTLV, T.Cruzi (4 weeks)	X								
ABO typing (4 weeks)	X								
DTM NAT testing (4 weeks)	X								
β-HCG / urine pregnancy test non menopausal women only (1 week)	X								
ECG (4 weeks)	X								
Mobilization therapy									
G-CSF (given in the morning)		X	X	X	X	X	X (or not)	X (or not)	
Plerixafor (given in the evening)					X (or not)	X (or not)	X (or not)	X (or not)	
Apheresis						X	X (or not)	X (or not)	
Peripheral CD34* count (in am)					X	X pre-apheresis	X (or not)	X (or not)	
Peripheral Blood MRD (FACS & molecular)	X				X	X (pre)	X (or not)	X (or not)	
Apheresis product MRD (FACS & molecular)						X	X (or not)		

3.6 OFF STUDY CRITERIA

3.6.1 Criteria for removal from protocol therapy

- Subject's decision
- Adverse event related to the filgrastim or plerixafor administration which, in the opinion of the PI/LAI, warrants discontinuation of the treatment.

3.6.2 Off-Study Criteria

- Adequate collection of $\geq$ 4x 10^6 CD34+ cells/kg: subject will be evaluated the day following the last apheresis procedure. If no significant complication from the procedure has arisen, the subject will be taken off study.
- Completed a second mobilization/collection cycle ("salvage cycle"), regardless of the total number of cells collected
- Any grade >2 adverse event possibly, probably or definitely related to the procedure will be followed until resolution or clinical stabilization before the subject is taken off study.

- Death
- PI decision to end this study

3.6.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is off protocol therapy and when a subject is taken off-study. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Analgesic medications may be needed during filgrastim therapy.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 Clinical end points

- Determination of the proportion of subjects requiring addition of plerixafor to the mobilization regimen
- Determination of the proportion of subjects achieving the target goal of 5 x 10^6 cells / Kg with one or two apheresis procedures with or without Plerixafor.

5.1.2 Biologic end points

- Determination of the degree of tumor cell contamination in the final product.
- Determination of the impact of plerixafor in the degree of tumor cell contamination of the final product.

5.1.2.1 Peripheral blood

- 20 cc in Green Top tube to the NCI Clinical Flow Cytometry core (Flow cytometry)
- 20 cc in Lavender Top tube to Dr. Figg's lab for processing and storage
- Time points:
  - At baseline,
  - day 4 (collected after the 4th dose of G-CSF),
  - day 5, pre-apheresis
  - and days 6, 7, if collected on these days.

5.1.2.2 Apheresis Product

For each day of apheresis

- 1-2 cc in red top tube to the NCI Clinical Flow Cytometry core (Flow cytometry)
- 1-2 cc in red top tube to Dr. Figg's lab for processing and storage+

Note for Figg's lab blood collection: Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964qaaas.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 Clinical HPC, Apheresis Products

The cryopreserved HPCs will be stored in the Cell Processing laboratory until they are infused for autologous transplantation. In the event a subject wishes to undergo AHCT at an outside institution, the HPC product may be shipped to that institution in accordance with regulations and DTM Standard Operating Procedures. If all or part of the HPC products is no longer needed for autologous transplantation, the cells with either be issued to the investigator for IRB approved research or disposed of.

5.2.2 Storage/Tracking

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Research samples will not be sent outside NIH without IRB notification and an executed MTA.

5.2.2.1 Labeling of Samples

All specimens are to be labeled per the local site's standard procedures. The following information, if not provided on the specimen label, must be linked to the specimen label and provided on the inventory sheet:

- patient study ID #
- sample type
- date/time of draw (DD/MMM/YY 24:00)
- timepoint (ex. Day 4, 5, 6, 7, etc.)
- any collection issues (short draw, delayed processing, etc.)
- protocol title/number
- institute name
- contact information

Do not include the patient name, medical record number, or initials.

5.2.2.2 Sample Data Collection

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.2.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.3 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB approved protocol and patient consent or the OSHRP Authorization Form stipulating that the activity is exempt from IRB review.

Samples, and associated data, can only be permanently archived if the subject has provided informed consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the Preclinical Service laboratory.

The Preclinical Service staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (e.g. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher. The Principal Investigators will annually report this information to the IRB.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS and, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

- All patients' data must be recorded in the progress notes and flow sheets of the patient chart maintained by the Medical Records Department of participating institutions or available electronically on the CRIS system of the NIH Clinical Center. Duplicate of key data *may* be kept in a research folder maintained by the Experimental Transplantation & Immunology Branch or the research office of participating institutions.
- Patient's demographics will be collected.
- No specific toxicity data or adverse event related to the myeloma therapy will be collected for study purposes.
- Data on Adverse Events requiring IRB reporting (see section**7.3**) following filgrastim and plerixafor administration will be collected.
- All clinical data pertaining to a subject's death while on protocol will be collected.
- Data will be prospectively collected and entered in real time into the Cancer Central Clinical Data System database (NCI C3D; information at http://ccrtrials.nci.nih.gov). It is expected that clinical data be entered into C3D no later than after 10 business days of the occurrence. The NCI PI and research nurse will have access to this data via web access.
- All patient records will be kept confidential according to individual institution policies and procedures concerning patient information.
- All grade 3 and grade 4 non hematologic adverse events will be recorded (see section **7.3.2** for exceptions).

6.2 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DATA REPORTING & RECORDS TO BE KEPT

All clinical data will be recorded in the patient's chart as per institutions' practices (maintained by the NIH Clinical Center Department of Medical Records and on the electronic chart CRIS system). The patient records will be maintained by the Clinical Associate and other protocol personnel. Each patient's NIH Clinical Center medical record must reflect all of the following information:

- The patient met all eligibility criteria.
- Signed Informed Consent document was obtained before treatment.
- Specific dates and times of all treatments specified in the protocol, doses administered, and documentation for the reason for any dose modification.
- Documentation of all toxicities with grading according to NCI CTCAE version 4.0 as specified in the protocol.
- Documentation of all follow-ups as specified in the protocol.

7.2 DEFINITIONS

7.2.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section **7.3**

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.2.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.2.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.2.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.2.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.2.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

7.2.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.2.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 NCI-IRB AND CLINICAL DIRECTOR REPORTING

As subjects will be enrolled on protocol at the time they are receiving concurrent, off-protocol, standard of care therapy with expected toxicity, the toxicity of any concurrent therapy will not be reported for this study. Adverse Event reporting will be limited to events occurring during or immediately following the apheresis procedure.

7.3.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.3.3 Exceptions to reporting:

The following events that are possibly, probably or definitely related to the research will not be reported:

- Of any grade: Leukocytosis or neutrophilia, elevated LDH, paresthesias, bone pain, fever, fatigue, muscle cramps, back/leg pain, splenomegaly
- Of grade $\leq$3: Thrombocytopenia, anemia, hypocalcemia, hypomagnesemia, elevated transaminases or alkaline phosphatase, diarrhea, nausea, vomiting, flatulence, fatigue, arthralgia, headache and dizziness, mild injection site reactions.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

In order to assure optimal concordance between the protocol requirements and the best possible clinical care of the patients, the PI/LAI or designate will co-sign a patient registration check list (Section **12**).

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or designate. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The Principal Investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The Principal Investigator will personally conduct or supervise the

investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

The primary clinical purpose of this protocol is to permit collection of apheresis products as needed in connection with AHCT in subjects with Plasma Cell Myeloma (PCM). The overall success rate of the algorithm shown in **Table 1**and in section **3.1** will be evaluated and will be considered the primary scientific endpoint for the study. In addition, as a descriptive study, the percent of patients achieving either of two levels of CD34+ cell collection (optimum collection of $\geq 5 \times 10^6$ CD34+ cells/kg, or minimum collection of ≥ 2 but $< 5 \times 10^6$ CD34+ cells/kg) in one apheresis procedure, in two procedures, and in greater than two procedures will be determined according to whether patients have received filgrastim alone versus filgrastim plus plerixafor. Based on the algorithm shown in table 1 and in section **3.1**, patients either will or will not receive plerixafor to potentially boost the CD34 processed yield.

Sixty patients or more will be enrolled on this study during a three year period, and based on historical data, it is anticipated that approximately 75% will not need plerixafor (45) and 25% will need plerixafor (15). The overall success of the algorithm (percent of patients achieving optimum collection of $\square 5 \times 10^6$ CD34+ cells/kg in one mobilization cycle, who were predicted to do so using the algorithm) will be determined as follows. If 60 total patients are enrolled and if 50 or more of 60 have a successful collection, then the probability of this occurring will be 96.6% if the true rate of success were 90% while it would be 1.4% if the true rate of success were 70%. Thus, if a high fraction (50+/60) has a successful collection, there is a much greater likelihood that the true rate of overall success with the algorithm is 90% as opposed to 70%.

In addition, the success rate of the algorithm will be evaluated separately for those who do and do not receive plerixafor. If 41/45 not receiving plerixafor have a successful collection in one cycle, the associated 95% CI will extend from approximately 79 to 98%. Among those receiving plerixafor, if 13/15 have a successful collection in one apheresis, the 95% CI ranges from 60% to 98%. The overall success rate of the algorithm, as described above, and ideally, the fractions that have a successful collection would be high and success rates would be similar to one another in both groups, but the success rates will only be compared descriptively since there is limited power for any comparison. In addition to the fractions who have successful collections, the total number of apheresis procedures per patient and the total number of liters processed per patient during the collection course to achieve either the optimum or the minimum CD34+ cell dose will be reported and informally compared between patients receiving filgrastim alone versus filgrastim plus plerixafor.

As an exploratory, secondary analysis, if sufficient data are available, a multivariable logistic regression analysis may be performed, using patient and disease characteristics (available data potentially, but not mandatorily, from among: gender, race, age, weight, baseline hemoglobin, total WBC, neutrophil, monocyte, lymphocyte, and platelet count, number of prior cycles of cytotoxic chemotherapy, total prior dose of lenalidomide and similar agents per kg) to construct a model for risk of acceptable vs. non-acceptable CD34 mobilization with filgrastim alone.

Because of an expectation of limited patients, construction of a similar model for risk of poor mobilization with use of combined filgrastim plus plerixafor will not likely be attempted.

It is expected that up to 3 years may be required to obtain 60 evaluable subjects on this protocol. The accrual ceiling will be set at 70 patients to allow for flexibility.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

The study is open to all subjects with a clinical indication for autologous stem cell transplant for the treatment of multiple myeloma

9.2 PARTICIPATION OF CHILDREN

Children will not be enrolled on this study as PCM is not a disease seen in the pediatric population.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **0**, all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Subjects undergoing apheresis for collection of a mobilized HPC, Apheresis product may experience headache, bone and joint pain due to filgrastim, nausea and abdominal pain due to plerixafor, bleeding and pain due to the discomfort of central line insertion, hypocalcemic symptoms due to the citrate anticoagulant used during apheresis, and vasovagal events including bradycardia, hypotension, syncope and very rarely, seizures, associated with reflex neurovascular reactions to apheresis. Rarely, cardiovascular events may occur due to previously present but undiagnosed coronary or cerebrovascular occlusive conditions.

The benefit is to be able to undergo an autologous stem cell transplant which is known to improve outcome in PCM.

9.5 RISKS/BENEFITS ANALYSIS

The potential benefits outweigh the risk for a procedure considered worldwide a standard practice for the treatment of PCM.

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

Prior to receiving any therapy, patients must have their eligibility confirmed and must have signed an informed consent. The Principal Investigator or Lead Associate Investigator will review orders for mobilizing agent administration.

The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and benefits, and potential alternative therapies will be carefully explained to the subjects during the Informed Consent process. A signed Informed Consent document will be obtained prior to entry onto the study by the Principal Investigator or an Associate Investigator.

All patients must have a copy of their signed Informed Consent document maintained in the chart during therapy.

Results of the study or of individual patients may be reported at meetings or in scientific publications with removal of specific patient identifiers.

9.6.1 Telephone re-consent procedure

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.2 Short form consent process for non-English speaking patients

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2) and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

9.7 SUBJECT INFORMATION AND CONFIDENTIALITY

As information is gathered from this trial, clinical results will be shared with patients. Any new significant observation(s) found during the course of the research, which may affect a patient's willingness to participate further would be explained.

Confidentiality of information concerning participants will be maintained including in all publications and presentations resulting from this study. Names of participants or material identifying participants will not be released without permission, except as such release is required by law. Records at the National Cancer Institute are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

See section **5.2** for specifics of sample management and storage.

10 PHARMACEUTICAL INFORMATION

10.1 FILGRASTIM (NEUPOGEN®, G-CSF)

Neupogen® (filgrastim, G-CSF)is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Neupogen® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

10.1.1 Source

Neupogen® will be obtained from the commercial supply in the Clinical Center Pharmacy.

10.1.2 Adverse effects

Bone pain, which can sometimes be severe. Other adverse reactions include fever, fatigue, muscle cramps, back/leg pain, splenomegaly, thinning hair, allergic reactions and flare of known auto-immune disease.

10.1.3 Formulation, Storage, and Stability

Recombinant granulocyte-colony stimulating factor (G-CSF) manufactured by Amgen (Thousand Oaks, CA) is supplied as a clear sterile solution of 300 mcg/mL packaged into either 1-mL (300 mcg) or 1.6-mL (480 mcg) vials. Neupogen® should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, Neupogen® may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded. Do not freeze. G-CSF is stable for at least 1 year when refrigerated.

10.1.4 Administration

G-CSF will be administered as a subcutaneous injection to mobilize peripheral blood stem cells for collection by apheresis. See Section **3.3.1**for sliding scale G-CSF dosing algorithm for mobilization.

Patients may be instructed on the self-administration of G-CSF.

10.2 PLERIXAFOR (MOZOBIL®)

Plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α (SDF-1 α). It inhibits the retention of hematopoietic stem cells in bone marrow, and increases their number in peripheral blood. It is used with granulocyte colony-stimulating factor (G-CSF) to mobilize stem cells for collection and subsequent autologous transplantation.

10.2.1 Source

Mozobil® will be obtained from the commercial supply in the Clinical Center Pharmacy.

10.2.2 Adverse effects

Common adverse effects include diarrhea, nausea, vomiting, flatulence, fatigue, arthralgia, headache and dizziness, mild injection site reactions.

Less commonly, insomnia or systemic reactions occurring about 30 minutes after injection (urticaria, periorbital swelling, dyspnea, and hypoxia).

Some cases of vasovagal reactions, orthostatic hypotension, and syncope, within 1 hour of injection, have also been reported.

10.2.3 Formulation, Storage, and Stability

Subcutaneous Solution: 20 mg/ml

Inspect vial for particulate matter and discoloration prior to administration; do not use if particulate matter present or solution is discolored. (Prod Info MOZOBIL(R) subcutaneous injection, 2008).

Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F).

10.2.4 Administration

Plerixafor 240µg/kg will be administered for one to three consecutive days as a subcutaneous injection to mobilize peripheral blood stem cells for collection by apheresis.

Plerixafor will be administered on day 4 and possibly day 5 and 6 of filgrastim administration, 8 to 10 hours before apheresis begins.

10.2.5 Pharmacokinetics

Peak plasma concentrations of plerixafor occur about 30 to 60 minutes after a subcutaneous dose. It is about 58% bound to plasma proteins and largely confined to the extravascular fluid space. About 70% of a dose is eliminated in the urine within 24 hours after a dose, and the terminal half-life is about 3 to 5 hours.

Plerixafor is not metabolized using human liver microsomes or human primary hepatocytes. Additionally, plerixafor does not exhibit inhibitory activity towards the major drug metabolizing cytochrome P450 enzymes nor did it induce CYP1A2, CYP2B6, or CYP3A4.

11 REFERENCES

1. Jemal, A., et al., *Cancer statistics, 2008.* CA Cancer J Clin, 2008. **58**(2): p. 71-96.
2. Alexanian, R., B. Barlogie, and S. Tucker, *VAD-based regimens as primary treatment for multiple myeloma.* American journal of hematology, 1990. **33**(2): p. 86-9.
3. Tosi, P., et al., *Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma.* European journal of haematology, 2005. **74**(3): p. 212-6.
4. Rajkumar, S.V., et al., *Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group.* Journal of clinical oncology, 2006. **24**(3): p. 431-6.
5. Harousseau, J.L., et al., *VELCADE/Dexamethasone (Vel/D) Versus VAD as Induction Treatment Prior to Autologous Stem Cell Transplantion (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Updated Results of the IFM 2005/01 Trial.* ASH Annual Meeting Abstracts, 2007. **110**(11): p. 450-.
6. Weber, D.M., et al., *Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.* The New England journal of medicine, 2007. **357**(21): p. 2133-42.
7. Dimopoulos, M., et al., *Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.* The New England journal of medicine, 2007. **357**(21): p. 2123-32.
8. Richardson, P., *Management of the relapsed/refractory myeloma patient: strategies incorporating lenalidomide.* Semin.Hematol., 2005. **42**(4 Suppl 4): p. S9-15.
9. Kumar, S.K., et al., *Improved survival in multiple myeloma and the impact of novel therapies.* Blood, 2008. **111**(5): p. 2516-2520.
10. Rajkumar, S.V., et al., *A Randomized Trial of Lenalidomide Plus High-Dose Dexamethasone (RD) Versus Lenalidomide Plus Low-Dose Dexamethasone (Rd) in Newly Diagnosed Multiple Myeloma (E4A03): A Trial Coordinated by the Eastern Cooperative Oncology Group.* ASH Annual Meeting Abstracts, 2007. **110**(11): p. 74-.
11. Richardson, P., et al., *Lenalidomide, Bortezomib, and Dexamethasone (Rev/Vel/Dex) as Front-Line Therapy for Patients with Multiple Myeloma (MM): Preliminary Results of a Phase 1/2 Study.* Blood (ASH Annual Meeting Abstracts), 2007. **110**(11): p. 187.
12. Zonder, J.A., et al., *Superiority of Lenalidomide (Len) Plus High-Dose Dexamethasone (HD) Compared to HD Alone as Treatment of Newly-Diagnosed Multiple Myeloma (NDMM): Results of the Randomized, Double-Blinded, Placebo-Controlled SWOG Trial S0232.* Blood (ASH Annual Meeting Abstracts), 2007. **110**(11): p. 77.
13. Palumbo, A. and S.V. Rajkumar, *Treatment of newly diagnosed myeloma.* Leukemia, 2008.

14. Vesole, D.H., et al., *High-dose therapy for refractory multiple myeloma: improved prognosis with better supportive care and double transplants.* Blood, 1994. **84**(3): p. 950-956.

15. Attal, M., et al., *Single versus double autologous stem-cell transplantation for multiple myeloma.* New England Journal of Medicine, 2003. **349**(26): p. 2495-2502.

16. Child, J.A., et al., *High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma.* New England Journal of Medicine, 2003. **348**(19): p. 1875-1883.

17. Levy, V., et al., *A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy.* Medicine (Baltimore), 2005. **84**(4): p. 250-260.

18. Koreth, J., et al., *High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials.* Biol.Blood Marrow Transplant., 2007. **13**(2): p. 183-196.

19. Segeren, C.M., et al., *Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study.* Blood, 2003. **101**(6): p. 2144-2151.

20. Barlogie, B., et al., *Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321.* J.Clin.Oncol., 2006. **24**(6): p. 929-936.

21. Fermand, J.P., et al., *High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial.* Blood, 1998. **92**(9): p. 3131-6.

22. Gay, F., et al., *Complete response correlates with long-term progression-free and overall survivals in elderly myeloma treated with novel agents: analysis of 1175 patients.* Blood, 2010: p. blood-2010-09-307645.

23. van de Velde, H.J., et al., *Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma.* Haematologica, 2007. **92**(10): p. 1399-406.

24. Hatse, S., et al., *Chemokine receptor inhibition by AMD3100 is strictly confined to CXCR4.* FEBS Lett, 2002. **527**(1-3): p. 255-62.

25. Rosenkilde, M.M., et al., *Molecular mechanism of AMD3100 antagonism in the CXCR4 receptor: transfer of binding site to the CXCR3 receptor.* J Biol Chem, 2004. **279**(4): p. 3033-41.

26. Devine, S.M., et al., *Rapid mobilization of CD34+ cells following administration of the CXCR4 antagonist AMD3100 to patients with multiple myeloma and non-Hodgkin's lymphoma.* J Clin Oncol, 2004. **22**(6): p. 1095-102.

27. DiPersio, J.F., et al., *Plerixafor.* Nat Rev Drug Discov, 2009. **8**(2): p. 105-107.

28. Flomenberg, N., et al., *The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone.* Blood, 2005. **106**(5): p. 1867-74.

29. DiPersio, J.F., et al., *Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma.* Blood, 2009. **113**(23): p. 5720-6.

30. DiPersio, J.F., et al., *Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma.* J Clin Oncol, 2009. **27**(28): p. 4767-73.

31. Flomenberg, N., et al., *Plerixafor (Mozobil) alone to mobilize hematopoietic stem cells from multiple myeloma patients for autologous transplantation.* Biol Blood Marrow Transplant, 2010. **16**(5): p. 695-700.

32. Devine, S.M., et al., *Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction.* Blood, 2008. **112**(4): p. 990-8.

33. Vasu, S., et al., *Donor demographic and laboratory predictors of allogeneic peripheral blood stem cell mobilization in an ethnically diverse population.* Blood, 2008. **112**(5): p. 2092-100.

34. San Miguel, J.F., et al., *Immunophenotypic evaluation of the plasma cell compartment in multiple myeloma: a tool for comparing the efficacy of different treatment strategies and predicting outcome.* Blood, 2002. **99**(5): p. 1853-6.

35. Rawstron, A.C., et al., *Flow cytometric disease monitoring in multiple myeloma: the relationship between normal and neoplastic plasma cells predicts outcome after transplantation.* Blood, 2002. **100**(9): p. 3095-100.

36. Liu, H., et al., *Flow cytometric minimal residual disease monitoring in patients with multiple myeloma undergoing autologous stem cell transplantation: a retrospective study.* Leuk Lymphoma, 2008. **49**(2): p. 306-14.

37. Paiva, B., et al., *Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation.* Blood, 2008. **112**(10): p. 4017-23.

38. Paiva, B., et al., *Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients.* Haematologica, 2009. **94**(11): p. 1599-602.

39. Cavo, M., et al., *Molecular monitoring of minimal residual disease in patients in long-term complete remission after allogeneic stem cell transplantation for multiple myeloma.* Blood, 2000. **96**(1): p. 355-7.

40. Lemoli, R.M., et al., *Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy.* Blood, 2000. **95**(7): p. 2234-9.

41. Martinelli, G., et al., *Polymerase chain reaction-based detection of minimal residual disease in multiple myeloma patients receiving allogeneic stem cell transplantation.* Haematologica, 2000. **85**(9): p. 930-4.

42. Martinelli, G., et al., *Molecular remission after allogeneic or autologous transplantation of hematopoietic stem cells for multiple myeloma.* J Clin Oncol, 2000. **18**(11): p. 2273-81.

43. Fenk, R., et al., *Levels of minimal residual disease detected by quantitative molecular monitoring herald relapse in patients with multiple myeloma.* Haematologica, 2004. **89**(5): p. 557-66.

44. DiPersio, J.F., et al., *Relevance and Clinical Implications of Tumor Cell Mobilization in the Autologous Transplant Setting.* Biology of Blood and Marrow Transplantation, 2011. **17**(7): p. 943-955.

45. Stewart, A.K., et al., *Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: Results of a multicenter randomized controlled trial.* Journal of Clinical Oncology, 2001. **19**(17): p. 3771-3779.

46. Bourhis, J.-H., et al., *Relapse risk after autologous transplantation in patients with newly diagnosed myeloma is not related with infused tumor cell load and the outcome is not improved by CD34+ cell selection: long term follow-up of an EBMT phase III randomized study.* Haematologica, 2007. **92**(8): p. 1083-1090.

47. Attal, M. and J.L. Harousseau, *The role of high-dose therapy with autologous stem cell support in the era of novel agents.* Semin Hematol, 2009. **46**(2): p. 127-32.

48. Dimopoulos, M.A. and M. Attal, *Multiple myeloma in the era of novel agents.* Semin Hematol, 2009. **46**(2): p. 107-9.

49. Palumbo, A. and S.V. Rajkumar, *Multiple myeloma: chemotherapy or transplantation in the era of new drugs.* Eur J Haematol, 2010. **84**(5): p. 379-90.

12 APPENDIX 1: ON-STUDY CHECK LIST

Patient Name: _____ Protocol: _____ **Referring MD**: _____
DOB: _____ MR#: _____

Test	**Date**	**Result**	**Test**	**Date**	**Results**
H & P (2w)			**Disease evaluation**		
CBC with differential (2 wk)			Diagnostic Pathology:		
Acute, mineral and hepatic panel (2wk)			review at NCI		
PT, PTT, fibrinogen (2wk)			EKG, (4w)		
Pregnancy: βHCG or urine (1wk)					
Serologic tests for HBV, HCV, HIV, HTLV I/II, T.Cruzi (4wk)					
ABO typing, NAT testing (4wk)					

Plan:

☐ DTM called with treatment schedule ☐ Packet signed off by attending MD

Reviewed by coordinator: _____ Date: Signature:

Reviewed by RRN: _____ _____ Date: Signature:

Reviewed by PI: _____ ___ Date: Signature:

13 APPENDIX 2: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL

All of the following elements will be recorded in the C3D database.

13.1 PATIENT ENROLLMENT

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Performance Status
- Date of original diagnosis
- Stage at diagnosis
- Stage at study entry
- Tumor Histology and date of confirmation
- Date of Informed Consent signature, consent version and date of registration
- Baseline History/Physical
- Baseline Symptoms
- Number prior chemotherapy courses and anti-myeloma medications administered

13.2 STUDY DRUG ADMINISTRATION

- Doses of filgrastim and plerixafor

13.3 LABORATORY AND DIAGNOSTIC TEST DATA

- All Clinical laboratory and diagnostic test results done at screening
- Data collected by the DTM pertaining to the HPC, Apheresis collection
- All tests done to document resolution of adverse events

13.4 ADVERSE EVENTS

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research.
- All grade 3 and 4 adverse events that are possibly, probably or definitely related to the research will be recorded.

  Exceptions to reporting:

  The following events that are possibly, probably or definitely related to the research will not be reported:

  - Of any grade: Leukocytosis or neutrophilia, elevated LDH, paresthesias, bone pain, fever, fatigue, muscle cramps, back/leg pain, splenomegaly,
  - Of grade $\leq$3: Thrombocytopenia, anemia, hypocalcemia, hypomagnesemia, elevated transaminases, diarrhea, nausea, vomiting, flatulence, fatigue, arthralgia, headache and dizziness, mild injection site reactions.

13.5 CONCOMITANT MEASURES

- Baseline medications
- Therapy for recorded adverse events

13.6 OFF STUDY

- Date and reason for off study
- Date and cause of death
- PI decision to end this study

INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0074 PRINCIPAL INVESTIGATOR: Jennifer A. Kanakry, M.D.

STUDY TITLE: Mobilization and collection of Autologous Stem cell for transplantation (ASCT) for Plasma Cell Myeloma (PCM)

Continuing Review Approved by the IRB on 08/07/17
Amendment Approved by the IRB on 09/23/17 (H) Date Posted to Web: 10/05/17
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why are you being asked to take part in this study?

You are being invited to participate in a study to collect Hematopoietic Progenitor Cells (HPCs) from your blood for later use in the treatment of your Plasma Cell Myeloma (PCM).

You have been told by your doctors that high-dose chemotherapy followed by Autologous Stem Cell Transplant (ASCT) may be of benefit in the treatment of your Plasma Cell Myeloma.

Why is this study being done?

The main goal of the study is to collect your HPCs and to evaluate the best drug combination (one or two drugs) to use for "mobilizing" them out of your bone marrow into your bloodstream where they will be collected. HPCs are collected from the blood in a procedure called apheresis. After collection, they will be stored frozen until you are ready to undergo the ASCT procedure for the treatment of PCM.

Both drugs, filgrastim (Neupogen) and plerixafor (Mozobil) are approved by the FDA for use in mobilization in subjects with PCM. They are not experimental. Mobilization with filgrastim alone is considered to be the standard of care at this point. It has been shown that adding plerixafor to filgrastim increases the yield of the apheresis procedure. This study will try to determine what proportion of subjects may be adequately mobilized with a single drug (Neupogen) for the most efficient HPC collection and what proportion would benefit from adding plerixafor.

Description of Research Study

You will undergo HPC mobilization with a standard regimen of filgrastim: one injection under the skin for 5 days in a row. On the morning of the fourth day a special blood test will be performed to determine how many HPCs are in your blood stream. Based on previous research done at the Department of Transfusion Medicine (DTM) of NIH, the result of this test allows us to make a fairly accurate prediction of whether you would be likely to complete your HPC collection with a single apheresis procedure or if it is likely that you would need several procedures. If the DTM doctors believe, based on the blood test, that you are likely to need a second day of apheresis, you would be given a single dose of plerixafor on that evening, along with the fifth dose of filgrastim the next day. We believe that this would greatly increase your chances of completing the HPC collection with a single apheresis.

How many people will take part in this study?

A total of 60 people will be enrolled in this study.

What are the experimental procedures?

There is no experimental procedures in this study. The apheresis procedure has been widely accepted for many years as the standard procedure to collect HPCs (see details below).

What will happen if you take part in this research study?

To enter this study, you will need to undergo blood tests and an ECG to ensure that you can undergo the apheresis procedures safely.

- A blood test will be done to determine if you have had exposure to the human immunodeficiency virus (HIV) associated with the acquired immunodeficiency syndrome (AIDS). If you are infected with HIV, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
- Your blood will be tested for many other infectious agents (mostly viruses), including: Human T-lymphotrophic virus, T. Cruzi, and hepatitis B and C viruses. ABO typing will also be performed.
- Approximately 4 tablespoons of blood will be taken for these tests. You may not be allowed to participate in this study if you test positive for some of these viruses.
- All non-menopausal women entering the study will have either a blood or urine test for pregnancy. You will not be allowed to participate in this study if you are pregnant, or if you are not willing to stop breast feeding.

In addition to the tests listed above, you may need to have the following as part of this study:

- Insertion of a catheter placed into a large vein (central venous catheter) that will remain in place throughout the apheresis procedures. The catheter is placed under local (or sometimes general) anesthesia and you will be asked to sign a separate consent for this procedure.
- The DTM staff will determine based on the size of the veins in your arms if you will need a central venous catheter.

Apheresis Procedure

The collection of some of your own white blood cells (HPCs) from your blood is done through a procedure called apheresis. The collected HPCs may be stored frozen for the months that you complete your standard treatment. This procedure is quite routine; normal blood donor volunteers routinely undergo apheresis for platelets donation in Blood Centers (Red Cross or others). The procedure will take from three to five hours during which time you will have to remain in a bed or a reclining chair. You do not need to be hospitalized for the procedure. However, if you need a certain type of central venous catheter and require multiple apheresis procedures to complete the HPC collection, you would need to stay in the hospital overnight (in between the procedures).

Apheresis is done in the NIH Blood Bank (Department of Transfusion Medicine; DTM) and is supervised by Blood Bank physicians. During apheresis, blood is removed continuously through a vein in your arm (or your catheter), goes through the machine where the white blood cells are separated from the red blood cells and plasma and the red blood cells and most of plasma are returned continuously to you through the other line.

In some cases, the intravenous catheter placed to receive chemotherapy can be used for the apheresis procedure. However, you may be asked to have two intravenous lines placed, one in

each arm. On occasion, you may be asked to have a single, larger temporary intravenous line placed in a vein in your groin until the apheresis procedure is finished.
Apheresis will be performed daily until a sufficient number of cells is collected. Most people will need one or two apheresis to collect the desired cell number. The maximum number of apheresis procedures to be performed is 4.

The length of treatment

The total length of the study is about one week but depends on the number of apheresis procedures required to collect enough HPCs. You will need to be evaluated the day after the last apheresis.

When you are taken off this protocol, your care will return to your referring doctor (or your NCI treatment team if you are on an NIH protocol or will enroll on another one).

Participation in this study does not constitute an agreement for NIH to provide long-term medical care for your cancer or other medical needs at the NIH Clinical Center.

Risks or Discomforts of Participation

Medications sides effects:

Medications	Possible side effects		
	Likely	**Less Likely**	**Rare**
Filgrastim	• Bone pain, which can sometimes be severe. • Fatigue • Muscle cramps, back/leg pain	• Headache • Pain at the needle site • fevers • Tiredness • Thinning hair	• Filgrastim can cause rupture of the spleen, which can cause death
Plerixafor (Mozobil®)	• Diarrhea, nausea, vomiting, flatulence • Fatigue, joint pain, headache and dizziness • Mild injection site reactions • Trouble sleeping	• Hives • Swelling around the eyes • Shortness of breath, and low oxygen levels in your blood (occurring about 30 minutes after injection)	• Low blood pressure and fainting (within 1 hour of injection).

Central Venous Catheter: The general risks of placing this type of catheter include bleeding, infection, blood clots, a hole in the lung (called pneumothorax, causing breathing difficulties and possibly requiring placement of a tube to re-inflate the lung), and the risks of local or general anesthesia.

Apheresis: discomfort at the insertion sites of the catheters, bleeding, low blood pressure, fatigue, numbness or tingling in the extremities or the face. Numbness or tingling that you may experience during apheresis would be expected to go away after the procedure. Blood infections from contamination of the apheresis machine are a remote possibility, but this has not occurred at the NIH. Individuals with bleeding disorders can be harmed by this procedure and you will be evaluated for such a condition before apheresis is done. All attempts will be made to protect you from any complications.

Reproductive Risks: It is unknown what effects this experimental procedure may have on an unborn child. If you are a woman who is unwilling to stop breast-feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study experimental procedure, during study experimental procedure, and for 6 months after you finish study experimental procedure. If you think that you or your partner is pregnant, you should tell your study doctor or nurse immediately.

Effective forms of birth control include**:**

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Other Possible Hazards / Discomforts

Blood sampling: For medical management, you will be asked to give blood samples multiple times. The blood samples (about 1 to 5 tablespoons each time) are not expected to produce any important decrease in the total amount of blood in your body. These will be collected from your central line or by simple needle-stick from a vein in your arm in the same fashion as routine blood tests. Venipuncture can be associated with pain, bruising, and rarely bleeding or infection. Additionally, some patients can experience light-headedness or fainting during insertion of the needle. The samples collected will be used to both to monitor your medical condition and for research purposes. The total amount of blood which may be taken from you will not exceed 450 ml (one pint) every six weeks. Some of this blood may be obtained through apheresis (see above "apheresis procedure").

Potential Benefits of Participation

Collection of HPCs for later use in a transplant for the treatment of your PCM.

Alternative Treatments

The standard of care treatment that you should / will receive for your multiple myeloma is not part of this study.

Instead of being in this study, you have these options:

- Getting HPC collection for the care for your PCM done at another facility without being in a study
- Taking part in another study

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive the study treatment at no charge to you. This may include medicines and laboratory testing done at the Clinical Center, National Institutes of Health (NIH).
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even if they are not covered by your insurance company.
- Medicines that are not part of the study will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if new information shows that another treatment would be better for you
- If you have side effects from the treatment that your doctor thinks are too severe
- if the study doctor decides to end the study

If this is the case, you will be informed of the reason therapy is being stopped.

Participation in this research study is voluntary. You may stop your participation in the study at any time. There are no penalties for withdrawing from the study. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first. If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of

these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator: Jennifer Kanakry, M.D., Building 10, Room 3-3132, Telephone: 240-760-6172. If you have any questions about the use of your specimens or data for future research studies, you may contact the Office of the Clinical Director, NCI, telephone: 240-760-6070. You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM AUGUST 07, 2017 THROUGH AUGUST 06, 2018.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____