Amendment

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Protocol Title:	Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies				

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* 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.

Abbreviated Title: Outcomes after Allotransplant

NCI Protocol# 11-C-0125

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PROTOCOL TITLE: Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

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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
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G. Some/all research activities performed outside NIH

IND information: None

PRÉCIS

Background

- Cancer relapse is a significant clinical problem following allogeneic hematopoietic stem cell transplantation (allotransplant), affecting up to half of all patients. Effective treatment options are extremely limited and, for most cancers, rarely curative.
- Several CC protocols are evaluating treatment for post-allotransplant relapse. Relapse often progresses quickly; patients require rapid assessment of protocol options in order to expedite initiation of treatment.
- Basic information is needed to improve management of relapse after allotransplant – clinical information regarding risk of relapse and cancer behavior after allotransplant, and information on the biology of relapse after allotransplant – in order to identify risk factors, target prevention strategies, detect early relapse and develop effective treatments.

Objectives

Primary Objective

- To provide a mechanism for systematic, comprehensive evaluation of individuals with relapsed hematologic malignancy after allotransplant and, if available, their donors, to streamline identification of protocol options, enrollment and initiation of therapy.

Eligibility

- Individuals who have received allotransplant treatment for hematologic malignancy ("Recipient-Subjects"). Analyses (secondary aims) will consider two comparison cohorts:
    - Relapse Cohort: Cancer progression, relapse or persistently stable (unremitting) disease
    - Remission (Control) Cohort: Cancer response or remission at/after Day 100
- Individuals who are being enrolled on Clinical Center protocols to undergo allotransplant therapy for hematologic malignancies and are being evaluated at the Clinical Center for planned allotransplantation. ("Recipient-Subjects")
- Related donors of eligible allotransplant recipients ("Donor-Subjects")

Design

- Recipient-Subjects will have clinical and research evaluations at baseline and three and six months post-allotransplant, at six-month intervals through three years post-allotransplant, then yearly. Evaluation after relapse treatment response and for new protocol options is permitted.
- Donor-Subjects will be enrolled at the time of their clinical evaluation and cell collection for Recipient-Subject therapy. Return evaluation for additional clinical product collection is permitted.

- Accrual Ceiling: 500 consented subjects (350 Recipient-Subjects and 150 Donor-Subjects) over 5 years, averaging 70 Recipient-Subjects and 30 Donor-Subjects enrolled per year.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To provide a mechanism for systematic, comprehensive evaluation of individuals with relapsed hematologic malignancy after allotransplant and, if available, their donors, to streamline identification of protocol options, enrollment and initiation of therapy.

1.1.2 Secondary Objectives

- To study the clinical features of relapse after allotransplant.
- To study biologic features of relapse after allotransplant.
- To facilitate post-allotransplant clinical care for individuals who received allotransplant on CC protocols, as a bridge between treatment protocols.
- To catalogue regimens used to treat relapse, vis-à-vis safety and efficacy for clinical management of relapse after allotransplant.

1.2 BACKGROUND AND RATIONALE

1.2.1 Definition Note

The term "relapse" is used broadly in this protocol to include any cancer that remains uncontrolled after allogeneic hematopoietic stem cell transplantation (allotransplant). Specifically, *relapse* will include cancer progression or recurrence after allotransplant, or cancer persistence that has not regressed over a two-month period of observation.

1.2.2 Study Overview

This is a study of treatment outcomes following allotransplant in individuals with hematologic malignancy. Data and tissue samples collected on this study will be used to identify and prioritize available protocol options, and to examine clinical, laboratory and basic science questions regarding the clinical characteristics, cancer behavior, natural history, and immunology distinguishing cancer relapse after allotransplant. While initial evaluation for treatment protocol options is the primary aim, Recipient-Subjects will enroll prior to allotransplant, which will permit prospective investigation of determinants of relapse risk, and will remain on-study indefinitely, permitting: investigation of immune system development and senescence following allotransplant and potential correlates with outcomes; monitoring of our patients long-term, in order to guide appropriate post-transplant clinical care; and obtaining follow-up data on the natural history of relapse after allotransplant. Initially, clinical data will be collected at the Recipient-Subjects' primary allotransplant protocol evaluations, with limited tissue sampling for research permitted (Day 100, semiannually from 6 – 30 months post-transplant). Long-term follow-up evaluations and tissue (blood) sampling will continue beyond those required by allotransplant protocols, annually from 3 to 6 years post-transplant and biennially thereafter. Additional study time-point evaluations and research sampling is permitted at a diagnosis of cancer relapse or progression, after a relapse treatment response and when there is a opportunity to reevaluate protocol options. Although donor participation is not required for Recipient-Subject

enrollment, related donors are strongly encouraged to participate in order provide cells for clinical administration and for research (control samples).

1.2.3 Primary Objective

Our primary objective is to evaluate individuals with relapse in order to ascertain protocol eligibility and prioritize protocols with respect to sequencing among multiple options. Relapse after allotransplant is a major programmatic focus of the ETIB and POB, with bench research studies ongoing and clinical treatment trials underway. The management of cancer relapse following allotransplant is a significant clinical problem which, depending on tumor type, affects one-third to one-half - or more - of those who receive allotransplant.[1] While allotransplant is definitive therapy for many hematologic malignancies, there is no established treatment with curative potential for tumor relapse.[2,3]

Initial treatment for early relapse and/or indolent tumors often includes withdrawal of immune suppression (WIS) and donor lymphocyte infusions (DLI). This approach has resulted in durable remissions, best described in chronic myelogenous leukemia (CML).[4-7] Indolent lymphoid cancers also respond to DLI.[8-10] However, for those that do not respond and for most aggressive malignancies, proven treatment options are not unavailable. Combinations of cytotoxic regimens plus DLI are often tried, but reports of durable remissions are anecdotal at best.

Individuals with relapse after allotransplant are heterogeneous with respect to behavior of their cancer, sustained adverse effects of prior therapies, and treatment options. Often relapse presents with urgency, and the window of opportunity to provide effective therapy is short, requiring rapid assessment and decision-making. This is particularly true after allotransplant, for which relapse therapy often attempts to boost or ignite a "graft-vs.-leukemia" (GVL, or graft-vs.-tumor, "GVT") effect. Even highly successful cellular therapy can require weeks before clinical benefit is observed, and treatment delays hinder efficacy. To study new relapse therapies, rapid evaluation of potential subjects and their donors is required to quickly decide among protocol options, enroll subjects with relapse, and initiate treatment. This protocol provides a platform for streamlined screening assessment across open CC protocols, multidisciplinary review of study options and donor enrollment and collection of required cell products.

Collaborative research efforts between ETIB and other NCI/CCR Branches which provide unique resources for investigating post-allotransplant therapies, based on a common mission to develop novel, effective therapeutics for cancer. Treatment of relapse is a major programmatic focus. There are several accruing NCI protocols specifically studying treatments for this patient population; others permit enrollment of allotransplant recipients, including treatment with cancer therapies that might work synergistically with GVL, i.e., through immunomodulatory effects.

1.2.4 Secondary Objectives

This protocol provides an opportunity to prospectively study clinical behavior and biologic features of relapse after allotransplant. Inclusion of allotransplant recipients in remission as a control population will permit comparisons with relapse subjects and strengthen the information gained from study observations. Such comparisons will be used to investigate risk factors for relapse, clinical markers of early relapse, identify potential treatment targets, and develop strategies to prevent relapse and improve outcomes after allotransplant.

1.2.5 Clinical Features of Relapse

1.2.5.1 Evaluate Clinical Features of Relapse and Outcome

Hypothesis: Patterns of tumor behavior suggestive of allograft effect (and GVL activity) predict better treatment response; survival.

Anecdotal reports and case series suggest the need to define tumor behavior after allotransplant, including how to monitor for relapse; sites of disease, patterns of recurrence and the clinical significance of minimal residual disease appear to differ before and after allotransplant.[11-14] This was identified as a priority at the NCI First International Workshop on the Biology, Prevention and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation.[15-17] In our experience as well, relapse after allotransplant can affect new organs or tissues, even when prior sites do not recur. It is plausible that this reflects tumor evolution in response to anti-tumor immune responses after allotransplant. New sites of relapse may not be identified with standard staging studies. Examples from our patients include isolated bony relapse in non-Hodgkin's lymphoma (NHL), plasmacytomas in multiple myeloma (MM), and chloromas in acute myelogenous leukemia (AML).

Diversity of key clinical features (e.g., tumor histology, allotransplant regimen and post-allotransplant clinical course) contributes to the protean manifestations of relapse, and certainly to the complexity of studying relapse risk, prognosis and treatment options. While hampering systematic investigation of relapse, these variables are important determinants of outcome after allotransplant,[18] and may influence outcome after relapse as well. Specifically, allotransplant response rates differ according tumor characteristics (better in early/indolent than in late/aggressive disease,[19-22] chemosensitive disease[23,24]); donor characteristics, such as relationship and the degree of human leukocyte antigen (HLA) mismatch[20,21,25] and sex mismatch;[25-28] transplant regimen characteristics, such as intensity of cytotoxic conditioning, donor stem cell source,[29,30] allograft manipulation (e.g., T cell depletion)[31-33] and engineering (e.g., selected depletion of alloreactive lymphocytes);[34,35] and recipient characteristics/clinical course, including graft rejection, the kinetics of donor chimerism and development of acute and chronic graft-versus-host disease (GVHD).[21,36-38]

While the immunologic GVL effect is a key component of allotransplant efficacy, direct measures of GVL are not defined.[39] In fact, while convincing, the evidence for the GVL effect in allotransplant is indirect as well (see section **1.2.6**). Nonetheless, there are relapse scenarios that suggest prior GVL effect, which might influence choice of treatment and clinical outcomes, *e.g.*:

- Late relapse;
- Relapse following initiation of systemic immune suppression to treat GVHD;
- Limited/novel sites of recurrence;
- Slower tumor progression than prior to allotransplant; and
- New or renewed sensitivity to cancer therapies after allotransplant.

There are also response scenarios that suggest a GVL effect, which might distinguish lower relapse risk, *e.g.*:

- Response after recovery from conditioning;
- Response associated with donor lymphoid engraftment and/or coincident with GVHD onset; and

- Response to WIS and/or to DLI.

1.2.5.2 Evaluate Clinical Immunity and Inflammation and Relapse Risk

Hypotheses: (1) Clinical blood markers of inflammation will be normal or low in Recipient-Subjects with relapse; low or falling levels may herald imminent relapse. (2) The incidence of relapse is increased in individuals with poor recovery of clinical immunity after allotransplant. (3) Individuals with relapse who demonstrate recovery of clinical immunity have a selective absence of tumor immune response (GVL), identifying cancers that are unlikely to respond to DLI-based therapy.

Clinical management of allotransplant recipients would be aided by the identification of additional clinical indicators of risk of relapse. Clinical parameters associated with relapse might provide a monitoring tool for early cancer progression/relapse, before the establishment of widespread disease, and treatment may be more effective. In light of the immune-mediated therapeutic function of allotransplant, it is plausible that commonly used clinical parameters of inflammation and immune function may serve to stratify risk of relapse and early disease detection. Common markers of systemic inflammation can be helpful in establishing certain diagnoses in non-transplant clinical settings. Examples include brain natriuretic protein (BNP) in congestive heart failure[40], erythrocyte sedimentation rate (ESR) in osteomyelitis or temporal arteritis, lactate dehydrogenase (LDH) in hemolysis, and C-reactive protein (CRP) in autoimmune diseases and to increase the diagnostic specificity of other inflammatory markers. We have observed that these markers of inflammation frequently are not informative in our post-allotransplant population. They are frequently elevated in our patients, and further workup for the condition of interest often does not support the diagnosis. While they have lost their traditional diagnostic utility, it is possible that they would be useful in monitoring alloreactivity. Perhaps ongoing GVL could leave an inflammatory "signature" that could be detected with these inflammatory markers, either individually or in combination. Given their loss of diagnostic specificity in allotransplant recipients as conventionally used, it is plausible that these markers of inflammation could be useful in monitoring anti-tumor immune responses. Loss of the "inflammatory signature" might identify loss of ongoing "GVL", indicating imminent risk of relapse or heralding early relapse.

Further, it is not known whether recovery of immune function differs in individuals who relapse. To the extent that relapse represents failure of the allogeneic immune system, characterization of patients who relapse and comparison with patients in sustained remission may be informative. Clinical measures of immune function, such as serologic responses to prior infections or vaccines and delayed-type hypersensitivity responses to pathogens (*i.e.,* the PPD anergy panel) could provide information regarding relapse risk and/or prognosis of individuals with relapse.

1.2.5.3 Survey of Clinical Features of Relapse

Hypothesis: (1) Clinical behavior of cancer relapse after allotransplant differs from cancer behavior prior to treatment, affecting management, e.g., monitoring requirements and treatment options. (2) Patterns of tumor behavior suggestive of a post-treatment effect after allotransplant identify GVL activity and predict better treatment response and survival. The following features can be used to identify a GVL effect:

- Relapse after Day 100 or following initiation of systemic treatment for GVHD
- Prior tumor response to withdrawal of GVHD prophylaxis and/or DLI
- Limited/novel sites of recurrence
- Slower tumor progression than prior to allotransplant
- New or renewed sensitivity to cancer therapies after allotransplant

In order to develop rational treatment strategies, much more needs to be understood about how complex factors influence cancer relapse and subsequent response to treatment. An important initial step is description of clinical features of relapse after allotransplant in the context of key variables in donor, transplant, and post-transplant events. A survey of this kind is not feasible in many transplant centers, given site-specific transplant approaches, disease specialization and protocol restrictions and limited resources from external funding and clinical reimbursements. The NCI is uniquely able to perform this clinical survey in conjunction with evaluation and screening for ongoing relapse treatment protocols. An important component of this descriptive survey is the natural history of malignancy after allotransplant. Survival after relapse is highly variable, and likely determinants are heavily influenced by institutional transplant approaches and disease emphases. Prognosis affects clinician and patient decision-making with respect to treatment.

Despite relapse being the most common cause of death after allotransplant, there have been few studies, mostly retrospective, that have dealt with the clinical manifestations of relapse or its treatment.[3,41-51] Evaluation of allotransplant recipients with relapse, longitudinally and after relapse treatment response, and of allotransplant recipients in remission, longitudinally and if subsequent relapse, will permit systematic investigation of the clinical features of relapse. It will allow comparisons between those with and without relapse, and permit examination of the influences of cancer histology, transplant/donor characteristics, and post-transplant clinical features.

The wealth of information collected during evaluation of CC protocol options will provide an opportunity to examine clinical parameters that: identify risk of relapse; suggest development of early relapse; and predict treatment response and survival. Inclusion of Recipient-Subjects in remission will permit comparative analyses in order to identify whether there are clinical determinants of risk for relapse. Recipient-Subjects who are enrolled while in remission but subsequently relapse may be reevaluated on-study to rapidly identify treatment protocol options. Prospective clinical data from these Recipient-Subjects with comparison of parameters before and after relapse will provide an invaluable means of validating parameters distinguishing relapse and in remission.

Clinical guidelines are needed for management, including evaluation, monitoring and treatment of relapse after allotransplant. Engagement of broad NIH intramural expertise – tumor-specific and in allotransplant – to review prospectively collected clinical data would: provide a forum for critical assessment; increase knowledge of relapse tumor behavior after allotransplant; and provide a foundation of information for developing relapse management guidelines.

1.2.6 Biologic Features of Relapse

The specific aims of the proposed studies of the biology of relapse are to identify factors in patients with relapsing or persistent disease after allogeneic transplant which may support earlier diagnosis of relapse, be prognostic of outcome or suggest new approaches to treatment.

It is now widely accepted that the donor immune response is a major therapeutic component of allotransplant for malignancy. It was originally observed that leukemic relapse rates were lower for patients with chronic myelogenous leukemia (CML) who received T-cell replete allogeneic bone marrow than for those who received either syngeneic (identical twin) or T-cell depleted bone marrow.[31,52] Subsequently, reports of durable molecular remissions of CML following donor lymphocyte infusion (DLI) provided convincing evidence for a clinically relevant graft-versus-leukemia (GVL) effect,[5,7,53-55] more recently demonstrated in other indolent hematologic malignancies[8,9,56] and even some carcinomas.[37,57] Additionally, associations between GVHD, particularly chronic GVHD (cGVHD), and improved relapse-free and overall survival are well described.[1,58,59] These observations have strengthened the concept that GVL-mediated cancer control can sustain long-term remissions after allotransplant.

Some patients, however, appear to have little if any benefit from GVL, with relentless tumor progression in spite of successful donor cell engraftment or early relapse after initial response to cytotoxic conditioning. Others appear to have an initial GVL response, but subsequently experience cancer progression or recurrence.[36,60] Many factors contributing to relapse after allogeneic transplantation may have been operant in the original malignancy: lack of "danger signals" and/or T cell costimulation, activation-induced apoptosis of tumor-reactive T cells, tumor cell defects in death receptor signaling, tumor cell down-regulation of HLA and/or immunogenic tumor antigens, microenvironmental factors limiting immune cell trafficking to tumor, and tumor production of immunosuppressive cytokines and/or recruitment of regulatory T cell populations.[61-67] Other factors affecting donor-anti-tumor (i.e., GVL) responsiveness may have developed as a consequence of transplantation. Limited renewal of thymopoiesis after allotransplant may restrict the potential numbers and repertoire of T effectors.[68] Differential recovery after transplantation of effector and regulatory T cell populations may influence the generation of a GVL response.[69,70] Improved understanding of the biological features of relapse is needed to refine current allotransplant therapy and to develop novel treatment strategies for relapse after allotransplant.[71-73 1,3,15,16,39,74,75] Coordinated analyses of the tumor sites in individuals that relapse after allogeneic transplantation and in those in the process of donor-mediated tumor rejection may provide information to guide improvement in post-transplant therapies against relapse.

The hypotheses to be tested in this natural history protocol have grown out of ETIB's analyses of immune recovery and donor-anti-host activity after allogeneic transplantation. The central hypothesis to be tested is that rejection of hematologic malignancies (GVL) will be associated with tumor infiltration by functional effector T and NK donor lymphocytes and evidence of a shift in the tumor microenvironment toward production of cytokines and chemokines that support lymphocyte trafficking and infiltration. A correlate is that sites of relapse and progressive disease after transplantation will evidence infiltration by donor-derived regulatory cell populations, e.g., Tregs and other suppressor cells, with the tumor microenvironment characterized by the cytokines and chemokines these cells produce.

ETIB studies on donor infiltrates in cGVHD have proposed that interferon (IFN)-induced processes play a critical role in the development of donor-anti-host attack.[76] Using immunohistochemistry, we have demonstrated the dominant presence of $CD8^+$ cytotoxic T cells in inflammatory sites of donor attack on host cells. These T cells expressed the transcription factor T-bet, consistent with IFN-γ producing Th1/Tc1 cells, expressed markers of cytotoxic effectors (granzyme, TIA-1) and were located next to apoptotic host cells. The T cells also expressed the T-bet induced chemokine receptor CXCR3, which binds IFN-induced chemokines. Plasmacytoid dendritic cells, known to be major producers of IFN-α, were increased in the infiltrate, along with elevated levels of IFN-induced factors, including the chemokine CXCL9 and the cytokine IL-15. These IFN-induced factors could have contributed to recruiting and maintaining Th1/Tc1 T effectors at the tissue site. These changes were evident systemically, not merely in severely affected tissue sites. Elevated levels of IFN-induced factors such as BAFF and MIG were also found in the plasma of cGVHD patients and IFN-induced genes were upregulated in circulating monocytes (Hakim *et al*., manuscript in preparation). This pattern of IFN-induced tissue attack is consistent with those identified in microarrays of inflamed tissues and peripheral blood in patients with autoimmune tissue destruction from systemic lupus erythematosus and systemic sclerosis. IFN-induced pathways in autoimmune disorders are highly relevant to reactions against tumor because both involve responses against targets that are mostly self-antigens, overexpressed or slightly mutated. Moreover, there are striking similarities between these processes and those observed in gene expression studies in solid tumors undergoing rejection following autologous immune therapy.[77-79] In IL-2 induced melanoma rejection and in imiquimod-activated rejection of carcinoma, expression of genes indicating infiltration of NK cells and cytotoxic T effectors increased in the tumor site, concurrent with upregulation of IFN-induced factors. These studies have identified an IFN-induced gene 'signature of rejection' in tumor sites with successful immune therapies.[80] In contrast, in tumors that failed to respond to therapy, these marker genes were not upregulated and markers of suppression such at overexpression of IL-10 predominated.[79] We propose that similar markers of suppressive pathways may distinguish hematopoietic malignancies that relapse after allogeneic transplantation. Preliminary ETIB studies of tumor nodules from patients with relapsed Hodgkin and non-Hodgkin lymphoma after transplantation (07-C-0064) have demonstrated the suppressive aspect of the hypothesis, finding that donor-derived $FoxP3^+$ Treg cells constitute as much as 30% of tumor-infiltrating donor-derived CD4 cells, while $T\text{-}bet^+$ effector T cells are a small minority of the T cell infiltrate.

The proposed ETIB studies in this relapse screening and natural history protocol, as well as in associated therapeutic protocols, will focus on characterizing the donor populations and cytokine milieu of sites of disease in patients with cancer progression or relapse after allotransplant. Potential sources of cancer tissue for study include lymph nodes, tumor nodules, bone marrow, malignant ascites and pleural effusions. Depending upon availability of tissue, these studies will involve immunohistochemistry of paraffin-embedded tissues, multiparameter flow cytometry of isolated cells, and molecular assays of gene expression. These studies will assess the relative frequency of cytotoxic effectors ($T\text{-}bet^+$, $perforin^+$, NK and T cells) and IFN-induced genes (such as CXCL9, IFIT, IFI44) as compared to the relative frequency of suppressive factors and cells (FoxP3, IL-10). In ongoing investigations of donor lymphoid engraftment and repopulation in subjects treated on ETIB allotransplant protocols, we have developed extensive fluorescent antibody panel and multi-color flow cytometry assay using the 10-color/3-laser Gallios™ Flow

Cytometer (Beckman Coulter, Miami, FL). This permits quantitative assessment of complex cell surface and intracellular parameters that can be used to distinguish functionally distinct lymphocyte populations. These panels have been used to explore populations in lymph nodes and marrow sites of lymphoma relapse after allotransplant under protocol 07-C-0064. Under this screening and relapse natural history protocol, these studies will be continued and include comparison of peripheral blood and bone marrow between Recipient-Subjects with and without relapse, and comparison of individual Recipient-Subjects' cancer tissue before and during effective relapse treatment. Immunohistochemistry analyses utilizing the antibody panels and experience gained from studies of CGVD tissues will focus on the frequency and organization of effector and regulatory T cell populations infiltrating tumor areas. Fine needle aspirates of tumor sites would be used to permit assessment of gene expression in tumors that cannot be resected for study and to allow serial examination of tumor sites in moving from natural history into therapeutic relapse protocols. These studies would use microarray and multiplex quantitative gene expression assays (nCounter Analysis System, described below) to assess expression of genes that have been associated with tumor rejection by Drs. Wang and Marincola, our collaborators in NIH/CC/DTM/Immunogenetics Section.[77,79,80]

Studies of peripheral blood in patients enrolled in therapeutic protocols for treatment of relapse after allotransplant will focus on serial analyses in parallel with treatment. These studies will be extended to patients in the natural history protocol to provide a broad cross-sectional assessment of lymphocyte and monocyte populations after allotransplant. These studies will include analyses of regulatory and effector T cell populations by multiparameter flow cytometry, including markers of T lineage (transcription factors such as FoxP3), functional activity or anergy, cytokine/chemokine receptors and naïve/memory/effector status. In order to test the hypothesis that tumor rejection is associated with the development of a pattern of IFN-induced activation, we propose to test (a) the plasma levels of IFN-induced and other inflammatory cytokines/chemokines (such as MIG, IP-10, BAFF, IL-6, IL-1□ (b) the phenotypic markers on circulating monocytes consistent with ongoing exposure to Th1, Th2 and Treg cytokines, and (c) the level of expression of IFN-induced genes in circulating monocytes. Donor-Subject peripheral blood will provide normative controls for individual Recipient-Subject variation in cell phenotypes and plasma factors.

Studies of monocyte gene expression are based on the concept of using monocytes as reporter cells to assess cytokine/chemokine production in the tissues. Monocytes express receptors for multiple cytokines, including IFN, IL-4 and TGFβ and respond to these cytokines by initiating alternative patterns of gene expression. We have observed up-regulation of IFN-induced genes in monocytes in patients with CGVHD, in association with elevated plasma cytokines and evidence of IFN-mediated pathways in inflamed tissues. An ongoing project is the molecular profiling of CGVHD monocytes, using nCounter™ Analysis System (NanoString Technologies, Seattle, WA). This system, supported by the NCI Advanced Technologies program, provides highly multiplexed, direct digital detection and counting of individual biological molecules in a single reaction. The nCounter™ technology has the advantage of requiring very small specimens, allowing detailed molecular profiling of sorted monocytes. Validating the use of monocytes as reporters for systemic shifts in cytokine profile would support use of this assessment in therapeutic protocols studies of relapse.

The biology of T cell homeostasis is also a focus of ETIB research. A major goal of studying of the biologic mechanisms of T cell homeostasis is to identify potential therapeutic targets to improve recovery of immune function and, potentially, to increase GVL. ETIB has an extensive history of collaboration in basic, translational and clinical studies of mediators of T cell homeostasis. Examples of ETIB laboratory investigations for which clinical evaluation is in development, in progress or in press include interleukin (IL)-7,[81-85] IL-15,[86,87] thymic epithelial cell growth factors (e.g., KGF, IGF-1)[88] and androgen withdrawal.[89] A goal of extending this work to study of the allogeneic immune system in individuals with relapse is to similarly identify strategies to improve immune responses against tumor.

1.2.7 Post-Allotransplant Clinical Care

It is essential to maintain a mechanism to provide clinical care for individuals who receive allotransplant at the NCI, including collection and/or administration of donor cell products that may be required outside the context of a clinical trial. Frequently, NCI clinical research subjects are removed from their primary allotransplant or subsequent treatment protocols if they receive treatment that could compromise the integrity of toxicity monitoring data on an investigational transplant or relapse treatment protocol. Their donors may be taken off study at that time, also. Often referring physicians and/or local health care facilities cannot provide the specialized care required by our allotransplant recipients. Continuity of care is particularly important in this patient population, as patients often have complex, transplant-related health issues.[101] Further, allotransplant recipients frequently require donor cell products for cancer therapy and/or hematopoietic support. For those transplanted at the CC, donor products are not available through outside clinical facilities, which may not have the means of collecting products and/or mechanisms for cost reimbursement.

1.2.8 Catalogue and Consensus Guidelines

Treatment of relapse after allotransplant with conventional therapies is frequently tried, but has not been nor likely will be systematically studied with respect to safety and efficacy in this unique patient population. Specific safety issues are graft function (bone marrow toxicity) and GVHD, due to immunomodulatory effects – intended or secondary - of many conventional treatments. Efficacy of conventional agents may also differ in relapsed tumor. We have observed responses after allotransplant to regimens that had lost potency prior to allotransplant. Whether this is due to altered tumor biology in response to selective pressures exerted by GVL effects and/or due to immunomodulatory effects of the therapy are speculative.

The comprehensive clinical evaluation undertaken to meet the primary objective of this protocol will gather a large body of information on safety and efficacy of conventional therapy. The CC has broad range of tumor-specific and allotransplant expertise; collective review of the relapse treatment history would improve knowledge of treatment after allotransplant. While the data will be limited by retrospective collection, better data are not available to guide treatment decisions. A catalogue of data on conventional treatments used in this patient population, including major toxicities and efficacy, would contribute toward filling critical information gaps. The NCI's 1st and 2nd International Post-Transplant Relapse Workshops (November 2009 and November 2012[102-105]) have successfully initiated a consortium of investigators and institutions to study relapse and institute trials for prevention and treatment of post-transplant relapse. This catalogue

will provide basic, heretofore unavailable, information to guide considering treatment regimens for consortium trials. Ultimately it is hoped that this catalogue can contribute toward the development of consensus guidelines for the management of relapse.

1.2.9 Approach to Prospective Data Collection

1.2.9.1 Primary Objective

In order provide a mechanism for systematic, comprehensive, and streamlined evaluation of allotransplant recipients with relapse and, if available, their donors, potential subjects will be evaluated at the CC in the multidisciplinary NCI Allotransplant Relapse Clinic. Evaluation will include screening studies for CC protocols that have been identified as potential treatment options. In order to maximize efficient evaluation and avoid redundant procedures, studies and tissue samples obtained outside of this study will be used to meet study requirements whenever possible. Following evaluation, potential subjects will be presented at the recently developed multidisciplinary Allotransplant Relapse Tumor Board, for identification and prioritization of CC treatment protocol options (see section **3.3.6**).

Recipient-Subjects enrolled on this study will be followed according to two clinical scenarios:

- Recipient-Subjects with relapse will be evaluated for CC treatment protocols at the time of enrollment and upon change in protocol options and/or clinical status affecting eligibility.
- Recipient-Subjects who are enrolled at the time of allotransplant at the CC and/or who are enrolled post-transplant but whose tumors are responding or are in remission at the time of enrollment evaluation will be followed in conjunction with landmark assessments performed under their primary transplant protocol and may return for evaluation for CC treatment protocols in the unfortunate case of subsequent cancer relapse.

While it is hoped that treatment protocol options will be identified for most study participants with relapse, inevitably some who are evaluated will not be eligible for accruing trials. Recipient-Subjects who are not eligible for other CC protocols will continue to receive routine care and therapy with their primary allotransplant provider.

Recipient-Subjects may remain on this study beyond enrollment on other NCI treatment protocols and/or while they are being treated by a local physician outside of the NCI or under another protocol, including treatment with conventional agents at home or with investigational agents (on protocol or compassionate-use basis). Return study visits will be permitted for evaluation of responses and CC protocol options.

1.2.9.2 Secondary Objectives

1.2.9.2.1 In order to study the clinical features of relapse after allotransplant in individuals with hematologic malignancy, a thorough medical record review, clinical history and physical examination will be carried out at the CC. Evaluation will include radiographic studies and collection of blood and malignant tissue for clinical staging, confirmation of histology and research. When possible, pre- and post-allotransplant studies and specimens will be obtained for review and comparison.

1.2.9.2.2 In order to prospectively explore patient and tumor characteristics of relapse and response after allotransplant or post-allotransplant therapy, Recipient-Subjects may

remain on study beyond enrollment on other NCI treatment protocols. Recipient-Subjects will be seen at the CC for evaluation and collection of clinical and research specimens at six months and then yearly, with additional follow-up permitted after a response and/or for identification of protocol options. For comparison, Recipient-Subjects in remission after allotransplant will have for evaluation and collection of clinical and research specimens at parallel time points, with additional follow-up permitted in the event of subsequent relapse.

1.2.9.2.3 In order to provide continuous access to specialized allotransplant clinical care for CC patients (*e.g.,* a bridge between CC treatment studies), standard clinical evaluation and treatment will be permitted for Recipient-Subjects enrolled on-study. Permitted treatments include approved antineoplastic agents and supportive therapy with approved drugs and cell products, including donor cell products (e.g., stem cells, lymphocytes). The protocol allows collection and storage of donor cell products for use on this and/or other CC protocols, and Donor-Subjects may remain on-study with their respective Recipient-Subjects.

1.2.9.2.4 A detailed treatment history will be obtained during CC evaluations, from which a catalogue of conventional treatment safety and efficacy will be maintained.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria – Recipient-Subjects

2.1.1.1 Individuals who are candidates for allotransplant therapy for hematologic malignancies and are being evaluated at the Clinical Center for planned allotransplantation.

2.1.1.2 Individuals who have received allotransplant treatment for hematologic malignancy and have:

2.1.1.2.1 Hematologic recovery after allotransplant: e.g., have had neutrophil recovery to 500 cells/mcL. Secondary cytopenias or cytopenias due to disease progression will be permitted. Note: this requirement will not apply to subjects enrolling pre-transplant, i.e., who receive transplant-related medical care at the CC.

2.1.1.2.2 An ongoing relationship with a primary oncologist who will continue to provide continuity of care during and after study participation.

2.1.1.2.3 Following record review and information exchange between the patient's primary oncologist and the NCI PI/Designee, the PI/Designee determines that the individual reasonably could be expected to safely tolerate travel to and from the CC to undergo evaluation as defined in the protocol, in the event that the patient is ineligible or uninterested in participating in open treatment protocols.

2.1.1.3 Age 18-99 years

2.1.1.4 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Inclusion Criteria – Donor-Subjects

2.1.2.1 Individuals who are/will be the donors of allogeneic hematopoietic stem cell transplants received by Recipient-Subjects who are to be enrolled on this protocol.

2.1.2.2 Age 18-99 years.

2.1.2.3 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2.4 Individuals with evidence of infection with transfusion-transmittable agents (Hepatitis B and C Viruses (HBV, HCV); Human Immunodeficiency Virus (HIV 1/2), Human T-Lymphotrophic Virus (HTLV I/II), West Nile Virus (WNV) and *Trypanosoma cruzi*) will not be excluded from study participation. However, Donor-Subjects with evidence of HIV infection will only be able to donate cells for research. Donors with a history of HBV or HCV infection will be able to donate for research, and may be eligible to donate for therapeutic administration. However, determination of permissibility for clinical donation will require a hepatology consultation and the consent of the intended recipient after discussion of the risk/benefit of the donor cell product and the possibility/consequences of transmission. The PI/ Designee will make the final determination of permissibility of donation for recipient cell therapy.

2.1.2.5 Unrelated donor selection will be in accordance with the National Marrow Donor Program (NMDP) standards. When a potentially eligible recipient of an unrelated donor product from an NMDP Center is identified, the recipient will complete an NMDP search transfer request to allow NIH NMDP staff to contact the NMDP Coordinating Center, who will, in turn, contact the donor's prior Donor Center. The NMDP Policy for Subsequent Donation Requests will be followed and the appropriate forms (Subsequent Donation Request Form and Therapeutic T Cell Collection Prescription Form, (see Section **10.5**) will be submitted as required.

2.1.3 Exclusion Criteria – Recipient-Subjects

2.1.3.1 Individuals with rapid disease progression or aggressive cancer histology who, in the opinion of the PI/ Designee, require urgent therapy within 30 days in order to preserve organ function or quality of life. This restriction will not apply if there is no approved therapy with a reasonable chance of disease response, if the patient does not have access to an effective therapy and the patient appears to be eligible for an accruing CC treatment protocol or if the patient is enrolled on an NIH/CC clinical protocol, e.g., allotransplant protocol.

2.1.3.2 Pregnancy or lactating. Additionally, Recipient-Subjects of childbearing potential that will receive cancer treatment under this protocol must be willing to use an effective method of contraception (Section **4.8**).

2.1.4 Exclusion Criteria – Donor-Subjects

2.1.4.1 None.

2.1.4.2 Adult donors who are not eligible for clinical donation (Section Error! Reference source not found.) will not be excluded from study participation, but will only be able to donate cells for research.

2.2 SCREENING EVALUATION FOR RECIPIENT-SUBJECTS

Individuals who have received or are being evaluated for allotransplant for hematologic malignancy will be evaluated according to the guidelines of standard medical care, with screening studies as dictated by the relevant CC treatment protocol, but include as a minimum the following:

2.2.1 History and physical examination.

2.2.2 Disease-related evaluation demonstrating relapsed hematologic malignancy after allotransplant (Relapse Cohort only). Results from clinical assessments within two weeks of screening and any studies performed by patients' treating physicians since completion of last cancer treatment may be used for the initial eligibility assessment, provided there is direct contact between the AI/LAI/Designee and the treating physician to confirm eligibility requirements.

2.2.3 NCI Laboratory of Pathology review of tumor and/or bone marrow biopsy specimen (including tissue block or unstained slides, if possible)

2.2.3.1 Pathologic review will include tumor biopsies obtained before and after allotransplant, if available.

2.2.3.2 In cases that tumor biopsy material is not available for NCI review, a tumor or bone marrow biopsy procedure will be permitted during the eligibility evaluation. Specimens obtained as part of the eligibility evaluation may be used for the Initial Cancer Tissue Evaluation (Section **3.3.4.1**).

2.2.4 Serum/urine β-HCG in females of childbearing potential, within two weeks of screening

2.3 REGISTRATION PROCEDURES

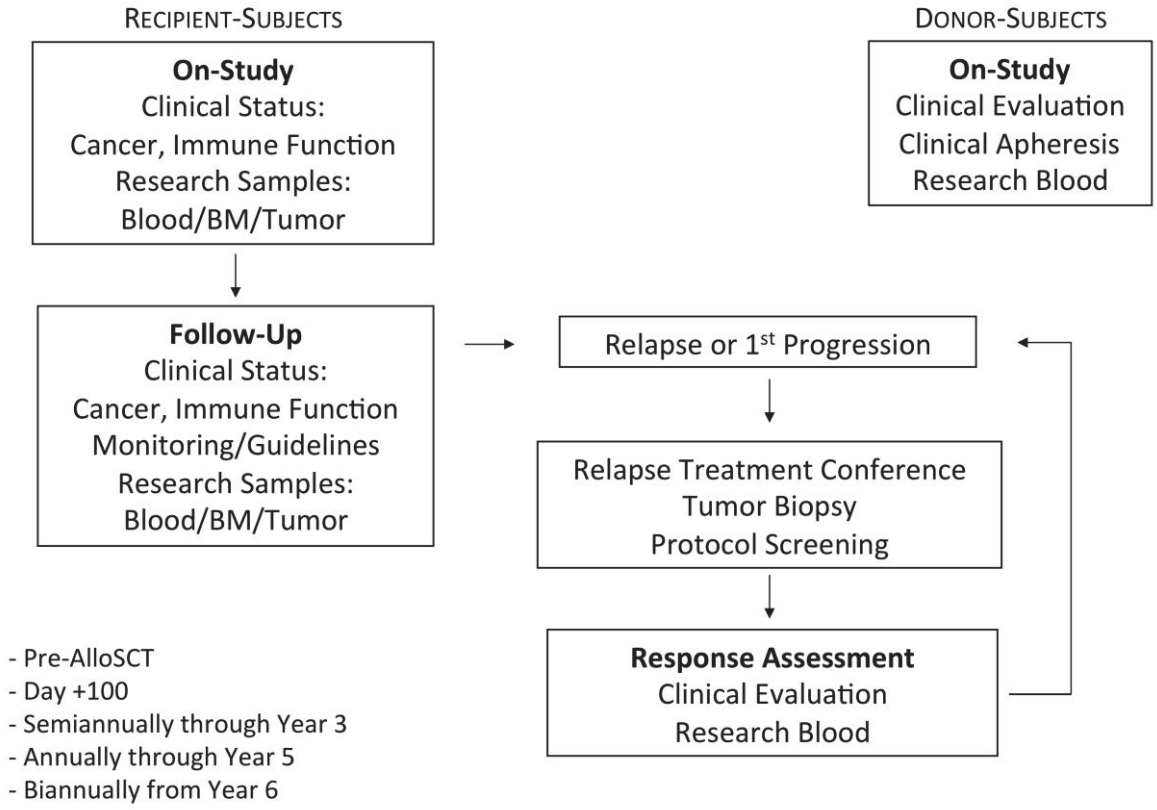
2.3.1 Authorized staff must register an eligible candidate with Central Registration Office (CRO) no later than 24 hours after the Recipient-Subject has signed the consent form. All Subjects must be registered prior to beginning this study. A registration Eligibility Checklist is available from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) and must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>. For questions regarding registration, authorized staff should call 301-402-1732 between the hours of 8:30 a.m. and 5:00 p.m., Monday through Friday. Voicemail is available during non-business hours.

2.3.2 Donors at NIH will be registered on this study prior to donor apheresis.

2.3.3 Unrelated donors from NMDP Centers will be consented on an approved NMDP consent prior to eligibility evaluation. NIH UID numbers will be generated on unrelated donors while maintaining the anonymity required by the NMDP and registered using NIH UID numbers with the Central Registration Office as described above.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN



3.2 STUDY CALENDAR

See **Appendix I: Schedule of Samples and Studies**

3.3 RECIPIENT-SUBJECT EVALUATIONS

3.3.1 Time Points for Study Evaluations

Note: These evaluation visits coincide with allotransplant protocol evaluations and will be scheduled to maximize coordination with other protocols to minimize inconvenience and cost.

- Initial visit to include the on-study evaluation; coincident with transplant protocol screening evaluation in subjects enrolled prior to allotransplant.

Dating from the day of allotransplant:

- Day 100

- Semiannually, at 6, 12, 18, 24, and 30
- Annually from 3 to 6 years post-transplant Biennially after Year 6

3.3.2 Relapse Evaluations

Note: These evaluations will be scheduled to coincide with clinical management visits and may be omitted at the discretion of the PI/AI/Designee if s/he deems the evaluation would pose undue burden to the Recipient-Subject.

- Diagnosis of new cancer relapse or first progression after allotransplant; evaluation will be encouraged as soon as feasibly possible, ideally prior to initiation of relapse treatment.
- Treatment response evaluation (four to eight weeks after initiation of cancer therapy; timing will be determined by PI/AI/Designee to coincide with clinical visit for second cycle of therapy or, e.g., one-cycle therapy, at time of clinical evaluation to determine recovery from treatment side-effects)
- New protocol option evaluation

3.3.3 Recipient-Subject Clinical Center Evaluations

Recipient-Subjects will undergo a clinical evaluation with NCI Transplant Oncology in accordance with their primary CC transplant treatment protocol while they remain on that study. Subsequently, evaluation will be performed in accordance with standard post-transplant guidelines, as detailed in **Appendix I: Schedule of Samples and Studies**. In order to reduce redundancy, risks and/or exposures, clinical testing performed at outside institutions may be submitted for NIH interpretation and substitute for clinical studies required in this protocol, if review by the AI/LAI/Designee determines that the timing and quality of the study are adequate.

The following studies will be performed at indicated study time-points if not done under the primary treatment protocol.

3.3.3.1 Clinical History (Section 10.9)

3.3.3.2 Detailed Physical Examination with GVHD Assessment (Sections 10.1 and 10.2)

3.3.3.3 Routine Clinical Blood Tests (See Section 10.9)

3.3.3.4 Assessment of post-transplant health maintenance requirements (Sections 10.9 and 10.10).

3.3.3.4.1 A Health Maintenance Record, including current recommended procedures/interventions, will be provided to Recipient-Subjects, their transplant study team, and their home medical providers at each time-point evaluation.

3.3.3.4.2 Provision of this care but may be under the Recipient-Subject's primary transplant protocol and/or under the care of their home medical providers.

3.3.3.4.3 Provision of post-transplant health maintenance care is permitted on this study if the PI/AI/Designee determines it is in the Recipient-Subject's best interest to provide this

care at the CC, e.g., if physical, logistical and/or financial burden would preclude acquisition of this care from an outside provider.

3.3.3.5 Clinical Evaluation of Immunity & Inflammation

Required to address secondary protocol research objectives, including blood testing for clinical markers of inflammation, lymphocyte recovery and recovery of Immune Function, as detailed in Section **10.9**, **Appendix I: Schedule of Samples and Studies**.

3.3.3.6 Disease-Specific Staging Studies (see Sections 10.3 and 10.9)

3.3.3.7 Other Studies

3.3.3.7.1 Additional diagnostic testing, *e.g.*, cardiopulmonary functional assessment, etc., may be performed to address issues of concern and/or eligibility requirements for potential treatment protocols at PI/LAI/Designee discretion.

3.3.3.7.2 Further assessments may be carried out by clinical teams with expertise in the Recipient-Subject's specific treatment issues, e.g., disease-specific Medical Oncology, Chronic Graft-vs.-Host Disease Clinic, Radiation Oncology, Transplant Infectious Disease, or specific ancillary care issues, e.g., Pharmacy, Social Work, Nutrition, Pain & Palliative Care, according to individual Recipient-Subject requirements at the discretion of the PI/LAI/Designee.

3.3.4 Tissue Specimens for Clinical and Research Use

The following specimens will be collected at the initial evaluation, at the time of initial relapse (if applicable) and at the time of relapse treatment response, if feasible. Additional procedures will be limited to sampling required for: restaging (specified in Section **10.3**); new treatment protocol screening; and/or clinical indication. All tissue sampling solely for research under this study that imposes greater than minimal risk is optional for all subjects. Further, unless performed in conjunction with a clinically indicated or treatment protocol-required surgical procedure, general anesthesia will not be used for research sampling.

3.3.4.1 Cancer Tissue Evaluation

Clinically indicated biopsies will be performed if safe and feasible at the time of initial evaluation (in subjects enrolled at the time of allotransplantation and in Subjects with relapse) and at the first diagnosis of relapse (when applicable). In adults, biopsies will preferably include two cancer sites.

As feasible, Subjects who have extramedullary sites of tumor may have additional biopsies prior to initiating new treatment and during a clinical response. In adults, biopsies will preferably include two cancer sites.

- Biopsy of one site will preferably be obtained by excision through the Surgery Consult Service, if accessible through a minimally invasive procedure; otherwise, sample preference is core needle biopsy over FNA, through Interventional Radiology. Note: excisional or core-needle biopsies will be performed as feasible and required to confirm diagnosis or for specific treatment protocol eligibility. Clinical sample to Surgical Pathology; research sample to ETIB Preclinical Core Lab (10/12C216).
- Biopsy of another site will preferably be obtained with FNA, through Interventional Radiology, so that repeat sampling of the same lesion may be possible after treatment

response Note: biopsies will be performed as feasible at the initial evaluation and evaluation of a tumor treatment response. Clinical sample to Molecular Hematology for chimerism; research sample to ETIB Preclinical Core Lab (10/12C216).
*Required to address secondary protocol research objectives

At the initial evaluation, as feasible, Recipient-Subjects in remission may have tissue biopsies of a responding or previously involved site of cancer for research purposes, as long as the biopsy does not pose risk of significant discomfort or complication.
*Required to address secondary protocol research objectives.

- This research biopsy is optional. Subsequent biopsies of recipient-subjects initially in remission may be performed for clinical indication (e.g., relapse suspicion). In the case of relapse, tumor biopsy requirements are as described for initial assessment for Recipient-Subjects with relapse, detailed in Section **3.3.3**, as part of screening for treatment protocols.
- Biopsy will preferably be obtained with FNA, to minimize discomfort and, in the unfortunate case of subsequent relapse, to permit repeat sampling of the same lesion. Clinical sample to CC/DLM/Molecular Hematology for chimerism; research sample to NCI ETIB Preclinical Core Lab (10/12C216).

3.3.4.2 Bone Marrow Evaluation (Aspiration and Biopsy)

- Clinical samples to Hematopathology for diagnostic evaluation, Molecular Hematology for chimerism, other pathology labs for disease-specific evaluation, per Section **10.3**.
- Following clinical collection, the aspiration needle tip will be redirected, and 5-10 mL will be collected in a heparinized syringe for research. This specimen will be delivered to the ETIB Preclinical Core Lab (10/12C216).
- After the initial evaluation, bone marrow evaluation may be omitted at the discretion of the PI/LAI/Designee (i.e., if unnecessary for clinical restaging).

3.3.4.3 Apheresis for Research
*Required to address secondary protocol research objectives

Apheresis for research is permitted under this protocol at the Initial Evaluation, at 30 months post-transplant, at diagnosis of new relapse, and at evaluation of a tumor response, per Section **10.9**. If apheresis cannot be performed safely or comfortably or if it would pose significant treatment delay or inconvenience to the Subject, a large-volume blood draw may be substituted. Recipient-Subjects who will undergo apheresis will be seen in the CC/DTM/Dowling Apheresis Clinic for a venous access Assessment.

3.3.4.3.1 Isovolumetric Single-Pass apheresis (2L, CS-3000 or an equivalent machine).

3.3.4.3.1.1 Apheresis procedures will use Anticoagulant Citrate Dextrose Solution A (ACD-A), or heparin, per standard operating procedure of the NIH Department of Transfusion Medicine (DTM).

3.3.4.3.1.2 Apheresis product will be delivered to the ETIB Preclinical Core Lab (10/12C216), where it will be divided into aliquots and cryopreserved.

3.3.4.3.2 Immediately following apheresis (not required for large-volume blood draws), blood samples will be drawn for research:

3.3.4.3.2.1 2 red-and-green CPT tubes will be delivered to the ETIB Preclinical Core Lab, Building 10, Room 12C216

3.3.4.3.2.2 A simultaneous CBC and diff will be performed.

3.3.4.4 Large-Volume Blood Draw (to substitute for apheresis, per Section **3.3.4.3**)

3.3.4.4.1 Up to 56 mL (7 Red-and-Green CPT 8 mL-tubes), not to exceed 1 mL/kg. Note: a reduced blood volume may be collected at the discretion of the PI/AI/Designee, e.g., if clinically indicated blood sampling and/or patient anemia warrant.

3.3.4.4.2 Delivered to ETIB Preclinical Core Lab (10/12C216)

3.3.4.5 Blood Sampling for Research
*Required to address secondary protocol research objectives

- At on-study and follow-up evaluations at the CC, per Section **10.9**
- 16 mL (two Red-and-Green CPT 8 mL tubes)
- Delivered to the ETIB Preclinical Core Lab, Building 10, Room 12C216 for processing, aliquoting, cryopreservation and distribution for studies

3.3.5 Recipient-Subject Clinical Updates

In the event that a Recipient-Subject is unable to return to the Clinical Center for a scheduled evaluation, a Brief Clinical Update will be obtained through phone or written contact with the Recipient-Subject/Designee and/or treating physician/Designee and recorded in CRIS. Data collection will include current care/status: cancer-directed therapy; palliative/hospice care only; deceased (date).

3.3.6 Multidisciplinary Conference Review

3.3.6.1 Following Initial Evaluation and Follow-up Evaluations for new protocol options, Recipient-Subjects with relapse will be presented at the Allotransplant Relapse Tumor Board for case discussion and recommendations for protocol and/or non-investigational treatment options.

3.3.6.2 Allotransplant Relapse Tumor Board is held on an ad-hoc basis in conjunction with the weekly ETIB Multidisciplinary Clinical Conference. The following disciplines participate:

- Transplant Oncology (NCI/ETIB, NCI/POB, NHLBI/HB), Radiology, NCI/Pathology, CC/DLM/Hematology, Disease-Specific Oncology, Radiation Oncology
- Additional representation from the following communities is encouraged: NCI Phase O/I Investigators, Infectious Disease, Pharmacy, Pain & Palliative Care, Complementary and Alternative Medicine, Clinical Trainees

3.3.6.3 Allotransplant Relapse Tumor Board discussions will address priorities for protocol options or non-investigational clinical options.

3.3.6.3.1 Recipient-Subjects with relapsed disease who are not currently eligible for ongoing or planned treatment protocols may remain on study while they receive routine care and therapy at home.

3.3.6.3.2 Tumor Board discussion summaries will be included in communications with referring physicians.

3.3.6.4 The Allotransplant Relapse Tumor Board will serve as a venue for continuing review and discussion of catalogued response data collected on Recipient-Subjects who received prior treatment for relapse and to inform management recommendations.

3.4 DONOR-SUBJECT EVALUATION FOR DONATION OF CLINICAL PRODUCTS

3.4.1 Donor Clinical Evaluation for Medical Clearance to Donate

In general, donors will be screened for suitability according to (and under) the recipient's primary treatment protocol, and cell collections will usually be performed under the recipient's treatment protocol.

In the unusual case that a Recipient-Subject enrolled on this study requires treatment with a donor cell product under this protocol, and the cells are collection for clinical administration under this study, the following screening evaluation will be performed prior to cell collection.

Unless otherwise specified, the following components of allotransplant donor evaluations must be performed within 28 days of each clinical cell product collection(s).

3.4.1.1 Donors Screened at the NIH/CC

- Donation-directed history and physical examination
- Clinical Laboratory Tests
- CBC with differential (must be repeated within 72 hours of collection), PT/PTT, and ABO typing (at initial CC evaluation only)
- Urinalysis
- Serum or urine β-HCG in females of childbearing potential (must be within 72 hours of collection)
- Chem-14 panel (must be within 72 hours of collection)
- Blood PCR for VNTR sequences of DNA mini-satellite regions for chimerism analyses of the Recipient-Subject recipient (initial CC evaluation only)
- Infection Screening Panels
- DTM Viral Marker (Transplant Donor Screening Panel). Current screening includes testing for infection with Hepatitis B and C Viruses (HBV, HCV); Human Immunodeficiency Virus (HIV 1/2), Human T-Lymphotrophic Virus (HTLV I/II), West Nile Virus (WNV) and *Trypanosoma cruzi*.
- Serologic testing for evidence of prior infection with the following organism, which influence clinical management of Recipient-Subjects: Cytomegalovirus (CMV), Adenovirus, Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV 1/2), *Toxoplasma gondii* and syphilis. Evidence of active infection with any of these agents will not exclude their study enrollment, nor will it exclude *a priori*, the Donor-Subject's ability to donate cells for clinical administration.
- Electrocardiogram

- Venous Access Assessment, Dowling Apheresis Clinic, CC
- Additional studies at PI/AI/Designee discretion, to determine safety of collection for the donor and of cell products for the recipient.

3.4.2 Cell Donation

Consenting related allograft Donor-Subjects who are evaluated at the CC will undergo steady-state apheresis for lymphocyte collection for 1) treatment for their respective allotransplant recipient and 2) research, i.e., control samples for Recipient-Subject research studies. Note: research-only donations are optional.

Research lymphocyte collections will generally be obtained at the time of clinical lymphocyte apheresis. Donors who are not providing a clinical product who opt to provide lymphocytes for research will donate through a steady-state collection, i.e., without filgrastim.

3.4.2.1 In donors who are scheduled for stem-cell mobilized collection or bone marrow stem cell harvests harvest (under their recipient's primary transplant protocol), donation of research lymphocytes will be obtained via blood sample prior to initiation of mobilization therapy or in conjunction with their marrow harvest procedure.

3.4.2.2 An aliquot of the clinical cell collection may be donated for research use under this protocol, as detailed in Section **3.4.2.4.4** provided its use is permitted under the primary research trial and that the quantity of cells that may be donated are approved by that study's PI.

3.4.2.3 Donor cell collections for therapeutic use may be either steady-state or after stem-cell mobilization with filgrastim, depending on therapeutic requirements of the Recipient-Subject, provided standard DTM donation criteria are met and the Donor-Subject signs the procedural consent at time of collection. Filgrastim mobilization is voluntary, and willingness to undergo mobilized collection will not affect study participation. Donor-Subjects will only be requested to undergo a mobilized collection when their Recipient-Subject has a clinical indication for stem cells, e.g., bone marrow failure due to infection, medications, etc. or a clinical indication for medical therapy that is anticipated to suppress bone marrow function which could not be safely administered without ability to provide stem cell support. Procedure for mobilized collections is detailed in Section **10.5**. The PI/LAI/Designee will determine whether need for a mobilized collection is anticipated following Recipient-Subject Evaluation.

3.4.2.4 Steady-state lymphocyte collections for clinical use will involve a 5-10 liter apheresis procedure (CS-3000 or an equivalent machine).

3.4.2.4.1 Apheresis procedures will use Anticoagulant Citrate Dextrose Solution A (ACD-A), or heparin, per standard operating procedure of the NIH Department of Transfusion Medicine (DTM).

3.4.2.4.2 The concentration of $CD3^+$ cells in the apheresis product will be determined by flow cytometry, and the number of CD3+ cells in each cryopreserved bag calculated.

3.4.2.4.3 From Donor-Subjects consented to donate cells for clinical use, a minimum of 1×10^8 CD3+ cells/kg (recipient weight), will be cryopreserved for clinical use according to standard operating procedure of the NIH DTM, in the following aliquots (CD3+

cells/kg recipient weight): 5 x 10^6 (2); 1 x 10^7 (2); 2 x 10^7 (1); 5 x 10^7 (1). Different collection targets, e.g., CD34+ cell collections, aliquot sizes or cell processing, e.g., CD34+ cell selected products, may be requested following Recipient-Subject evaluation, depending on treatment protocol requirements or clinical indications.

3.4.2.4.4 From Donor-Subjects consented to donate cells for research use, a portion of the clinical apheresis product or bone marrow harvest product, up to 1 x 10^8 cells, will be delivered fresh to the ETIB Preclinical Core Lab, Building 10, Room 12C216, to be divided and stored for research studies, Section **5.1**. Cells collected under anther CC study (apheresis of peripheral cells and/or cells collected with bone marrow harvest) may be stored for research under this protocol provided the donor is enrolled on this study and has consented for research, and the primary protocol PI/LAI/designee approves.

3.4.2.4.5 In the unusual case in which Donor-Subjects is eligible/consented to donate for research only, collections will involve a 2-liter apheresis procedure or a large-volume blood draw.

3.4.2.5 Immediately following apheresis, blood samples will be drawn for research:

- Red-and-Green CPT tubes will be delivered to the ETIB Preclinical Core Lab, Building 10, Room 12C216
- A simultaneous CBC and diff will be performed.

3.4.3 Donor-Subject Blood Sampling for Research

Following study enrollment but not during mobilization or peripheral blood stem cell collection, 16 mL of blood will be drawn for research (two Red-and-Green CPT 8 mL tubes) and delivered to the ETIB Preclinical Core Lab, Building 10, Room 12C216 for processing, aliquoting, cryopreservation and distribution for studies.

3.4.4 Clinical Donation Exclusions

3.4.4.1 Hypertension that is not controlled by medication, stroke, or severe heart disease (donors with symptomatic angina will be excluded). Donor-Subjects with a history of coronary artery bypass grafting or angioplasty who are symptom-free may receive a cardiology evaluation and be considered on a case-by-case basis.

3.4.4.2 Pregnancy: Additionally, Donor-Subjects of childbearing potential must be willing to use an effective method of contraception (Section **4.8**) until after completion of apheresis. Potential fetal risks of apheresis, with or without use of exogenous hematopoietic growth factors, are unknown. Lactating donors will be eligible provided they are willing to express and discard milk that is produced while receiving exogenous hematopoietic growth factors. The quantity of excretion into breast milk during receipt of exogenous growth factors is unknown and its safety has not been evaluated in breast-fed infants.

3.4.4.3 History of prior malignancy: Donor-Subjects with a history of prior malignancy will not be able to donate cells for therapeutic administration. Exceptions may be made for individuals who have a history of low-risk cancers that have been fully resected (e.g., nonmelanomatous skin cancers, carcinoma-in-situ, etc.) and/or cancer survivors who

have undergone potentially curative therapy and have had no evidence of that disease for at least five years; these individuals may be considered for therapeutic cell donation on a case-by-case basis. Donor-Subjects who are not able to donate cells for therapeutic administration may participate in cell collections intended for research.

3.4.4.4 Anemia (Hb < 11 gm/dl) or thrombocytopenia (platelets < 100,000/µl): However, potential donors with Hb levels < 11 gm/dl due to iron deficiency will be eligible as long as the donor is initiated on iron replacement therapy. The NIH Clinical Center, Department of Transfusion Medicine will determine the appropriateness of anemic individuals as donors. Anemic donors who are not able to donate cells for therapeutic administration may participate in cell collections intended for research.

3.4.5 Return for Donation of Additional Therapeutic Donor Products

Donor-Subjects may undergo additional clinical evaluation (Section **3.4.1.1**) and collection of clinical products.

For additional collections, to facilitate scheduling and minimize disruption and inconvenience to the donor, e.g., when a mobilized collection would require several days of filgrastim administration between the time of assessment and cell collection, at the discretion of the PI/AI/Designee, the clinical evaluation for additional collections may be performed by the Donor-Subject's local primary care physician.

Donor products will be processed and stored by DTM per standard procedure, for Recipient-Subject clinical use on this or any CC Protocol.

These additional clinical product collections may be either steady state or after stem-cell mobilization.

3.4.6 NMDP Collections for URD Recipient-Subject Clinical Products

This protocol permits collection of unrelated donor cell products through the NMDP for clinical administration on this or other NCI treatment protocols. At the time it is determined that an URD Recipient-Subject has potential protocol options or clinical need for a therapeutic donor cell product, the donor will be screened at an NMDP Center according to NMDP standards. When a potentially eligible recipient of an unrelated donor product from an NMDP Center is identified, the recipient will complete an NMDP search transfer request to allow NIH NMDP staff to contact the NMDP Coordinating Center, who will, in turn, contact the donor's prior Donor Center. The NMDP Policy for Subsequent Donation Requests will be followed and the appropriate forms (Subsequent Donation Request Form and Therapeutic T Cell Collection Prescription (see Section **10.5**) will be submitted as required.

3.5 OFF-STUDY CRITERIA

3.5.1 Recipient-Subjects may be taken off study for any of the following:

- Patient will not undergo planned allotransplant procedure
- Withdrawal of consent
- Patient death
- Per principal investigator's discretion
- Closure of the protocol

- Physician determination that continued follow up has become burdensome to the Recipient-Subject or is no longer necessary to meet the objectives of this protocol
- Lost to Follow-Up
- PI decision to end this study
- Recipient subject becomes decisionally impaired

3.5.2 Donor-Subjects may be taken off study for any of the following:

- Their Recipient-Subject is taken off study
- Withdrawal of consent
- Donor-Subject Death
- Closure of the protocol
- Donor subject becomes decisionally impaired
- Lost to Follow-Up

3.5.3 Off Study Procedure

Authorized personnel must notify the Central Registration Office when a Recipient-Subject is taken off study. An off-study 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 (HOIS) <ncicentralregistration-l@mail.nih.gov>.

4 SUPPORTIVE CARE

In general, supportive therapy will be provided under the Subject's primary treatment protocol.

4.1 DONOR CELL PRODUCT SUPPORT

Recipient-Subjects who require donor cell product support (e.g., for mixed donor chimerism, tumor progression, stem cell support for bone marrow failure) may receive donor cell infusions on this protocol, provided that a source of their donor cells is available to CC-DTM.

No investigational cell products will be used on this study.

Recipient-Subjects receiving a donor cell product will be asked to sign a separate consent outlining the therapy, associated risks, and availability of receiving the same treatment elsewhere, outside of a research protocol.

Clinical monitoring requirements will follow standard clinical practice, and monitoring by referring and/or local physicians will be permitted.

4.2 CANCER TREATMENT

Adult Recipient-Subjects who may otherwise be eligible for enrollment on an open Clinical Center Treatment Protocol but who require disease control or stabilization for which a non-investigational agent or modality is available may receive such therapy on this protocol.

Permitted therapies include but are not limited to radiation, surgical procedures, chemotherapy, targeted antitumor agents, and/or immunotherapy. No investigational agents or modalities will be used on this study. Off-label use of approved agents will be supported by peer-reviewed reports of efficacy in the type of malignancy being treated.

Recipient-Subjects receiving a treatment will be counseled by the treating clinician (PI/AI) prior to initiation of cancer therapy, outlining the therapy, associated risks, and availability of receiving the same treatment outside the NIH/Clinical Center. The ASCO chemotherapy consent template is provided as an example in **Appendix F**.

Clinical monitoring will follow standard clinical practice, with monitoring by referring and/or local physicians permitted.

Clinical decision-making based on response to cancer therapy will follow disease-specific standard practice, following established guidelines maintained by the National Comprehensive Cancer Network (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

4.3 Infection Prophylaxis

Administration of antimicrobial agents will follow the NIH Transplant Consortium Guidelines http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml

4.4 Blood Product Support

Administration of blood products will follow the NIH Transplant Consortium Guidelines http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml

All red blood cells, platelets, and granulocyte transfusions will be irradiated.

Leucocyte filters will be utilized for all red cell and platelet transfusions to decrease sensitization to transfused leukocytes and decrease the risk of CMV infection.

Note: Donor cell therapy products, *e.g.,* hematopoietic stem cells and donor lymphocytes, should NOT undergo irradiation or leucofiltration.

4.5 Anti-emetics

Anti-emetics will follow Clinical Center Guidelines, NIH Transplant Consortium Guidelines (http://internal.cc.nih.gov/formulary/ccfs/emetic.htm).

4.6 Hematopoietic Growth Factor Support

Growth factor support may be given for the treatment of cytopenias at the clinical discretion of the PA/LAI/Designee.

4.7 Graft-versus-Host Disease Management

Subjects may be continued on the GVHD medication they were on at the time of enrollment. Additional GVHD prophylaxis may be added prior to treatment if there is a high risk of GVHD. Choice of prophylaxis will be individualized, based on review of GVHD history, prior immune suppression and potential drug interactions.

Evaluation: New diagnosis of GVHD, including a new site of involvement, will be supported by evaluation of tissue biopsy. Biopsy may be omitted at the discretion of the PI/LAI/Designee; if it is determined that biopsy would unnecessarily compromise the health or well-being of the Recipient-Subject. Standard clinical criteria will be used to establish the diagnosis, grade and stage of GVHD (Sections **10.1** and **10.2**).

GVHD will usually be managed by the active treating physician, e.g., the treatment protocol's PI, the Recipient-Subjects referring physician, etc. If GVHD develops during cancer treatment

on this protocol, the PI/LAI/Designee will be responsible for management, in consultation with referring physician and/or future protocol PI. In general, treatment of Acute GHVD will follow the NIH Transplant Consortium Guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml). As there are no standard guidelines for treating chronic GVHD, choice of therapy will be supported by evaluation in the NCI Chronic GVHD Clinic.

4.8 CONTRACEPTION

Donor-subjects of childbearing potential must use an effective form of contraception until completion of the apheresis procedure.

Recipient-Subjects of childbearing potential who receive cancer treatment on this protocol must agree to use an effective form of contraception until recovery from effects of treatment. Pregnancy testing will be performed at all scheduled protocol evaluations (Section **3.2**) and as clinically indicated, e.g., prior to initiation of cancer therapy, radiologic and/or invasive procedures.

5 BIOSPECIMEN COLLECTION

5.1 RECIPIENT-SUBJECT BLOOD AND TISSUE COLLECTION REQUIREMENTS

Tissue sampling for research is permitted as outlined in Section **3.3.4** and Section **10.9**. Sampling and collection requirements and restrictions are detailed below. Blood and apheresis samples from consenting Donor-Subjects will be used as controls for research studies, when available. Research studies conducted on these samples are described below.

5.1.1 Sampling Restrictions for Research Purposes and Monitoring Procedures

5.1.1.1 Subjects may be enrolled on multiple research protocols simultaneously. ETIB Research Nurses will review the research tissue sampling and radiologic study requirements for protocols on which subjects are enrolled. Coordination of protocol time points is attempted when possible in order to minimize sample collections.

5.1.1.2 A research blood log is used to track research sample volumes, to ensure that sampling does not exceed guidelines per MAS Policy 95-9 (currently, for Adult Subjects, the smaller of 10.5 mL/kg or 550 mL per 8-week period) unless an IRB-approved exception is in place.

5.1.1.3 Tumor biopsies are permitted at the initial evaluation, at subsequent evaluations: (1) at the time of new relapse or progression; (2) at the time of treatment response; and/or (3) need to assess treatment protocol options, and/or for clinical indication. Therefore it is anticipated that research biopsies will be infrequent events; in the unlikely event that a Recipient-Subject requires frequent assessments within the guidelines stated above, requests for research tumor biopsies will be limited to no more than two in any one month and core- and fine- needle biopsies limited to three ‘passes’ per site.

5.1.1.4 Bone marrow biopsies are permitted at the initial evaluation and subsequent evaluations at the time of treatment response or need to assess treatment protocol options; all marrow specimens will be submitted for diagnostic evaluation. It is anticipated that bone marrows collected primarily for research (e.g., evaluation of treatment response)

and will be infrequent; further, the number of bone marrow collections primarily for research (e.g., assessment of a treatment response when bone marrow has not had evidence of prior cancer infiltration) will be limited to no more than one bone marrow biopsy in any one month.

5.1.1.5 When possible, the subject's protocol calendar will be adjusted to avoid exceeding the limits for research blood draws. If a scheduled research blood draw would exceed the guidelines, the protocol PI is notified and research sampling prioritized to keep the research blood volume in accordance with MAS Policy 95-9.

5.1.2 Tissue Allocation Procedures

5.1.2.1 All tissue biopsies will be sent for clinical examination and also used for research as outlined in Section **5.2**. Specimens will be divided, with portions going to the Laboratory of Pathology and ETIB Preclinical Core Lab, Building 10, Room 12C216.

5.1.2.2 Tissue samples obtained on other Clinical Center protocols may be used for the tissue acquisitions listed below, if available with the protocol's PI approval.

5.1.3 Tissue Biopsy Procedures and Consents

The following pertains to all biopsy procedures, including non-blood fluid sampling, e.g., tumor biopsy, bone marrow aspiration and biopsy, tissue biopsy for diagnosis (i.e., GVHD), lumbar puncture for CSF evaluation and/or abnormal fluid collection samples (i.e., effusions, ascites, etc.) All tissue specimens will be submitted for clinical evaluation; as tissue permits, specimens will be used for research, as outlined in Section **5.2.**

Use of samples in excess of clinical requirements and of data generated from samples acquired for treatment protocols (if permitted by treatment protocol PI) is allowed on this study. The research questions identified in secondary objectives can then be analyzed with the power of prospective data collection while minimizing the imposition of additional procedures, risk and time commitments beyond those required of treatment protocols.

Unless clinically indicated, biopsies for research will be obtained only if the procedure would pose no more than minimal risk. For example, research biopsies would be obtained only if they are superficial or extracavitary.

For clinically indicated biopsies, e.g., at the initial evaluation (in subjects enrolled pre-Allotransplantation) and at the first diagnosis of relapse (when applicable), the preferred biopsies will be excisional biopsies, if feasible to perform with minimal risk.

- The appropriate surgical service performs excisional biopsies after review of the Recipient-Subjects' clinical status and tissue accessibility.
- At other time points, site and method of biopsies will be based on clinical evaluation by the performing service (e.g., surgery, interventional radiology, etc.) and the decision will be determined by the safest approach.
- Interventional Radiology performs needle biopsies under local anesthesia, and (in adults), with sedation as required. When feasible and with no more than minimal additional risk, needle biopsies will include two sites within a lesion (i.e., two "passes") to decrease sampling error.

Specific consent for planned procedures and sedation requirements will be obtained at the time of the biopsy.

5.2 CORRELATIVE STUDIES ON RESEARCH SAMPLES

As sample availability permits, investigation of the biologic features of relapse will include characterization of tumor and immunologic features of those who relapse after allotransplant over time, with comparisons of individual tissues obtained prior to allotransplant and following treatment response. Immunologic studies will include comparisons with individuals in remission and with donors.

5.2.1 Malignant Tissue Investigations (tumor biopsies, malignant fluid collections, involved bone marrow)

Characterize immune cell populations and tumor microenvironment in sites of active malignancy (active relapse) and prior disease (remission, e.g., lymph nodes, marrow) after allotransplant with respect to identification and quantification of cell populations, origin (donor/recipient), phenotype (*e.g.,* naïve/memory; effector/regulatory) and function (*e.g.,* cytokine profile, tumor reactivity) *e.g.*:

- Quantitative, phenotypic and chimerism analyses of TIL populations
- Compare gene expression of tumor tissue before and after treatment response and of residual tissue from those in remission.
- As sample availability permits, samples may be used for preclinical development of cell therapies for persistent malignancy after allotransplant.

5.2.2 Benign Tissue Immunologic Investigations

5.2.2.1 Peripheral Blood

Planned studies include characterization of lymphocyte population subsets and plasma cytokines in Recipient-Subjects with and without relapse, with Donor-Subject controls.

5.2.2.2 Bone Marrow: ETIB: Characterize immune cell populations in individuals with relapse after allotransplant.

- Planned studies include identification and quantification of cell populations, phenotype (e.g., T cell subset analysis: naïve/memory; effector/regulatory) and function (cytokine profile, tumor reactivity, senescence), and origin (chimerism).
- As sample availability permits, samples may be used for preclinical development of cell therapies for persistent malignancy after allotransplant.

5.2.3 Additional Studies

The studies listed in this protocol consist of the current primary focus of our research. Blood and tissue specimens collected in the course of this research project may be cryopreserved and used in the future to investigate new scientific questions related to this study. However, this research would only be done if the risks of the new questions were covered in the consent document. If new risks are associated with the research (e.g. analysis of germ line genetic mutations) protocol amendment will be required and informed consent will be obtained from all research subjects to whom these new studies and risks pertain. Anonymized samples may be provided to investigators and laboratories in support of the objectives of this study, i.e., when new or

promising additional techniques and/or technologies become available that may provide insight into the biology of this patient population. Prior to sample distribution, storage facility staff will remove all Recipient-Subject and Donor-Subject identifiers and create anonymized aliquots of stored samples. Otherwise, an amendment would be submitted to the NCI IRB to include additional testing of subject-linked samples.

For all tissues obtained from study subjects, planned in-vitro studies fall under the general category of "Immune Characterization." They will focus on characterization of the quantitative, phenotypic and functional properties of distinct cell subsets or tissue/tumor characteristics that may influence an immune response. In-vitro assays may include immunohistochemistry, confocal microscopy, flow cytometry, cell proliferation, cytokine production, gene expression, and cytotoxicity. However, the specific assays to be used in the on-going data analyses are subject to be modified, deleted or replaced with evolution of technology and knowledge in the field during the course of the study, without constituting a change in research aims. No change in research subject risk is foreseen from the knowledge acquired from study data. However, if in the judgment of the PI, this should change in the course of the study or if a significant departure from this "Immune Characterization" is contemplated based on accumulated data, then the NCI IRB will be informed to evaluate the eventual need for modification in subject consent process or for re-contacting subjects.

5.3 SAMPLE STORAGE FOR SAMPLES OBTAINED ON OTHER PROTOCOLS

Subjects who received a transplant or cell therapy donors on any ETIB affiliated trial at the National Cancer Institute may have their samples obtained under those trials transferred to this protocol if they are also enrolled on this protocol. These studies include (but are not limited to):07C0064. Upon termination of the above protocols, available stored specimens obtained in each of the protocols listed above will be transferred to this protocol for future research use.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

Blood and tissue collected during the course of this study will follow NIH guidelines for the research use of human samples. Research samples will initially be sent to the ETIB Support Service using established procedures for sample storage and tracking outlined in Section **10.7**.

Samples will be ordered and tracked through the CRIS Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss.

If the patient withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI. Any new use of the samples, specimens, or data will require prospective IRB review and approval or an appropriate exemption from IRB review by OSHRP.

5.5 PROTOCOL COMPLETION/SAMPLE DESTRUCTION

At the termination of this protocol, if additional studies are to be performed on any human subject samples retaining patient identifiers obtained during the conduct of this trial, a Request to Conduct Research for Stored Human Samples Specimens, or Data Collected in a Terminated NCI-IRB Protocol will be submitted. Otherwise, specimens will be disposed of in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland. Any new uses of human subject samples collected during the course of this trial must be reviewed and approved by the NCI IRB. Any loss or unintentional destruction of the samples will be reported 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 human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary 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 breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Data will be prospectively collected and entered within 10 business days into LabMatrix. Data will include but will not be limited to demographics prior history, disease status, laboratory and clinical evaluations, complications, treatment and response data. For quality assurance, the research nurse will verify at least 20% of each subject's enrollment data entered into LabMatrix on an ongoing basis; data questions and/or discrepancies will be reviewed by the PI/AI on a monthly basis. Documentation of data verification will be tracked in LabMatrix. There is no experimental therapy being administered on this protocol, however, some procedures may be performed primarily for research purposes. Therefore unexpected grade 3 events and all grade 4

and 5 adverse events that are at least possibly related to the research will be collected and recorded into LabMatrix.

Only events that meet the definition of an unanticipated problem or a grade 5 event will be recorded if the event occurs as a result of standard treatments that patients may receive on this protocol.

A safety evaluation will be a component of all clinical assessments following any donor cell product or cancer therapies administered on this study. The safety evaluation will and will include, at a minimum, an interim history and physical examination, Performance Status, CBC with differential and Chem-14, and Acute and Chronic GVHD Staging Evaluation (Sections **10.1** and **10.2**).

Data from subjects participating in NCI clinical treatment protocols may also be collected for correlation with research study results. All data will be coded with a patient identification number, and linked to samples by that identification number in Labmatrix. Access to personally identifiable information (PII) is limited to the PI and study personnel who interact directly with the patient and their samples.

The key for assignment of patient code identification numbers with the personal identifiers will be stored in a secure database. This key will not be shared with other investigators. Investigators conducting the individual sample testing will only have access to coded identification numbers and coded patient information (i.e. treatment responses, diagnoses, pathology information)

6.1.1 Data collection will include (see Section **10.4**)

- Current care/status: cancer-directed therapy; palliative/hospice care only; deceased (date)
- Interim therapy: response, indication for discontinuation

6.1.2 Post-Transplant Health Maintenance Monitoring

At each scheduled time point (Section **10.9**), Recipient-Subject records will be assessed to determine what, if any procedures or interventions are necessary for standard post-transplant health maintenance.

Post-transplant health maintenance requirements will follow the National Marrow Donor Program Survival Guidelines.[101] Guidelines are kept current on the NMDP website: http://bethematch.org/Physicians/Post-Transplant_Care/Post-Transplant_Care.aspx. For reference, the current guidelines are included in Appendices I and J (Sections **10.9** and **10.10**).

A Health Maintenance Record will be maintained in the Recipient-Subject's Electronic Medical Record, updated at each study time-point evaluation.

The Health Maintenance Record, including current recommended procedures/interventions, will be provided to Recipient-Subjects, their transplant study team, and their home medical providers at each time-point evaluation.

6.2 TOXICITY CRITERIA

This is a natural history and tissue acquisition study, not a therapeutic trial, and therefore no unexpected adverse events are expected. In the unlikely event that an adverse event occurs

during the sample collection or a procedure, the CTCAE criteria below will be used for grading such events.

A safety evaluation will be a component of all clinical assessments following any donor cell product or cancer therapies administered on this study. The safety evaluation will and will include, at a minimum, an interim history and physical examination, Performance Status, CBC with differential and Chem-14, and Acute and Chronic GVHD Staging Evaluation (see sections **10.1** and **10.2**).

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).

6.3 STATISTICAL CONSIDERATIONS

This is a broad study primarily intended to serve as a platform for evaluating individuals with cancer relapse after allotransplant, in order to expedite treatment protocol screening and prioritize options; it will also serve as a mechanism to gather data on the natural history of relapse across multiple diseases and, by including individuals who were transplanted at other institutions, across multiple clinical transplant approaches. Amendment B provides for enrollment of Individuals prior to allotransplantation. These subjects will be subsequently assigned to the Relapse or Remission Cohort by Day 100, as appropriate, permitting comparisons of samples collected pre-transplant with samples collected post-allotransplant. The objectives are mainly broadly stated and describe the range but not necessarily the limits of explorations to be undertaken.

The primary objective of this trial is to provide a mechanism for systematic, comprehensive evaluation of individuals with relapsed hematologic malignancy after allotransplant and, if available, their donors, to streamline identification of protocol options, enrollment and initiation of therapy.

The secondary objectives of this protocol include but are not limited to the following:

- To study the clinical features of relapse after allotransplant.
- To study biologic features of relapse after allotransplant.
- To facilitate post-allotransplant clinical care for individuals who received allotransplant on CC protocols, as a bridge between treatment protocols.
- To catalogue regimens used to treat relapse, vis-à-vis safety and efficacy, and develop consensus guidelines for clinical management of relapse after allotransplant.

Recipient-Subjects will provide data from a minimum of one comprehensive clinical and laboratory assessment and prospective data on outcome, which will be part of an overall descriptive characterization of individuals who do or do not have disease progression after allotransplant.

Many Recipient-Subjects with relapse will provide prospectively collected data on the evolution of clinical and biological parameters that distinguish relapse treatment response and/or clinical outcome.

Recipient-Subjects in remission will provide data toward the overall descriptive characterization described above. As these Recipient-Subjects are at risk for relapse, they will also provide prospectively collected data on the evolution of clinical and biological parameters that distinguish sustained remission from relapse.

6.3.1 Planned Analyses

As indicated above, this study will provide a platform for systematic assessment of potential protocol eligibility. Clinical data that are collected will contribute to largely descriptive analyses, and will address specific questions relating laboratory data and clinical outcomes to the extent possible.

Comparative assessments will be possible between Recipient-Subjects with relapse and Recipient-Subjects in remission; Recipient-Subjects with relapse before and after a therapeutic response; in many cases, related Donor-Subject samples will be available as "normal" controls. Unfortunately, some Recipient-Subjects in remission will experience relapse after initial evaluation, permitting prospective comparisons of clinical parameters in Recipient-Subjects before and after relapse.

6.3.1.1 Clinical Features of Relapse

6.3.1.1.1 Survey of Clinical Features of Relapse

Hypothesis: Clinical behavior of cancer relapse after allotransplant differs from cancer behavior prior to treatment, affecting management, e.g., monitoring requirements and treatment options.

Planned Analyses: Descriptive evaluation, including:

1. Tumor Characteristics (Histology, Patterns of Relapse)
2. Transplant Characteristics (Conditioning, Donor, Stem Cells, Graft Prophylaxis)
3. Post-transplant Clinical Characteristics (Engraftment, GVHD/Immune Suppression, Infection)
4. Natural History of Relapse (Survival)
   a. Effect of time to progression after allotransplant on survival
   b. Effect of treatment response on survival

6.3.1.1.2 Evaluate Clinical Immunity and Inflammation and Relapse Risk

Hypotheses:

1. Clinical blood markers of inflammation will be normal or low in Recipient-Subjects with relapse; low or falling levels may herald imminent relapse.
2. The incidence of relapse is increased in individuals with poor recovery of clinical immunity after allotransplant.
3. Individuals with relapse who demonstrate recovery of clinical immunity have a selective absence of tumor immune response (GVL), identifying cancers that are unlikely to respond to DLI-based therapy.

Planned Analyses: Comparisons between Recipient-Subjects with relapse (before and after treatment response) and Recipient-Subjects in remission (before and after relapse); as numbers permit, analyses may include comparisons within histologic diagnoses, and use of multiple regression analysis**.**

1. Markers of Inflammation (Section **3.3.3.5**): Compare common clinical laboratory markers to look for a "relapse inflammatory signature" that would identify increased risk of relapse and/or suggest early relapse.
2. Clinical Immune Function: Compare functional immune status (*e.g.*, serologies for vaccine response, prior infections; anergy skin testing) to assess utility in identification of relapse risk and/or heralding early relapse after allotransplant.

6.3.1.1.3 Evaluate Clinical Features of Relapse and Outcome

Hypothesis: Patterns of tumor behavior suggestive of a post-treatment effect after allotransplant identify GVL activity and predict better treatment response and survival. The following features can be used to identify a GVL effect:

1. Relapse after Day 100 or following initiation of systemic treatment for GVHD
2. Prior tumor response to withdrawal of GVHD prophylaxis and/or DLI
3. Limited/novel sites of recurrence
4. Slower tumor progression than prior to allotransplant
5. New or renewed sensitivity to cancer therapies after allotransplant

Planned Analyses: Prospective comparisons of treatment responses and survival in Recipient-Subjects with relapse with or without a history of one or more of the features suggestive of a GVL effect.

6.3.1.2 Biologic Features of Relapse

The specific aims of the proposed studies of the biology of relapse are to identify factors in patients with relapsing or persistent disease after allogeneic transplant which may support earlier diagnosis of relapse, be prognostic of outcome or suggest new approaches to treatment.

Planned Analyses (as tissue availability permits)

1. Cancer Tissue Comparisons:
   a. Between Recipient-Subjects with relapse and Recipient-Subjects whose cancer is responding after allotransplant
   b. Before and after a cancer treatment response
   c. Before and after relapse
2. Blood Comparisons:
   a. Between Recipient-Subjects with relapse and in remission at parallel time points (six, twelve and 24-months post-transplant)
   b. Before and after a cancer treatment response. (Recipient-Subjects with relapse)
   c. Before and after relapse
   d. As numbers permit, comparisons may include "normalization" of data with respect Donor-Subject values.
3. Bone Marrow: Analyses of sample data will include comparisons:
   a. Between Recipient-Subjects with relapse and Recipient-Subjects in remission.
   b. Before and after a relapse treatment response.

c. As numbers permit, comparison of samples over time (e.g., from those for whom repeat marrow evaluations are required for staging at follow-up)
d. Before and after relapse in Recipient-Subjects initially evaluated in remission.

6.3.1.3 Post-Transplant Clinical Care after Relapse

Safety and efficacy data will be recorded on all Recipient-Subjects who receive cancer therapy on this protocol. This data will contribute to the descriptive analyses planned for the Secondary Objective: To catalogue regimens used to treat relapse, vis-à-vis safety and efficacy for clinical management of relapse after allotransplant.

6.3.1.4 Catalogue of Relapse Treatments

Data on therapies received, responses and major toxicities will be collected at CC evaluations and semi-annual updates. These retrospective data will be used to compile a catalogue of disease-specific regimens. This catalogue will be used to inform the development of Post-Transplant Relapse Consortium[102] trials evaluating the management of relapse after allotransplant. Additionally, the catalogue may be surveyed, as numbers permit, to address specific questions, e.g.:

1. Is regimen-specific sensitivity restored after allotransplant
2. Are there regimens that appear to have higher response rates than others?
3. Are their regimens or agents that appear to have significantly increased toxicity after allotransplant?
   a. GVHD
   b. Bone marrow suppression/cytopenias

6.3.2 Sample Size Requirements

This is intended to be a descriptive and exploratory study without absolute formal requirements regarding the number of subjects to be enrolled. Analyses performed will be largely descriptive, and, when hypothesis-generating, will likely be performed using non-parametric methods and reported without formal adjustment for multiple comparisons.

The number of patients who are transplanted at the CC each year will be the primary determinant of enrollment onto this trial. Based on current enrollment, approximately 100 patients per year will undergo allotransplant at NCI for hematologic malignancies. About two-thirds of these patients will have related donors who may be available for enrollment. (Unrelated donors, including cord blood donors, are anonymous and not available for enrollment.) From among these, 20 – 50%, depending on diagnosis and transplant characteristics, will have disease relapse. Based on accrual patterns onto a study of the natural history of Chronic Graft-vs.-Host Disease, initial accrual from outside institutions may be minimal during the first year, but will likely increase over time.

Each year, on average, approximately 50 NCI patients, 20 non-NCI patients, and 30 donors would be expected to enroll onto this protocol. It is expected that up to half of the patients will have relapse at the time of enrollment and, conservatively, one-third of the Remission Group will subsequently relapse. In order to limit the study to a 5-year period of enrollment, and no more than 5 years of additional follow-up, the accrual ceiling will be set at 500 total subjects (350 Recipient-Subjects and 150 Donor-Subjects).

As a general guideline for sample sizes in order to address scientific questions, formal comparisons between two groups will not be performed unless 30-40 total individuals in both groups are available for a specific comparison (to permit a given comparison to have approximately 80% power for a test with an effect size of 1.0 and a 0.05 two-sided alpha level). For example, in a comparison of clinical and biological parameters between Recipient-Subjects with relapse who do and do not also have GVHD, analysis of 17 Recipient-Subjects with GVHD and 17 Recipient-Subjects without GVHD relapse would fit this definition.

For evaluation of changes from baseline in individual Recipient-Subjects, e.g., relapse in those initially in remission, observations from at least 10-20 individuals will have to be available for a specific endpoint in order to allow for a paired test with at least 80% power for an effect size of 1.0 and a 0.05 two-sided alpha level. Larger numbers of subjects in a group may be analyzed if felt to be desirable by the study statistician. If possible, planned analyses will be performed separately for Recipient-Subjects who received treatments directed at their disease and for Recipient-Subjects who did not. Analyses will all be interpreted as hypothesis-generating and results will be presented without formal adjustment for multiple comparisons. It is hoped that the information learned will provide at least the frequencies of the manifestations evaluated, and their change over time. As very little published data exists on clinical manifestations of persistent disease after allotransplant, knowledge of the frequencies will contribute to our understanding and ability to monitor for persistent disease after allotransplant.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 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 research procedures, whether or not the event is considered related to the research procedures 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 that occur in association with a study visit or procedure that is performed for/under this study, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed under this protocol until satisfactory resolution. AEs should be reported up to 30 days following the study-related procedure.

AEs that occur in association with a study visit and/or procedure on/under the primary treatment protocol will be reported and followed under that study and will therefore not be reported under this protocol.

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.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the research caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the research procedure and 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 the research.

7.1.3 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.

7.1.4 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.

7.1.5 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
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 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.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)

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

7.1.9 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

7.1.10 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 the 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.

7.2 NCI-IRB AND NCI CLINICAL DIRECTOR REPORTING

7.2.1 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.

7.2.2 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 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 and 2 events are not required to be reported.

7.3 DATA SAFETY AND MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. 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 HUMAN SUBJECT PROTECTIONS

8.1 RATIONALE FOR SUBJECT SELECTION

Allotransplant is considered standard of care for multiple types of cancer. Patients of all races, ages and genders undergo allotransplant and many experience recurrent or progressive disease after therapy. All individuals with hematologic malignancies who will be having or who have had allogeneic transplantation will be eligible for study on this trial. Efforts will be made to extend accrual to a representative population, but in a biology trial of this nature, it may be difficult if not impossible to achieve complete balance in this regard. The study will be listed on the NCI and NIH websites. In addition, related donors of allogeneic transplant recipients will be asked to participate in the evaluation and sampling procedures, and mobilized donation if required based on treatment recommendations.

8.2 PARTICIPATION OF CHILDREN

Children will not be enrolled in this study.

8.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. Patients who become incapacitated or cognitively impaired during the course of the study will come off study since there are no direct benefit to the subjects.

8.4 EVALUATION OF BENEFITS AND RISK/BENEFIT ANALYSIS

8.4.1 Recipient Subjects

A primary aim of this study is to provide a comprehensive screening assessment for relapse treatment studies. Subjects enrolled prior to allotransplant may benefit from seamless evaluation for treatment options at the time relapse is detected, without the added stress of reviewing a

relapse-oriented protocol. Recipient subjects with cancer relapse may benefit from comprehensive screening for potential treatment studies, which, through review of their cancer by the multidisciplinary Allotransplant Relapse Tumor Board, may provide information to prioritize among multiple treatment options and optimize chances of successful therapy. Comprehensive relapse treatment protocol screening may avoid delays or errors that result from evaluations that must be tailored to the standard NCI screening protocol. Further, this group of individuals may benefit from PI/AI/Tumor Board identification of non-investigational cancer treatment options. This may be particularly helpful to subjects who are not eligible for ongoing treatment studies. Recipient Subjects may also benefit from identification of previously undiagnosed medical conditions, treatment of which could result in improved health and/or wellbeing. New diagnoses are not infrequently identified during the extensive studies performed during a screening evaluation. These individuals may benefit from obtaining additional information and/or recommendation regarding their particular concerns or conditions through the "second opinion" function of a screening evaluation and/or obtaining consultations (either subject- or investigator-initiated, e.g., Nutrition, Pharmacy, Rehabilitation Medicine, Pain and Palliative Care). Recipient subjects who receive cancer treatment on this study may directly benefit by the multi-disciplinary approach to treatment and may receive direct benefit from the standard care therapy administered. This patient population has no curative options available for their advanced malignancies, and this protocol would allow treatment with standard cancer therapies as a bridge between protocol participations or to meet eligibility requirements. Finally, Recipient-Subjects may benefit from having the means to receive donor cell product support, which could facilitate protocol eligibility or permit treatment with standard medical therapy that could not be safely administered otherwise.

Recipient-Subjects who enroll at the time of their allotransplant and those who enroll while their cancer is in remission may benefit from additional clinical assessments, with identification of medical conditions, which, if treated, could result in improved health and/or wellbeing, or of early, treatable cancer recurrence. These individuals may receive an altruistic benefit from contributing to scientific understanding of cancer relapse, which could result in effective treatment options for others. Recipient-subjects whose cancer subsequently relapses may benefit from expedited evaluation and/or identification of investigational treatment options, as they would already be on study and have study baseline results for comparison.

8.4.2 Potential benefit

As outlined in this protocol, Recipient-Subjects with relapsed malignancy may receive direct benefit from receipt of expert-led disease-specific treatment guidelines and Donor-Subjects may receive psychological benefit from contributing to medical care designed to improve the health of the related Recipient-Subject and the knowledge they may help advance scientific knowledge about the treatment of cancer. Additionally, Recipient-Subjects may benefit from protocol monitoring to ensure that Post-Transplant Health Maintenance Guidelines are being followed.

Donor Subjects will receive a thorough medical assessment prior to clinical donation, and may benefit from identification of medical conditions that would respond to treatment and improve their health. Also, Donor-Subjects may receive an altruistic benefit from contributing to scientific understanding of cancer relapse that may result in effective treatment options. In the event that a donor's lymphocytes are used in therapy, Donor-Subjects may experience psychological benefit from the knowledge they have helped a family member.

8.4.3 Samples

Studies will only be performed on samples obtained as prescribed by medical care standards for patients with hematologic malignancies or, if solely for research through no more than minimal risk procedures. Subjects who enroll at the time of their allotransplant will have biopsies to confirm their diagnosis and permit research assessment of their cancers. These biopsy procedures may be performed if it is anticipated that they could incur no more than minimal risk. In all cases, research sample volume will be limited. Research samples from Recipient-Subjects will be obtained at the time of a regularly scheduled specimen collection (for clinical evaluation) and only if the additional sampling poses no more than minimal risk. In Recipient-Subjects, additional sampling may be performed (apheresis, blood draws or biopsy) on an optional basis and only when it poses no more than minimal risk. Thus, this research involves no more than minimal risk to subjects.

8.4.4 Apheresis

Consenting Donor-Subjects will undergo apheresis (with or without mobilization). Samples for research will only be retained with explicit consent. The potential risks of collecting cells by apheresis in this trial are as follows:

The most common side effects of apheresis are pain and bruising at IV sites.

During apheresis, mild side effects from citrate anticoagulant are common and include chills, numbness and tingling ("pins and needles"), anxiety, muscle cramps, and nausea. More serious side effects due to citrate-induced hypocalcemia are uncommon and include low blood pressure, seizures, weakness, and tetany. Citrate reactions rapidly resolve when the collection is slowed down or stopped. Prophylactic IV CaCl2 and MgSO4 infusions may be administered to Donor-Subjects deemed to be at high risk of citrate toxicity. Risks of parenteral calcium and magnesium include extravasation necrosis and cardiovascular effects including bradycardia and blood pressure changes. However, side effects are unlikely given the low rate of infusion and use of large bore catheters for apheresis.

Transient mild thrombocytopenia is common after apheresis, but bleeding is unlikely.

Dilutional anemia occurs during apheresis, but this is unlikely to be clinically significant.

8.4.5 Other risks

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

The potential risk of biopsy includes pain, bleeding and infection.

8.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The procedures involved in this protocol, with their attendant risks and discomforts, potential benefits, and alternatives will be carefully explained to the Recipient-Subjects. A signed, informed consent document will be obtained from the Recipient-Subjects by the Principal Investigator, an associate investigator or designee of this study, prior to entry on this study. If it is recommended that the Recipient-Subject receive therapeutic DLI, or other therapy on this study, a signed, informed consent document will be obtained from the Recipient-Subject prior to initiating any therapy. The consent document will outline the treatment regimen, Recipient-Subject requirements, and potential side effects/risk, and alternatives for the recommended

treatment. In addition, the Principal Investigator, or their designee will provide oral consent and will be available to answer all patient questions. A copy of the informed consent document will be retained by the Principal Investigator, and a copy of the informed consent will be given to the Recipient-Subject/Donor-Subject.

The procedures and risks involved in participating in this protocol will also be explained to Donor-Subjects. All Donor-Subjects are requested to consent to an initial apheresis procedure. Should future Recipient-Subject treatment recommendations include DLI, additional apheresis procedures will be optional.

8.5.1 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.

8.5.2 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, OSHRP 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.

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10 APPENDICES

10.1 APPENDIX A: GRADING OF GVHD

Clinical Grading of Acute GVHD[106]

	STAGE		
GRADE	**Skin**	**Liver**	**Gut**
0 (none)	0	0	0
I	+ to ++	0	0
II	+ to +++	+	+
III	++ to +++	++ to +++	++ to +++
IV	++ to ++++	++ to ++++	++ to ++++

Late-Acute GVHD

Late-acute GVHD will be defined as GVHD that presents with signs and symptoms typical of acute GVHD but presenting after Day 100 post-allotransplant. It will be graded and treated as acute GVHD.

Clinical Grading of Chronic GVHD (Appendix B, Chronic GVHD Score Sheet)[107]

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites).

Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD.

Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

10.2 APPENDIX B: GLOBAL SCORING OF CHRONIC GVHD[107]

10.2 APPENDIX B: GLOBAL SCORING OF CHRONIC GVHD[107]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: (Appendix H) **KPS ECOG LPS** ☐	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* Maculopapular rash Lichen planus-like features Papulosquamous lesions or ichthyosis Hyperpigmentation Hypopigmentation Keratosis pilaris Erythema Erythroderma Poikiloderma Sclerotic features Pruritus Hair involvement Nail involvement **% BSA involved** ☐	No Symptoms	**<**18% BSA with disease signs but **NO** sclerotic features	19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	>50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): >10 6-10 <5 Not done	No symptoms	Mild dry eye symptoms not affecting ADL (requiring eyedrops < 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	No symptoms	Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	Symptoms associated with mild to moderate weight loss (5-15%)	Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LIVER	Normal LFT	Elevated Bilirubin, AP*, AST or ALT <2 x ULN	Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	Bilirubin or enzymes >5 x ULN
LUNGS* **FEV1** ☐ **DLCO** ☐	No symptoms FEV1 ≥80% **OR** LFS=2	Mild symptoms (shortness of breath after climbing one flight of steps) FEV1 60-79% **OR** LFS 3-5	Moderate symptoms (shortness of breath after walking on flat ground) FEV1 40-59% **OR** LFS 6-9	Severe symptoms (shortness of breath at rest; requiring 0_2) FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	No symptoms	Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

*"AP may be elevated in growing children, and not reflective of liver dysfunction"

Other indicators, clinical manifestations or complications related to cGVHD (check all that apply and assign a score to its severity based on its functional impact (none – 0, mild – 1, moderate – 2, severe – 3):

___Esophageal stricture or web ___Pericardial Effusion ___Pleural Effusion(s)
___Ascites (serositis) ___Nephrotic syndrome ___Peripheral Neuropathy
___Myasthenia Gravis ___Cardiomyopathy ___Eosinophilia >500µl
___Polymyositis ___Cardiac conduction defects ___Coronary artery involvement
___Platelets <100,000/µl ___Progressive onset
___**OTHERS:**"

_____

_____

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites). Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

10.3 APPENDIX C: DISEASE-SPECIFIC STAGING

I. Staging Studies

a. Whole-body FDG-PET/CT scan (may be omitted at PI/LAI/Designee discretion, e.g., acute leukemia if in remission and no prior history of extramedullary disease)

b. CT scans of neck, chest, abdomen, and pelvis (may be omitted at PI/LAI/Designee discretion for acute leukemia, MDS/MPN and multiple myeloma)

c. CT or MRI scan of the head (may be omitted at PI/LAI/Designee discretion for acute leukemia, MDS/MPN and multiple myeloma)

d. Disease-specific special studies as detailed in the following tables, from published summaries of the NCI Workshop on the Biology, Prevention and Treatment of Relapse after Allogeneic HSCT.[17,108]

e. Multiple Myeloma[17]

- Serum - protein electrophoresis with M protein; immunofixation; quantitative immunoglobulins, serum free light chains
- Urine - 24h collection for protein excretion, protein electrophoresis and M protein
- Blood [redacted]2-microglobulin, C-Reactive Protein/High-Sensitivity
- Skeletal survey (omitted in those who undergo PET-CT (head-to-toe exam)
- Bone marrow for flow cytometry, cytogenetics, FISH, PCR for IgH gene rearrangement. (Some studies may be omitted at PI/LAI/Designee discretion based on results of prior studies.)

f. For Recipient-Subjects with ALL, AML, MDS[17]

- Bone marrow for flow cytometry (To include CD33; B-ALL to include CD19, CD20, CD22, CD25, CD30), cytogenetics, molecular genetics for mutation analysis, FISH (Some studies may be omitted at PI/LAI/Designee discretion based on subtype and prior studies)
- Lumbar Puncture (all Recipient-Subjects with ALL, and any with symptoms or history of CNS involvement) - Cerebrospinal fluid cell count, chemistries, ADA, cytology

g. MPN, PMF[106]

h. For Recipient-Subjects with CML

- Bone marrow for flow cytometry, cytogenetics, FISH, molecular genetic analysis for ABL-KD mutation (PI/LAI/Designee discretion based on prior studies)
- Peripheral blood for quantitative BCR-ABL P210

i. For Recipient-Subjects with CLL/SLL

- Bone marrow/PBL for flow cytometry (CD19, CD20, CD22, CD25, CD30; CD38 and Zap70), cytogenetics, FISH, PCR for IgH gene rearrangement, molecular genetic analysis for IgV_H mutation. (Some studies may be omitted at PI/LAI/Designee discretion based on prior studies.
- Peripheral blood for quantitative lymphocyte phenotyping (TBNK)

j. For Recipient-Subjects with Hodgkin's and non-Hodgkin's Lymphomas

- Bone marrow for flow cytometry
- Tumor tissue for Surg Path/IHC, for B-cell, to include CD19, CD20, CD22, CD25, CD30; flow cytometry, cytogenetics, FISH, PCR for IgH and TCR gene rearrangements, FISH, molecular genetic analysis for gene rearrangements, e.g., antigen receptor, BCL1, BCL2, BCL6, MYC (PI/LAI/Designee discretion based on histology and prior studies)
- Mantle Cell: colonoscopy with biopsies

Lumbar Puncture (high-grade diagnosis, or symptoms or history of CNS involvement) - Cerebrospinal fluid cell count, chemistries, ADA, cytology.

Table 8. Response and Relapse Definitions after AlloHSCT—Application of Monitoring Methodologies

Disease	Definition of Complete Remission	Definition of Relapse	Molecular Markers	Cytogenetics	Chimerism	Imaging	Flow Cytometry	Other Methods
Multiple myeloma	1) EBMT 2) IWG	1) EBMT 2) IWG	ASO-primer (IgH)	Chromosome banding analysis, FISH	PCR or VNTR/STR	MRI PET-CT	4-8 color flow	Free light chain assay
Applicable	All patients	All patients	40%-80%	subgroups	All patients	All patients	All patients	Subgroups
Comment	Accepted but less sensitive.	Accepted but less sensitive.	Important, but not included in EBMT and IWG definition.	May be useful.*	Mononuclear cell donor chimerism not useful. Lineage-specific donor chimerism ($CD138^+$ plasma cells) predicts relapse.*	Not established, but useful for extramedullary disease.*	More sensitive than EBMT/IWG in predicting relapse.*	Proposed by IWG, but no valid data.*
Lymphoma	Cheson criteria	Cheson criteria	ASO-primer (IgH) for B-cell NHL	Chromosome banding analysis, FISH	PCR or VNTR/STR	CT/PET	4-6 color flow	
Applicable	All patients	All Patients	Subgroups	Subgroups	All Patients	All Patients	Subgroups	
Comment	Well established for all lymphomas.	Well established for all lymphomas.	Bcl-2 for FL. Bcl-1for about 30% of MCL. Clonal TCR rearrangements for T-NHL.	t(14;18) for FL. t(11,14) for MCL.	Monitoring T cell by PCR useful in NHL. Role not established in HD.	Well established in all lymphomas.	Could be helpful for FL and MCL.*	
CML	Hematologic Cytogenetic Molecular	Hematologic Cytogenetic Molecular	*BCR-ABL1* RT-PCR	Chromosome banding analysis, FISH	PCR or VNTR/STR		4-6 color flow	
Applicable	All patients	All patients	All patients	All patients	All patients	Not applicable	Subgroups	
Comment			qPCR identifies relapse risk groups.	Not as sensitive as qPCR for MRD detection.			Only helpful in identifying aberrant blasts in advanced phase disease.	
Myelofibrosis	IWG-MRT	IWG-MRT	*JAK2/MPL*	Chromosome banding analysis, FISH	PCR or VNTR/STR	MRI	Flow cytometry	
Applicable	All patients	All patients	Subgroups	Subgroups	All patients	All patients	All patients	
Comment	Not fully applicable.	Not fully applicable.	High sensitivity and predictive for relapse.*	Not investigated.*	Correlates with molecular marker, but less specific.*	Correlates with fibrosis regression.*	Circulating CD34+ cells may be useful.*	
CLL	IW-CLL/NCI	IW-CLL/NCI	ASO-primer *IGH* qPCR	Chromosome banding analysis, FISH	PCR or VNTR/STR	CT	MRD flow	
Applicable	All patients	All patients	~90%	Subgroups	All patients	All patients	>95%	
Comment	iwCLL definition of MRD negativity: MRD $<10^{-4}$ by qPCR or flow.		Predictive for sustained remission if $<10^{-4}$ 1 year post-SCT. More sensitive than flow ($<10^{-4}$).	No role in relapse monitoring.	Complete donor chimerism usually prerequisite for MRD negativity, but not suitable as MRD marker.	Only to be used if CR by clinical methods or in clinical trials.	Predictive for sustained remission if $< 10^{-4}$ 1 year post-alloHSCT. Equally sensitive and specific as qPCR up to10^{-4}.	

FL indicates follicular lymphoma; flow, multiparameter flow cytometry; MCL, mantle cell lymphoma; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; qPCR, quantitative real-time PCR; RT-PCR, reverse-transcription PCR; TCR, T cell receptor; VNTR, variable number tandem repeats; PET, positron emission tomography; CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; FISH, fluorescence in situ hybridization; EBMT, European Blood and Marrow Transplant; IWG, International Working Group; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment.
*Further studies needed

Disease-Specific Staging, Continued[17]

Table 6. Response and Relapse Definitions after alloHSCT—Application of Monitoring Methodologies

Disease	Definition of Complete Remission	Definition of Relapse	Molecular Marker	Cytogenetics	Chimerism	**Imaging**	**Flow Cytometry**
AML/MDS	IWG	IWG	Molecular mutations	Chromosome banding analysis, FISH	PCR or VNTR/STR		4-8 color flow
Applicable	All patients	All patients	Subgroups	Subgroups	All patients	Not applicable	All patients
Comment	Well established.	Well established, but less sensitive.	Expansion of MRD marker panel for posttransplant monitoring in AML (eg, *NPM1* mutations) or MDS (eg, *RUNX1/AML1* mutations).*	No standardization for MRD monitoring, useful for specific aberrations.*	Well-established, lack of specificity: investigation of $CD34^+$ specific chimerism*; and standardization of techniques.		Few studies.*
ALL	Less than 5% blasts in BM	More than 25% blasts in BM	TCR- and Ig- Gene rearrangement	Chromosome banding analysis, FISH	PCR or VNTR/STR		4-6 color flow
Applicable	All patients	All patients	90% of all patients	Subgroups	All patients	Not applicable	> 95% of patients
Comment			ASO primer: 80%–90% of patients. Ig VDJ: Most patients. *BCR-ABL1*: All Ph+ ALL.	Clinical not important for MRD assessment.	Gold standard: Singleplex PCR with fluorescent labelled STR primers. Importantly: product resolution using capillary electrophoresis.		Sensitivity in B-lineage ALL is limited after SCT because of large numbers of hematogones.

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; Flow, multiparameter flow cytometry; MDS, myelodysplastic syndromes; qPCR, quantitative real-time PCR; STR, short tandem repeats; VNTR, variable number tandem repeat.
*Further studies needed.

10.4 APPENDIX D: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL

The following elements will be collected and recorded in Lab Matrix. Minimum data requirements will include data that all transplant centers routinely collect and report to the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP). For Recipient Subjects who are treated with Allotransplant at the CC, these data will be collected at specified study time points and recorded in CRIS using the Pre-transplant and Transplant Protocol Visit Note Templates approved by the NIH Blood and Marrow Transplant Consortium (http://intranet.cc.nih.gov/bmt/transplant/transplant_specific.shtml). Referring physicians will be encouraged to provide data using the format submitted to the CIBMTR/NMDP.

Donor-Subjects
▪ Name/MRN
▪ Demographics
▪ Consent Date/Version; Registration Date/Number
▪ Recipient ID
▪ Date of Cell Donation
▪ Research Tissue Samples (Dates; Specimens)
Recipient-Subjects: Registration
▪ Name/MRN
▪ Demographics
▪ Consent Date/Version; Registration Date/Number
▪ Treatment Protocol Number
▪ NCI Pathology Review: Date, Tissue Type / Site, Date and Result of NCI Evaluation
Baseline (Pre-Transplant) Characteristics
▪ HLA
▪ Diagnosis (CIBMTR Terms)
▪ Tests Performed at Dx, Dates, Results (e.g., Histology, Cytology, Cytogenetics, etc.)
▪ Disease Status Prior to SCT Conditioning: Test Modalities, Dates
▪ Predisposing Condition? (Y/N) Specify Cancer Risk Factors…
▪ Prior Therapy, Date, #Cycles, Response
▪ Prior SCT? (Y/N); Date(s); Prior SCT Stem Cell Source: (Auto / Allo; Related / Unrelated); ▪ Indication for this SCT & Date Dx: Planned/Consolidation; Relapse/Progression; 2nd Cancer (Details); BM Failure/Graft Rejection; Other

Comorbid Conditions? (Defined below) (Y/N); □ Arrhythmia □ Cardiac □ Inflammatory Bowel Disease □ Diabetes □ Cerebrovascular Disease □ Psychiatric Disturbance □ Hepatic, Mild □ Obesity □ Infection □ Rheumatologic □ Peptic Ulcer □ Renal, Moderate/Severe □ Pulmonary, Moderate □ Prior Solid Tumor □ Heart Valve Disease □ Pulmonary, Severe □ Hepatic, Moderate/Severe

HCT Comorbidity Index Score (HCT-CI, "Sorror Score"): calculated from HCT-CI weighted scores,below)

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Table 4. Definitions of comorbidities included in the HCT-CI and HCT-CI scores compared with original

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI v
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	
Inflammatory bowel disease	Crohn disease or ulcerative colitis	
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	
Obesity†	Patients with a body mass index > 35 kg/m^2	
Infection†	Requiring continuation of antimicrobial treatment after day 0	
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	
Peptic ulcer	Requiring treatment	
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	
Heart valve disease	Except mitral valve prolapse	
Severe pulmonary‡	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	

- **Transplant Characteristics**
  - Patient / Donor Characteristics: CMV Serostatus; ABO Blood Type/Date; HLA Type/Date; Parity (Female)
  - Donor ID, HLA match, mobilization/collection/ harvest procedure
  - Stem Cell Graft: Product Manipulations/Infusion Date/ Cell Doses: TNC, CD34, CD3
  - Preparative regimen: Agents/Dates/Intensity (CIBMTR terms, myeloablative/reduced-intensity/non-myeloablative)
  - Post-Transplant Donor Cell Infusions (Planned): Dates/Products/Cell Doses
  - Pre/Post-Transplant Growth Factor Therapies (Planned): Agents/Doses/Dates
  - Pre/Post-Transplant Immune Suppression (Planned), i.e., Prophylaxis: Agents/Doses/Dates/Reason for Discontinuation
  - Post-Transplant Cancer Therapies (Planned), e.g., Preventive/Maintenance: Agent/Dose/Dates/Reason for Discontinuation

Transplant Course (Recorded from Day 100 **Assessment)**

- Acute GVHD: Max Stage/Grade/Sites

▪ Response to AlloSCT @ D28
▪ Best Response to AlloSCT @ D100
▪ Transplant-Related Morbidity, >Grade 2 (Y/N; Dx; Date): Cardiac Toxicity, Infection, Pulmonary Toxicity, VOD, Graft Rejection/Graft Failure, Engraftment Syndrome; Transplant-Associated Microangiopathy, Other
▪ Primary Hematologic Recovery (Dates: ANC > 0.5 x 10^9/L x 3D; platelets > 20 x 10^9/L, non-transfused)
Clinical Data**: At each Time Point, the following will be recorded for <u>both</u> Interim History and for Current Study Visit**
▪ Dx Chronic GVHD? (Y/N); New? (Y/N); Flare? (Y/N); Dates/Sites/Extent/NIH Score
▪ Dx 2nd Malignancy: New Dx? (Y/N); Date / Diagnosis / Tissue Sample(s) / Test Modalities / Chimerism / Results
▪ Dx of Cancer Relapse or Progression? (Y/N); 1st Dx? (Y/N); Date
▪ Cancer Status (Baseline=Pre-SCT: CR/PR/SD/PD): Assessed? (Y/N); Dates: Modalities / Results (Pos/Neg/Indet./Other)
▪ Disease Status, Missed Time Points (i.e., Subjects Enrolled Post-SCT)
▪ Bone Marrow Aspiration & Biopsy: Performed? (Y/N); Date, Detection Modalities/ Results, Chimerism (% Donor)
▪ Tumor Biopsy: Performed? (Y/N); Date, Bx Site, Bx Method, Testing Modalities/Results (Pos/Neg/Indet./Other), Chimerism (% Donor)
▪ Post-Transplant Health Maintenance Assessment ▪ Performed: □ Prophylaxis □ Immunizations □ Screening; Date; Deficiencies: □ Prophylaxis □ Immunizations □ Screening; Detail:
▪ Vaccines Administration: □ PCV □ PPSV23 □ DTaP □ Varivax; Dates ▪ Note: responses (serologic) to these immunizations will be collected to assess recovery of immune function.
Clinical Data, Current Study Visit (Collected at Study Time Points, except as noted)
▪ STR Chimerism Whole Blood, WBC (CD3/ Myeloid)
▪ CBC/Diff (WBC, Hb, PLT, Abs. Neutrophil Count, Abs. Lymph Count, Abs. Eos Count, Abs. Mono Count), PT, PTT, D-Dimer
▪ CRP, ESR, pro-BNP, haptoglobin
▪ Quant. Lymph. Subsets, TBNK; Quant. Immunoglobulins
▪ On-Study, 12-Month and 30-Month Time Points: ▪ Serologies (HBV, CMV, HSV, VZV) ▪ Vaccine Titers (Pneumococcus; Diphtheria, Tetanus, VZV) ▪ Anergy (Candida) Skin Testing: Date Placed, Date Read and Diameter (mm)
▪ Performance Status: Date, Scale, Score

▪ Research Specimens Collected? (Y/N); Specimen Type, Date
▪ Any Procedures Performed for THIS Study? (Y/N); Date, Procedure, Adverse Events
Therapies: At each Time Point, the following will be recorded for <u>both</u> Interim History and for Current Study Visit (Active Meds and Prescribed @ Current Study Time Point)
▪ Any Therapy Administered on THIS Study? (Y/N); Date, Procedure, Adverse Events
▪ Donor Cell Infusions, Unplanned (Therapeutic)? (Y/N); Indication / Cell Product Type/ Cell Dose/ Dates / Response
▪ Growth Factor Therapies (Therapeutic)? (Y/N); Agents/ Dates/ Indication/ Response / Current?
▪ Post-Transplant Immune Suppression, Unplanned (Therapeutic)? (Y/N); Indication / Agents / Doses / Dates / Response / Current?
▪ Post-Transplant Immune Therapy (Unplanned / Therapeutic)? (Y/N); Indications / Agents / Doses / Dates (e.g., IVIg) / Current?
▪ Post-Transplant Infection 2º Prophylaxis / Preemptive Rx / Suppressive Rx (Unplanned/ Therapeutic)? (Y/N); Indications / Agents / Dates (e.g., CMV, Mold, AFB) / Current?
▪ Relapse Cancer Therapy Post-SCT (Unplanned)? (Y/N); Indication / Agents/Dates-Start-Stop/ Cycles) /Current? No: Reason for Discontinuation
Clinical Updates: Events Occurring Outside or Precluding Study Visit
▪ Clinical Status: Cancer/Treatment, Palliative/Hospice Care, Death, Cause of Death (CIBMTR Terms); Date

10.5 APPENDIX E: DONOR COLLECTION PROCEDURES

10.5.1 Donor-Subject Stem-Cell Mobilized Cell Product Collection Procedure for Collections Performed at the NIH/CC

Consenting adult related allograft Donor-Subjects who are evaluated at the CC will undergo steady-state apheresis for lymphocyte collection for 1) treatment of their respective allotransplant recipient and/or 2) research, i.e., control samples for Recipient-Subject research studies. Filgrastim mobilized donor stem cell collections are permitted provided there is a clinical indication for therapeutic use. Stem cell collections are voluntary, i.e., Donor-Subject willingness to undergo mobilized collection will not affect study participation of Donor- or Recipient-Subjects. Prior to mobilization, the Donor-Subject will undergo clinical assessment (Section **3.4**) to confirm continued eligibility and safety of donation and to review risks of filgrastim and apheresis.

Approved donors will receive filgrastim as an outpatient (10 µg/kg/day each morning; subcutaneously) for 5, 6, or 7 days. In cases where it is anticipated that poor mobilization may occur (increased donor age, Caucasian race, low donor weight, high recipient weight), donors may receive filgrastim at an increased dose of 8 µg/kg BID. Donor should take filgrastim upon awakening in the morning. This is especially important on days 5, 6, and 7 of the injections.

A large-volume (15- to 25-liter), whole-blood apheresis will be performed in the NIH DTM via a two-armed approach or a temporary central venous catheter in the femoral position using the Baxter CS3000Plus, Cobe Spectra, or an equivalent instrument (typically, 4-6 hour procedure). The apheresis procedure will use ACD-A anti-coagulant, or heparin.

Apheresis will typically be performed on days 5 and 6 of this regimen. On some occasions, sufficient numbers of CD34+ cells might be obtained with a single apheresis on day 5; on other occasions, it may be necessary to perform additional apheresis procedures on days 6 and 7 to reach the target CD34+ cell number (usually 3 - 5 x 10^6 $CD34^+$ cells/kg-recipient). The PI/LAI/Designee will specify $CD34^+$ cell collection targets at time of collection, as they will depend on indication. The donor will be instructed to take filgrastim for the complete 7-day period, unless notified that adequate CD34+ cells were harvested before day 7.

The apheresis product will be cryopreserved and stored at –180° C in Plasmalyte A, Pentastarch, human serum albumin, DMSO, and preservative free heparin (10 U/ml) by the NIH DTM procedure (as defined in BB-IND #9164). The concentration of CD34+ cells in the apheresis product will be determined by flow cytometry, and the number of CD34+ cells in each cryopreserved bag calculated.

If donor and host are not ABO-compatible, red blood cells will be depleted from the stem cell product by standard DTM protocols.

The day after collection is completed, Donor-Subjects will have a clinical assessment, including a focused history and physical examination, blood draw for clinical laboratory evaluation, including CBC with differential and chemistry panel, and a reminder of clinical symptoms that require evaluation by a local physician or Emergency Room.

10.5.2 Request for NMDP Donor to Participate in a Research Study

Principal Investigator: _____ **TC Code:** ____ **DC C**☐☐☐

Name of Study:

TC Protocol ID Number: _____ **NMDP IRB Number:** IRB-____-____

Section 1: To be completed by Transplant Center
The following patient is enrolled on the above-listed protocol. In this instance, the donor is also considered a research subject.

Recipient ID ☐☐☐ ☐☐☐ ☐

Donor ID ☐☐☐☐ ☐☐☐☐ ☐

Anticipated transplant timeframe: ☐☐ ☐☐ ☐☐☐☐

Signature: _____ Date:_____
TC Coordinator *Date completed*

Fax to Search Coordinator with the work up request at 612/627-5810

Instructions to the Donor Center:
The donor listed above is being asked to participate in a research protocol. The NMDP Research Administration Department will send, under separate cover, the protocol and consent form. Please counsel the donor during the information session and seek their consent to participate in this study. After the information session, complete Section 2 of this form indicating the donor's decision and fax to the NMDP SCU at 612/627-5810.

Section 2: To be completed by Donor Center

☐ Donor consents to participate in research.
Date consent form signed: ☐☐ ☐☐ ☐☐☐☐

☐ Donor declines to participate.

Signature: _____ Date:_____
DC Coordinator *Date completed*

For Search Coordinating Unit Only

☐ Fax completed Section 1 to Res. Admin. (612/627-5899) and DC. Retain copy for file.
Managing SCID # _____ Date/Initial _____ DC Contact
_____

☐ Fax completed Section 2 to Res. Admin. (612/627-5899) and TC. Retain copy for file.
Managing SCID # _____ Date/Initial _____

For Research Administration Only

☐ Send consent/protocol/etc. to Donor Center. Date/Initial _____

10.5.3 NMDP Collection Prescription for Therapeutic Cells, T-Cells

NMDP Prescription for Therapeutic Cells, T-Cells

TC Code: _____ Recipient ID: _____ Donor ID: _____

♦ DO NOT include samples related to a transplant center research study (requiring NMDP IRB approval) on the prescription. Instead, include these research samples on the *Request for NMDP Donor to Participate in a Research Study* form.

PRE-COLLECTION BLOOD SAMPLES

♦ If donor is from an international donor center or cooperative registry, complete the NMDP Prescription Supplement to indicate pre-collection sample(s) requirements and designate who will perform infectious disease marker (IDM) testing.
♦ If requesting an international donor, the pre-collection blood sample space (below) should be empty.

SAMPLE REQUIREMENTS:

_____ mls Red top tube (no anticoagulant)
_____ mls Yellow top tube (ACD)
_____ mls Green top tube (sodium heparin)
_____ mls Purple top tube (EDTA)

Shipping Information

Attn/ Name: _____
Center: _____
Address Line 1. _____
Address Line 2. _____
City, State, Country, Zip: _____
Phone: _____

Specify when samples should be collected: _____

CELL DOSE CALCULATIONS

Recipient weight in kg:	_____ kg	
Multiply by desired $CD3^+$ cells / kg:	x _____ x 10^7/kg	
Total $CD3^+$ cells requested:	= _____ x 10^7	
Multiply by 2	x 2	
TOTAL mononuclear cells (TMC)	= _____ x 10^7	
Divided by 100 x 10^7 TMC/L	= _____ Liters processed	

- $CD3^+$ content is approximately 50% of Total Mononuclear Cells (TMC).
- Mononuclear cells are calculated from the sum of lymphocytes and monocytes on the standard differential count.
- The average leukapheresis yield is approximately 100 x 10^7 mononuclear cells per liter of blood processed.
- A maximum of 24 liters of donor blood will be processed in a single apheresis procedure to accommodate the request.

Designate transport temperature: ❒ Room Temperature ❒ Cooled with frozen gel packs
Will portions of the cells be cryopreserved? ❒ NO ❒ YES
Will the cells be manipulated prior to infusion? ❒ NO ❒ YES → Describe: _____

SAMPLES REQUIRED AT TIME OF COLLECTION

	Peripheral Blood	T-Cells Product
Red Tube (No anticoagulant)	*10+_____mls	_____mls
Yellow Tube (ACD)	_____mls	_____mls
Green Tube (Sodium Heparin)	_____mls	_____mls
Purple Tube (EDTA)	_____mls	_____mls

*Collect 10 mls of donor blood in a red top tube (No anticoagulant) the day of T-Cells collection.

Regarding the donor designated above, I verify that the ABO type, degree of HLA match, compatibility testing results and infectious disease results are acceptable to proceed with Therapeutic Cells, T-Cells collection for above patient.

_____ _____/_____/_____
Transplant center physician's signature Month Day Year

Document Number: F00235 version 3.0
Replaces: F00235 version 2.0

Item # 00190

10.6 APPENDIX F: ASCO SAMPLE CONSENT TO CHEMOTHERAPY

http://www.asco.org/quality-guidelines/informed-consent-chemotherapy-administration

9/2/07

[Name of Physician Practice]

Consent to Chemotherapy v1 0809

I, _____, understand that I have been diagnosed with _____.

I understand that the treatment suggested by my doctor, Dr. _____, will involve
_____
_____
_____ _____
_____.

The goal of my treatment is
_____
_____
_____.

I understand that health professionals at _____ will help my doctor provide this treatment. I also understand that other health care providers may be needed for my care.

I understand that there are benefits of this treatment if it is successful. I also understand that my doctors cannot be sure that the treatment will help me.

I understand that the chemotherapy medications recommended by my doctor can have short-term and long-term side effects. My doctor talked to me about the following side effects that I might experience because of my chemotherapy: *(check all that apply; additional space provided for physician comments)*

! Nausea/Vomiting _____

! Hair Loss_____

! Low red blood cell count/Anemia_____

! Fatigue_____

! Risk of Infection_____

_____ _____
Patient D.O.B. Patient I.D.

! Risk of Bleeding_____

! Constipation_____

! Diarrhea_____

! Sores of Mouth and Throat_____

! Skin Effects_____

! Muscle/Bone Effects_____

! Nerve Effects_____

! Kidney/Bladder Effects_____

! Sexual Effects_____

! Heart Effects _____

! Lung Effects_____

! Reproductive/Fertility Effects_____

! Other_____

I understand that complications from chemotherapy could cause my death.

I understand that I could have side effects from my chemotherapy that are not listed on this form. Each patient can respond differently to chemotherapy, and could have side effects that have not been reported by others.

The reasonable alternatives to this chemotherapy treatment have been explained to me, including:
_____
_____
_____.

_____ _____
Patient D.O.B. Patient I.D.

I also understand that I may stop this treatment at any time.

I have had the chance to ask questions about this treatment, and my questions have been answered to my satisfaction. I understand that I can contact my health care provider at any time if I have questions, by calling _____.

I will receive a copy of this consent form.

I understand that by signing this document I am consenting to receive the chemotherapy medicines proposed by my health care provider.

Patient Signature _____ _____ Date_____

For patients requiring translation or verbal reading of this document, the person reading/translating should document and sign below:

Reader/Translator Signature_____ ____ Date_____

10.7 APPENDIX G: ETIB PRECLINICAL SERVICE POLICY FOR SAMPLE HANDLING

10.7.1 Storage/Tracking

Normal donor and patient blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Experimental Transplantation and Immunology Branch, may be archived by the ETIB Preclinical Service. All data associated with archived clinical research samples is entered into the ETIB Preclinical Service's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB Preclinical Service folder. Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory has received annually updated NIH/CIT training and maintains standards of computer security.

The data recorded for each sample includes the patient ID, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e. g. peripheral blood, lymphopheresis, mobilized peripheral blood stem cells, marrow, pleural fluid) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records. As of January 2007, all newly received samples will receive a unique bar code number, which will be added to the sample Preclinical Service database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to subjects without authorized access to the Preclinical Service database. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.

Samples are stored in locked freezers at -85°C (sera and plasma) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the Preclinical Service laboratory (12C216) (-85° freezer) or in ETIB common equipment space (CRC/3-3273). Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol or through his/her submission and IRB approval of the NCI IRB Authorization Form (appended) stipulating whether IRB review is not necessary or IRB approval is granted for the pursuit of this new research activity. All researchers are required to sign a form (attached) stating that the samples are only to be used for research purposes associated with objectives of the original protocol for which the samples were collected, or (using only unlinked or coded samples) for an IRB approved protocol as stipulated on the IRB Authorization Form, and that any unused samples must be returned to the Preclinical Service laboratory.

10.7.2 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 (ex. 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.

10.8 APPENDIX H: PERFORMANCE STATUS SCALES

ECOG PERFORMANCE STATUS[110]

Grade	Activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

10.9 APPENDIX I: SCHEDULE OF SAMPLES AND STUDIES

Assessments	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14 days)**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**
Clinical Assessment											
H&P (CRIS Transplant Forms)	SCT	SCT	SCT	SCT	SCT	SCT	SCT	✓	✓	✓	✓
GVHD Evaluation		SCT	SCT	SCT	SCT	SCT	SCT	✓	✓	✓	✓
Screen: Endocrine Function		✓	✓CI	✓		✓CI	✓CI		✓CI	✓CI	✓CI
Screen: Cardiac Risk Factors		✓	✓	✓		✓	✓		✓	✓	✓
Screen: 2nd Cancer				✓			✓				
Screen: Psychosoc./Caregiver		✓	✓	✓		✓	✓		✓	✓	✓
Ophthalmology Evaluation		✓CI	✓CI	✓			✓CI				
Dental Evaluation				✓			✓CI				
GYN Evaluation			✓CI	✓		✓CI	✓		✓CI	✓CI	✓CI
Dermatology Evaluation				✓			✓CI				
Hepatology Evaluation				✓CI		✓CI	✓CI		✓CI	✓CI	✓CI
Clinical Phlebotomy											

Assessments	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14 days)**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**
STR Profile, Blood/Tissue Typing	SCT										
STR Chimerism Whole Blood and WBC (CD3/Myeloid)	SCT	SCT	SCT	SCT	SCT	SCT	SCT	✓	✓	✓	✓
CRP, ESR, pro-BNP, haptoglobin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Quant. Lymph.Subset/TBNK; Quant.Immunoglobulins	SCT	SCT	SCT	SCT	✓	✓	✓	✓	✓	✓	✓
Serologies: HBV, HSV, CMV, VZV	SCT			✓				✓			
Vaccine Titers (Pneumococcus; Diphtheria, Tetanus, VZV)	✓			✓				✓			
Blood PCR: CMV, EBV	✓	SCT	SCT	SCT	SCT	SCT	SCT	✓			
Assessments	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**

Assessments	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14 days)**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**
									days)		
CBC/diff, PT/PTT/D-Dimer	SCT	SCT	SCT	SCT	SCT	SCT	SCT	✓	✓	✓	✓
Thyroid Panel	✓			✓			✓				
LH, FSH, Estrodiol, Testosterone	✓			✓			✓CI				
HbA1C, Lipid Profile, VitD, PTH	✓	✓CI	✓	✓			✓CI		✓CI		
Ferritin	✓	✓CI	✓CI	✓							
Procedures: Cancer Monitoring, Immune Function and Post-Transplant Health Maintenance Guidelines											
Anergy (Candida) Skin Testing	✓			✓				✓			
Staging Studies (Appendix C)[C]	SCT	SCT	SCT	SCT	SCT	SCT	SCT	✓P	✓P	✓P	✓P
Bone Marrow Biopsy	SCT	SCT	SCT	SCT			SCT	✓P	✓P	✓O	✓P

Abbreviations: "✓": Performed on Study; CI: clinically indicated; GVHD: graft-vs.-host disease; O: optimal; P: permitted; SCT: Performed by SCT Study, Recorded on Study.

Assessments	On-Study	100 Day (+/- 7 days)	6M (+/- 7 days)	12M (+/- 7 days)	15M (+/- 7 days)	18M (+/- 14 days)	24M (+/- 14 days)	30M (+/- 14 days)	Annual (3-6Y) Biennial thereafter (+/- 14 days)	New Dx Relapse	Post-Rx for Relapse (4-8 Weeks)
Procedures, Continued											
Tumor Biopsy	✓O									✓O	✓P
Bone Densitometry			CI	X			CI		CI		
Echocardiogram		X		X			CI		CI	CI	
Electrocardiogram		X	X	X			CI		CI		
Pulmonary Function Test		X		X			CI		CI		
Research Phlebotomy											
Low-Volume (2 CPT)		✓	✓	✓	✓	✓	✓		✓		
Full (7 CPT) or Apheresis [R]	✓							✓		✓	✓
Monitoring Schedule: NMDP Guidelines for Post-Transplant Health Maintenance											
Review Prophylaxis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review Immunizations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Screening Guidelines Status		✓	✓	✓	✓	✓	✓	✓	✓		

Abbreviations: "✓": Performed on Study; CI: clinically indicated; GVHD: graft-vs.-host disease; O: optimal; P: permitted; SCT: Performed by SCT Study, Recorded on Study.

10.10 APPENDIX J: CONSENSUS GUIDELINES' SCHEDULE OF FOLLOW-UP CARE: IMMUNIZATIONS AND PROPHYLAXIS

Consensus Guidelines	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7 days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14 days)**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**
Immunization Guidelines. Updated Guidelines are maintained on the CC BMT Consortium Intranet Site: http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml.											
PCV (Pneumococcal 13-V)				X		X	cGVHD				
PPSV23 (Pneumococcal 23-V)							X				
DTaP				X	X		X				
Hib conjugate				X	X		X				
IPV				X	X		X				
Hepatitis A				X	X						
Hepatitis B				X	X		X				
Meningococcal				X							
MMR							X				
VZV (Varivax)							X				
Inactivated influenza	********** Seasonal, pre-transplant and resuming 4-6 months after transplant **********										
Prophylaxis Guidelines. Updated guidelines are maintained on the CC BMT Consortium Intranet Site: http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml.											
Pneumocystis	X	X	X	cGVHD Stero	cGVHD Stero	cGVHD Steroid	cGVHD Steroi	cGVHD Steroids	cGVHD Steroids	X	X

Consensus Guidelines	**On-Study**	**100 Day (+/- 7 days)**	**6M (+/- 7 days)**	**12M (+/- 7 days)**	**15M (+/- 7 days)**	**18M (+/- 14 days)**	**24M (+/- 14 days)**	**30M (+/- 14 days)**	**Annual (3-6Y) Biennial** thereafter **(+/- 14 days)**	**New Dx Relapse**	**Post-Rx for Relapse (4 Weeks)**
				ids	ids	s	ds				
Varicella	X	X	X	X	X	X	X	cGVHD Steroids	cGVHD Steroids	X	X
Encapsulated Organisms		cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	X	X
CMV Surveillance/ Rx	X	CI	CI	cGVHD Steroids	cGVHD Steroids	cGVHD Steroids	cGVHD Steroids	cGVHD Steroids	cGVHD Steroids	X	X
SBE PPx for Procedures	CI	CI	CI	CI	CI	CI	CI	CI	CI	CI	CI
Fungal	X	X	X	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	cGVHD PPx	X	X
HBV, HCV Monitoring	CI	CI	CI	CI	CI	CI	CI	CI	CI	CI	CI

Abbreviations: cGVHD: chronic graft-vs.-host disease; CI: clinically indicated HBV: Hepatitis B virus; HCV: Hepatitis C virus; SBE: subacute bacterial endocarditis; PPx: prophylaxis.

INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0125 PRINCIPAL INVESTIGATOR: Ronald Gress M.D.

STUDY TITLE: Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/16/17 (E) Date Posted to Web: 03/04/17

Donor-Subject

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 is this study being done?

Your family member has had an allogeneic hematopoietic stem cell transplantation (allotransplant) for his/her cancer. You donated cells previously for this allotransplant. The main purposes of this study are to:

1. Study the biology of cancer cells and the changes in the immune system to better understand why cancer in some patients goes away after allotransplant, and in other patients it does not or comes back (called cancer relapse);
2. Understand how 'graft-versus-tumor/leukemia (GVT)' works in cancer cells to fight cancer relapse.
3. Do systematic assessments of patients and their cancer to study the effects of treatment on cancer relapse.
4. Make recommendations for effective treatments in patients with cancer relapse after allotransplant.

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

You have donated stem cells, the "seeds" of the bone marrow, to your relative in the past for transplant. You may have also donated lymphocytes as part of their treatment program, called donor lymphocyte infusion (DLI). On this study you will be donating blood cells for research studies and, should your relative need treatment, you may also be donating lymphocytes to be given to your relative as DLI.

Although the immune cells in your relative's blood and in the cancer cells come from you from the previous transplant, they have likely gone through extensive changes in response to being in another person's body. It will be essential in our research to compare the immune cells we find in your relative's blood and cancer cells to the immune cells that remain in your blood, which have not yet seen your relative's body. We will study the specific cell types, cell functioning and chimerism (the genetic makeup of cells) in your relative's blood and compare to your blood results. These comparisons may help us understand how these cells change and how to improve their ability to fight cancer. After testing your blood to see if you are eligible to donate cells for therapy, if some of your blood and lymphocytes are left over, we will use them for research tests to evaluate why your family member has cancer relapse and to study new or more effective treatments for cancer.

One of the treatments that may help your family member is donor lymphocyte infusion (DLI). Some patients with blood system cancers respond to DLI, which we believe is the result of the donor T cells traveling to the cancer cells and attacking them. If our evaluation indicates this

treatment would be helpful, you may be donating lymphocytes to be given to your family member.
We may collect your cells on this study that would provide your relative with therapy, but we would obtain extra or unused cells to study for research purposes. The cells may be given to your relative as part of this study, which allows non-experimental treatment, including DLI or other donor cell therapy. The cells may be given to your relative as part of another NIH study, if your relative enrolls on to another research study that uses donor cells as part of an experimental therapy. A portion of your cell donation will be used for research. Depending on what kind of cell therapy the doctors decide would be of most help to your relative, your lymphocyte donation may or may not require you to take injections (shots) of a medicine called filgrastim.

You may have taken filgrastim when you donated stem cells for your relative's stem-cell transplant. Stem cells that can develop into different kinds of blood cells generally live and stay in the bone marrow. Sometimes donors have stem cells removed directly from the bone marrow in order to donate for their relative. Filgrastim is a chemical that the body makes naturally. Filgrastim can be thought of as a fertilizer for white blood cells in the bone marrow. The body makes more filgrastim when it senses an infection. Filgrastim stimulates the bone marrow to make more white blood cells to fight the infection. If extra filgrastim is given in the form of filgrastim injections, the bone marrow is stimulated to make more white blood cells; as a result, stem cells are released from the bone marrow into the circulating blood. During the apheresis cell collection, these stem cells can be removed from the blood along with lymphocytes. The U.S. Food and Drug Administration and the National Marrow Donor Program have both approved filgrastim for use in donor cell collection.

If you and your relative are adults, it is possible that we would ask you to return to the NIH more than once, if your relative needs additional cells. We could ask you to have an additional apheresis collection, depending upon the treatment plans of your family member. This consent does not obligate you to agree to return to the NIH, if you no longer are able or willing to donate cells.

How many people will take part in this study?

Up to 500 patients and 250 allotransplant donors will participate in this study over the next 5 years.

Description of Research Study

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

Before you begin the study

You will be evaluated to make sure that you are still able to serve as a lymphocyte and/or stem cell donor for your relative. On your first visit to NIH Clinical Center, you will see a physician

and other members of the research team. The doctor will take a medical history, perform a physical exam, and explain the procedures. Routine blood and urine testing will also be performed to test your kidney and liver function as well as your blood type and how your blood clots. To serve as a donor again, you must be in good health.

You will be tested for a number of infections that can be spread through the blood including Hepatitis A, B and C. As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV, Hepatitis B or C you will not be able to donate cells for therapy (DLI) but you can still participate in the study, and donate blood and/or lymphocytes cell donation for research 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. Results of your donor evaluation will be discussed with you. If any of the findings prevent you from being a donor, this will be explained. If any of the results suggest that you should undergo further evaluation or treatment, we can refer you for appropriate medical attention. If you are a woman of childbearing age, you will need to take a urine pregnancy test. Because of unknown health risks to the fetus or newborns, pregnant or breastfeeding women cannot be donors. If you are breastfeeding, you may still participate in this study; however, if you are asked to take filgrastim, you would need to express and discard milk that is produced while receiving filgrastim.

Birth Control

While receiving filgrastim and until blood cells are collected it is important that women who could become pregnant to use an effective form of birth control. If you think you or your partner is pregnant, you must 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

During the study

Apheresis:

Apheresis is a procedure that is used when only part of the cells or proteins in the blood are needed, to avoid having to take too much blood. In this case, it allows collection of large numbers of white blood cells, while the rest of the blood can be returned to the body. Apheresis will be done to collect cells for a treatment for your relative or to obtain cells to study for research (this is optional), or both. We will tell you its purpose before the apheresis procedure. The procedure for obtaining blood cells through apheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells are removed from your blood stream with a serum-cell separator machine. The machine divides whole blood into red cells, plasma (the serum part) and lymphocytes (or white cells). This requires putting a needle into one of your arms to send blood into the machine and a second needle into the other arm to return the unused portion of the blood to your blood stream. In a lymphocyte collection, the lymphocytes are taken out, and the plasma and red cells returned to your blood stream, along with a small amount of salt solution (saline) and blood thinning medication (anticoagulant). Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the procedure. The procedure takes approximately 4 to 6 hours to complete. Apheresis will be performed by trained personnel from the NIH Department of Transfusion Medicine (DTM). The I.V. tube(s) will be removed after the cells are collected.

As apheresis requires healthy, large veins, sometimes the arm veins cannot be used. In this case it would be necessary to insert a special I.V. known as a central venous catheter into a large vein in the groin area. If that is required, a separate consent would be obtained. In attempt to avoid this, the veins in the bends of your arms should not be used for blood drawing until after donation is completed if possible. If you are not donating for a therapeutic product, but for research only, we would only collect your cells from the arm veins; if that were not possible, an apheresis would not be done. Instead, you would have several tubes of blood drawn for research ("large-volume blood draw"). For safety, the amount of blood is determined by your weight.

If it is determined your relative would benefit from treatment with a stem cell donation, you would need to receive filgrastim. Filgrastim causes certain blood cells to travel from the bone marrow into the blood. Filgrastim will be given by subcutaneous injection (a shot under the skin much like insulin), usually once a day, twice per day for some people. We will teach you or a family member how to give these shots at home, or if needed, a nurse can administer the filgrastim. The shots will be given in the arm or thigh. They will be given for a period of 5, 6, or 7 days. Usually, you will be ready for the lymphocyte collection on day 5. A blood test will be drawn on the morning of the planned donation to help us decide when to start collection. An important part of our research will be to compare the immune cells we find in your relative's blood and cancer cells to the immune cells that remain in your blood, which have not yet seen your relative's body. We therefore request your permission to use some of the lymphocytes obtained during this apheresis for these research tests. Donating these cells will not require any additional time or effort on your part, nor will it affect the lymphocyte product intended for your

relative. This part of the research though is optional, and if you choose not to allow us to use your lymphocytes for research, your relative can still participate in the research study. Your permission for this will be obtained at the time of the Apheresis.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Lymphocyte donation is a safe procedure that is routinely performed in adults. There are a number of potential discomforts and side effects that are associated with donation.

Apheresis:
The most common side effects of apheresis are pain and bruising at the IV needle sites. Side effects of a temporary I.V. in the vein of the groin (if required) include bleeding, bruising, infection, blood clot, or pain. Medical personnel with experience in this procedure will place the I.V. They will discuss the procedure and possible risks in further detail with you before the procedure. Mild side effects from the blood thinning medication citrate are common and include chills, numbness and tingling sensations ("pins and needles") especially around the mouth, anxiety, muscle cramps, and nausea. These rapidly go away when the collection is slowed down.

More serious side effects due to citrate-induced low calcium levels are uncommon and include low blood pressure, seizures, weakness, and muscle stiffness. If this happens, the apheresis procedure will be stopped, in which case these side effects quickly go away. You will be monitored closely for any side effects and the procedure will be stopped and appropriate treatment administered if necessary.
Some people have a low number of blood platelets for a short period of time after donation. Platelets help the blood to clot. However, low platelet counts from stem cell donation have not caused an increased amount of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure.

Blood Draws: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When a large amount of blood is drawn, the red blood cell count may drop causing anemia. However, the amount of blood that you will donate in this study (a total of approximately 20 teaspoons) should not cause anemia. To be safe, we will check your red blood cell count before and after collection. If we find that you have anemia, we will prescribe iron tablets.

Filgrastim: Filgrastim (if you receive it) has been used in humans since the late 1980's and it has been shown to be very safe. However, this medication has the potential to cause side effects. Almost always, the side effects are minor and go away on their own when Filgrastim is stopped.

Filgrastim:

Likely:	Less likely:	Rare:

• Bone pain • Muscle aches • Pain or bruising at the injection site	• Some people who receive filgrastim shots and apheresis have a low number of blood platelets for a short period of time. Platelets help your blood to clot. However, low platelet count from filgrastim has not caused an increased amount of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure. • Fever • Chills • Tiredness • Headache • Other common lab abnormalities have been seen but are reversible once filgrastim is stopped. • Temporary worsening of pre-existing inflammatory conditions (such as psoriasis)	• Allergic reactions • Chest pain • Low blood pressure • There is a very rare but serious side effect (1 in 486,000 people) of ruptured spleen after filgrastim

Potential Benefits of Participation

Are there benefits to taking part in this study?

There are no direct benefits to the donor. It is hoped that your donation of cells will lead to an improvement in your relative's cancer. Your participation may also help advance our understanding of allotransplants and improve the way that we treat cancer in the future. Another potential benefit includes potential diagnosis of a previously unknown illness (such as viral

hepatitis) at the time you are screened to participate in this study, treatment of which could result in improvement in your general health and/or well-being.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

You can refuse to donate lymphocytes. If you refuse, your relative may still participate in this study.

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 study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the 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 treatment 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

Stopping Participation

Your doctor may decide to stop your participation in this study for the following reasons:

- if he/she believes that it is in your best interest
- if you have side effects from the apheresis that the doctor thinks are too severe
- if you lose your ability to provide informed consent

Whatever the reason, you will be informed of why you are being removed from this study.

You can stop taking part in the study at any time. 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 can**not** be recalled and destroyed.

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 they 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, Ronald Gress M.D., Building 10-CRC, Room 3E-3330, Telephone: 240-760-6167. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, 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 22, 2016 THROUGH AUGUST 21, 2017.

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

Print Name _____ Print Name _____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0125 PRINCIPAL INVESTIGATOR: Ronald Gress, M.D.

STUDY TITLE: Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/16/17 (E) Date Posted to Web: 03/04/17

Recipient- Relapse- Subject

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 have previously received an allogeneic hematopoietic stem cell transplant (or "allotransplant") with the intention of curing your blood-system cancer (such as leukemia, myelodysplastic syndrome, lymphoma, multiple myeloma). We are studying why some people's cancers continue to grow or spread after they have had an allotransplant, when for other people,

the allotransplant keeps the cancer from growing or coming back. We are asking for people who have had allotransplants for a cancer of the blood to participate, whether or not the cancer is in remission. If the cancer is not in remission, the tests that are done on this study will be used to determine whether you would be able to participate in one of several NIH protocols that are testing cancer treatments for people who still have cancer after an allotransplant. Why is this study being done?

The main purposes of this study are to:

1. Perform testing ("eligibility screening") to determine NIH treatment study options for an individual with cancer relapse.
2. Study the biology and behavior of cancer when it comes back after allotransplant.
3. Study changes in the immune system after allotransplant to better understand why some people's cancers keep growing or come back, while others may be cured.
4. Collect information about what kind of treatments people have received for relapse after allotransplant, how cancers have responded and how people have tolerated cancer therapies after an allotransplant. Cancer and transplant experts will study this information and develop guidelines to help doctors decide how to best treat an allotransplant recipient with cancer relapse.

Cancers are often well controlled (hopefully cured) after allotransplant, in part because the donor immune system is able to find and kill the cancer cells. However, sometimes after allotransplant, the cancer continues to grow ("progress") or goes away ("into remission") but then comes back ("relapses"). Unfortunately, when cancer grows after allotransplant there is no proven cure. We have several studies at the Clinical Center testing experimental treatments for cancer in people who have had an allotransplant. One goal of this study is to evaluate people who need cancer treatment after an allotransplant, in order to identify treatment protocol options at the NCI. Another goal is to study why some people's cancers are not controlled by the allotransplant. We will be examining cancer cells from samples taken during tumor biopsies, bone marrow biopsies, or abnormal fluid collections, and the immune system cells from samples taken during apheresis or blood draws, comparing people with cancer progression or relapse with people whose cancers are going away ("responding") or in remission. Our laboratory testing of tumor cells will include studying the specific immune cells present, the functioning of the tumor cells, and whether the genetic make-up of your tumor cells change after treatment. If we have enough tumor cells available we will also use them to study new treatments, including animal testing for cell treatments for conditions like yours. From blood samples (including apheresis procedures) we will examine the immune cells of both you and your donor (if available) to study why some patients' cancer responds and others do not. We hope that by learning more about why allotransplant does not work for some, we can find ways to treat relapse after an allotransplant and to prevent cancer relapse in the future.

You will have your medical history reviewed and a physical examination. You will have cancer staging studies, blood drawn, a bone marrow procedure, and, if it can be done safely, a biopsy of tissues that have cancer cells in them. This information and results will be part of a comparison between people whose cancer is not under control after allotransplant with people whose cancer is in remission or is responding. First, cancer experts will do a thorough evaluation of your

medical history, particularly your cancer and transplant history, perform a physical examination, test your blood for how well your organs and immune system are working, examine your cancer cells, your immune cells, and if possible, immune cells from your allotransplant donor. You will be asked to return to the NIH at your six (+/-7 days), 12(+/-7 days) and 24-month (+/-14 days) anniversaries from your allotransplant for a similar follow-up evaluation. We will contact you and/or your doctor's office at half-yearly intervals after the initial evaluation to get an update on how you are doing. If your cancer is in remission, you will not be required to return to the NIH or provide six-month updates after your 24-month post-transplant visit. However, you may remain on the study indefinitely, and at any point during your participation in this study you may return to the NIH for evaluation if it appears that there are new studies of interest for which you may be eligible.

If you need cancer treatment, you will have all the testing that is required to determine which treatment studies may be good options for you. These "screening studies" will help us determine your eligibility for multiple protocol options, so that you could enroll on a study and begin treatment as soon as possible. After each evaluation, the study doctors will discuss their recommendations with you and your primary oncologist, including any additional testing or medical specialty evaluations that may be needed, and treatment possibilities. If you are eligible for a treatment study at the NIH, this option will be discussed as well.

During your participation in this study, you will be asked to undergo many tests that are for research. Depending on the type of cancer and where it is, these research tests may include blood sampling, cancer biopsies, apheresis, and/or bone marrow biopsy. Everyone who agrees to participate in this study will have all of the research testing that can be done safely during the first study evaluation visit. How often the tests are repeated will depend upon how frequently you return to NIH, as detailed below.

How many people will take part in this study?

Up to 350 individuals who have had allotransplants and 150 allotransplant donors will participate in this study over the next 5 years.

Description of Research Study

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

Before you begin the study

Before you enter this study, we will help you arrange to have your medical records, radiology studies and cancer biopsy material sent to the NIH for review. We will discuss your medical history with you and, if you need treatment, with your physician. We will ask you to have a physical exam; this can be done at the NIH or with your local physician, who can send us the results. This will be done to make sure that you can safely travel to and from the NIH, and that that you will be able to enroll and undergo all study requirements. If the donor is available from your previous allotransplant, we will ask whether s/he would participate.

During the study

Initial Evaluation

Once you have signed the consent for this study, you will undergo a very thorough medical examination, depending upon the type and location of your cancer, which will include:

- History and physical examination.
- Routine laboratory tests of your blood and urine, to assess the function of your thyroid, liver, kidney, blood clotting, and immune system. They will also test your nutritional status, blood and tissue type, and for some infections you may have or have had (i.e., CMV, EBV, HSV 1 and 2, T. Cruzi (Chagas agent), Hepatitis A, B and C, HTLV-I and II, HHV-6, Toxoplasmosis, and varicella zoster (chicken pox). We will also test your immune status to common vaccines you may have received since allotransplant, including the pneumococcal (pneumonia) vaccine and the tetanus vaccine (either a tetanus shot or the DTaP vaccine). If you are female of childbearing potential, you will have a pregnancy test. As part of this study, you will be tested for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you have HIV infection, you would still able to participate in this study. If this is a new diagnosis, we would 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 anyone who may have been exposed or be at risk because of your HIV infection. These tests are similar to the tests that were done before your transplant.
- Cancer staging studies. Depending on the details of your cancer history and potential treatment protocol requirements, these may include a computerized tomography ("CT") or magnetic resonance imaging ("MRI") scan of the brain; CT scans of neck, chest, abdomen, and pelvis; whole-body positron emission tomography (PET-CT) scan; and/or a lumbar puncture (or "spinal tap"). If you have had these tests performed recently at the

NIH or the testing can be transferred for review at the NIH, it is possible that you may not need to have some studies repeated. A bone marrow aspiration and biopsy is part of the initial study evaluation for everyone.

- Tissue evaluation. Depending on the type, location and status of your cancer, this may include a biopsy of a tumor and/or having a sample of an abnormal fluid pocket, in order to study your cancer cells. Your tissue samples will be evaluated by medical specialists for diagnosis and staging of any cancer cells, to assist your doctor in making treatment decisions. If it safe to do so, we will obtain some additional tissue or fluid at the time it is being collected for medical testing and/or we will obtain any tissue or fluid left over after this testing to use for research studies.
- If required by a potential treatment study option, you may have additional procedures or assessments, including an apheresis procedure to collect immune cells from your blood; heart and/or lung testing, such as an electrocardiogram ("EKG"), echocardiogram or pulmonary function tests, ("PFTs").

If you are pregnant you are not eligible to enroll on this research study, as it includes radiology studies that may not be safe for a fetus. If you are breastfeeding you are not eligible to enroll onto this research study as the protocol uses radiology tests that require injection of radioactive materials that might be secreted in the breast milk. If you are female, you will have a pregnancy test at the beginning of the initial and follow-up evaluation visits; if pregnant or breastfeeding, parts of the evaluation would not be performed. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

If you need cancer treatment, once your evaluation is complete, a team of expert cancer doctors from the NIH will review all the information and make a recommendation about the best way to continue to evaluate you and/or treat your cancer. The treatment recommendations may include participation in an experimental treatment study at the NIH, or a non-investigational treatment, e.g., donor cell product infusions, conventional chemotherapy, new cancer treatments and/or radiation therapy. The specifics of the treatment plan will be discussed with you and your physician in detail. If the recommendation is for conventional therapy rather than an experimental treatment at the NIH, it is likely that you would not receive this treatment at the NIH. If you are eligible to participate on an NIH treatment study, the details of the study would be discussed with you at this time.

Follow-up Evaluations

1) If your cancer has not responded or has come back after allotransplant and you are eligible and enroll in an NIH treatment protocol, you will return to the NIH as required by that treatment protocol. In addition, you will be asked to come back to the NIH for

evaluation on this protocol at your six (+/-7 days), 12 (+/-7 days) and 24-month (+/-14 days) anniversaries of your allotransplant, then on a yearly basis. In order to minimize inconvenience and duplication of testing for you, we will coordinate this visit to coincide with other required restaging visits. Every effort will be made to use studies that you have had done recently. In addition, the NIH doctors or nurses will contact you and/or your doctor's office for an update on how you are doing, so that we either see you or get an update every six months. You may remain enrolled on the study indefinitely, and can return to the NIH for evaluation and screening for studies options should you need additional cancer treatment.

2) If your cancer has not responded or has come back after allotransplant, and you are not eligible or interested in an available NIH treatment protocol, you will continue to receive medical care with your primary cancer or transplant physician. You will be asked to come back to the NIH at your six(+/-7 days), 12(+/-7 days) and 24-month(+/-14 days) anniversaries of your allotransplant for follow-up, then on a yearly basis. If you are on another protocol at the NIH, we will coordinate this visit to coincide with other required restaging visits. Regardless of where you received your transplant, every effort will be made to use studies that you have had done recently, to minimize inconvenience and duplication of testing for you. In addition, the NIH doctors or nurses will contact you and/or your doctor's office for an update on how you are doing, so that we either see you or get an update every six months. You may remain enrolled on the study indefinitely, and can return to the NIH as needed for evaluation, including screening for treatment study options.

At each study follow-up evaluation, you will have a physical exam, blood work, and tests to see the status of your cancer, such as scans, x-rays, bone marrow aspiration/biopsy. Which tests you will have done will depend on your particular cancer diagnosis. A bone marrow aspiration and biopsy may be repeated at follow-up visits, if necessary to assess your particular cancer and/or if needed to determine your treatment protocol options. If you have had these tests performed recently at the NIH or if the films, slides, etc. can be transferred to the NIH for review, it is possible that you will not need to have some studies repeated.

In addition to testing for your clinical status, blood will be drawn at each visit for research studies of your immune system, including the types and numbers of different immune cells and the amounts of proteins these cells make when the immune system is activated. Some of the bone marrow would be used for research. We may ask you to undergo additional tests to obtain samples of your cancer cells or fluid for research tests. These tests are described in detail later in this consent. Examples include apheresis, tumor biopsy, or fluid sampling (e.g., spinal tap,

abdominal tap, lung tap). Additional testing that is solely for research would only be done if they can be performed with minimal risk to you.

The maximum amount of blood taken from you for research will not exceed the strict limit set for research by the NIH. The blood collections for research on this study are well below the NIH limit. However, if you are participating in more than one study at the NIH, we will monitor how much blood is being collected for research to make sure the total does not exceed the limit. Also, we will coordinate any other research collections with other protocols you may be on, to make sure that samples collected solely for research in any one-month period are no more than: 1 (one) bone marrow; or 2 (two) tumor biopsy procedures.

The Study Chart below outlines the assessments you will have while on this study.

Study Chart

Assessment	On-Study	6, 12 and 24-Month+ & Anniversary Follow-up	6 Month+ Contact	At Treatment Response	New Protocol Screening
Medical History Review	√	√		√	√
Brief Medical Update			√		
Physical Exam	√	√		√	√
"Routine" Blood Tests	√	√		√	√
Cancer Staging Scans/Tests	√	√		√	√
Research Blood Samples	√	√		√	√
Cancer Biopsies	√			√	Possible
Bone Marrow Procedure	√			Possible	Possible
Large Blood Draw or Apheresis	√			√	√

+ It is possible the visit dates will vary by 1-2 weeks

Standard, approved cancer therapies may be recommended. The NIH would not provide the approved therapies unless they are part of another NIH treatment study. The medications would be prescribed and given to you by your primary cancer doctor at home. In the unusual case that the

NIH would provide standard cancer treatment, including cells from your donor, you would be asked to sign a separate consent that explains the potential risks, side-effects and chances of the treatment controlling your cancer, and that the treatment is available outside of the NIH. In this case, we would closely watch your condition and look for possible side effects of the treatment. You could receive other treatments as needed, such as transfusions and antibiotics.

What does this study involve?

In addition to having a history and physical examination, blood drawn and standard scans and x-rays to evaluate you, the following procedures will also be done.

Bone marrow aspiration and biopsy:

At the beginning of the study, you will be asked to have bone marrow testing, with an aspiration and biopsy. Individuals with cancer cells in the bone marrow will be asked to have this testing repeated to evaluate any treatments and/or at follow-up evaluations when a complete assessment of your cancer is done. Bone marrow testing is done with a procedure in which a needle is inserted into your bone marrow, usually in your hipbone, and one-to-two tablespoons of the liquid portion of your bone marrow is removed ("aspirated"). Afterward, another hollow needle is inserted into the bone to obtain a piece of the marrow part of the bone ("biopsy"). Prior to putting the needle into your bone, the skin and bone are numbed with a medicine injected into the area.

Apheresis or Large-Volume Blood Draw:

Apheresis is a procedure that is used when only part of the cells or proteins in the blood are needed, to avoid having to take too much blood. It allows collection of the part that is needed, while the rest of the blood can be returned to the body. The procedure for obtaining blood cells through apheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells are removed from your blood stream with a serum-cell separator machine. The machine divides whole blood into red cells, plasma (the serum part) and lymphocytes (or white cells). This requires putting a needle into one of your arms to send blood into the machine and a second needle into the other arm to return the unused portion of the blood to your blood stream. In a lymphocyte collection, the lymphocytes are taken out, and the plasma and red cells returned to your blood stream, along with a small amount of salt solution (saline) and blood thinning medication (anticoagulant). Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the procedure. A research lymphocyte collection takes approximately 1-to-2 hours to complete. Apheresis will be performed by trained personnel from the NIH Department of Transfusion Medicine (DTM). The I.V. tube(s) will be removed after the cells are collected.

As apheresis requires healthy, large veins, sometimes the arm veins cannot be used. While larger veins could be used, since the cells are for research only, apheresis would not be done. If your arm veins cannot be used, instead of apheresis, you would have several tubes of blood drawn for

research ("large-volume blood draw"). For safety, the amount of blood is determined by your weight. Everyone will be asked to undergo an apheresis or research blood draw at the beginning of the study. Later, individuals who are being evaluated for an NIH treatment protocol may need to have it repeated if required for studies of interest.

Cancer Tissue Biopsy:

If you have an area with cancer cells that appears to be easy to sample, you will be evaluated by the Surgery Consult Service or Interventional Radiology to determine the safest and easiest way to take a sample of the tissue. The surgeon/radiologist, in consultation with your study doctor(s) will decide the exact procedure. Depending on the procedure that is required, you may have local anesthesia, where your skin is numbed and the sample is taken from your cancer tissue using a large needle or a small scalpel (knife). In some cases where a biopsy is done for medical reasons, to help your doctor make a diagnosis or determine whether your cancer has spread, you might need a surgical procedure in the operating room, possibly with general anesthesia. The specific details and risks of the procedure would be explained to you by the surgeon/radiologist before the biopsy takes place and you would be asked to sign a separate consent for the procedure. Everyone who has cancer tissue will be asked to undergo a cancer tissue biopsy at the beginning of the study if it can be performed with minimal discomfort and risk of complications. Later we might ask you if a second biopsy could be performed if you have a response to an experimental treatment.

In addition to the surgical or needle biopsy, you will have an evaluation with Interventional Radiology to determine whether there is a cancer site that would be safe to draw fluid from with a very thin needle ("Fine Needle Aspiration"). If so, you would have this done at the beginning of the study and it would be repeated during a follow-up evaluation if your cancer is responding to an experimental therapy. The radiologist would explain specific details of the procedure to you before the biopsy takes place and you would be asked to sign a separate consent for each procedure.

Standard Treatment:

Uncommonly, individuals require non-experimental cancer treatments while they are at the NIH. If you need cancer treatment with "standard" or "approved" treatments that need to be provided by the NIH, study doctors will describe the treatment plan to you in detail before proceeding with any treatment. Standard cancer treatments could include a single medication or a combination of medications, an infusion of donor cells, e.g., lymphocytes and/or stem cells, surgery or radiation therapy. These treatments would not be experimental. You will be asked to sign a separate consent form detailing potential risks and benefits for any treatment procedures not outlined in this consent.

Birth Control

If you receive cancer therapy at the NIH while participating on this study, and you are a woman who could become pregnant, or are the partner of a woman who could become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for three months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.
Effective forms of birth control include:

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

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

The side effects or risks of participating in this study result from the procedures performed initially or during this study and are the same as the risks expected if these procedures were performed by your local medical doctor. In addition, if you receive standard treatments on this study, the chemotherapy, Donor Lymphocytes, immune therapy or radiation therapy have side effects. All the treatments that will be recommended have been approved by the US Food and Drug Administration (FDA). These risks and side effects will be explained to you in detail when your doctor explains the recommended treatment plan with you. At no time will you be given an experimental treatment or procedure on this study.

Risks of Procedures During Evaluations

CT and/or FDG-PET-CT Scans

You will be receiving radiology tests, often including CT and/or PET-CT scans, as part of your evaluation. However, a major goal of this study is to make sure we learn how to monitor patients after relapse. We and others have noticed that the way cancers behave if they grow or come back after an allotransplant can be different than usual patterns before transplant. Standard monitoring studies used for cancer before transplant may not be helpful to monitor cancer after allotransplant. Most radiologic procedures involve a low level exposure to radiation. While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence that any radiation exposure may not be completely safe. There may be a very slight increase in the

risk of a new cancer from any radiologic procedure, depending on the dose of radiation it uses.

Bone marrow aspiration & biopsy:

This procedure usually causes temporary pain and bruising at the needle site. Pain can usually be managed with acetaminophen (Tylenol). Very rarely, infection or bleeding may occur at the needle site. Serious risks are very rare but include fat embolism (fat from the bone marrow enters the blood and goes to another part of the body, blocking the blood flow), and the risks of any sedation or anesthesia you require. You will be given these risks and asked to sign separate consent(s) for the bone marrow aspiration/biopsy (and for sedation, if required) before the procedure.

Apheresis:

The most common side effects of apheresis are pain and bruising at the IV needle sites. Mild side effects from the blood thinning medication citrate used in the apheresis procedure are common and include:

- Chills
- Numbness and tingling sensations ("pins and needles") especially around the mouth
- Anxiety
- Muscle cramps
- Nausea

These rapidly go away when the collection is slowed down or stopped. More serious side effects due to citrate-induced low calcium levels are uncommon and include:

- Low blood pressure
- Seizures
- Weakness
- Muscle stiffness or cramping.

If this happens, the apheresis procedure will be stopped, in which case these side effects quickly go away. You will be watched closely for any side effects and the procedure will be stopped and appropriate treatment given if necessary. If you require calcium to be given through your I.V., there is a small risk of damage to your skin and veins around the I.V., slowed heart rate or changes in blood pressure. Some people have a low number of blood platelets for a short period of time after donation. Platelets help the blood to clot. However, low platelet counts from apheresis have not caused an increased risk of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure.

Cancer Tissue Biopsy:

The primary risks are from pain at the site of biopsy and a slight risk of infection, bleeding or injury to nearby tissue. This biopsy will only be done if required for evaluation of your cancer, or if only for research, if it is relatively easy and safe to do. If you develop any complications you could require close monitoring, blood products, antibiotics or a surgical procedure to repair tissue injury. Specific risks of the procedure will be discussed with you during the consent process at the time of the procedures.

Graft-Versus-Host Disease (GVHD):

Evaluation at study visits will include an assessment for GVHD. Any cancer treatment taken after an allotransplant may cause GVHD to occur or make it worse. Acute GVHD occurs in the first 100 days after transplantation. Mild acute GVHD (skin rash only) can be treated with steroid lotions that you can apply on your skin. More severe acute GVHD can cause blistering of the skin, abdominal pain and diarrhea, disturbances in liver function and jaundice (yellowing of the skin) and require stronger treatment including steroids, which are given intravenously (through the vein). Occasionally, severe acute GVHD does not respond to steroids or even more potent immune suppression, and can cause death. Sometimes GVHD can present with the kinds of problems that occur in acute GVHD, but it develops after Day 100. This is often called "Late-Acute GVHD." It tends to behave and respond to treatment much like acute GVHD.

Delayed or chronic GVHD may also occur. Typically, this occurs after the first 100 days following transplantation. The risk of chronic GVHD seems to be about the same as the risk for acute GVHD. Symptoms include dryness of the mouth and eyes, skin rash, joint stiffness, weight loss, liver damage (including jaundice), and/or lung damage leading to cough and shortness of breath. Sometimes chronic GVHD produces minor symptoms that require little, if any treatment. Other times, symptoms and damage can come and go over time; chronic GVHD can also be severe, with symptoms and damage getting worse over time. Chronic GVHD is treated with drugs that suppress the immune system, such as cyclosporine and/or steroids given by mouth. Chronic GVHD can persist to various degrees for the rest of your life. Both acute and chronic GVHD, and the drugs we use to treat them, can place patients at significant risk for infections. Infections can be severe, require hospitalization, and even cause death.

If you receive any cancer treatment on this or other NIH study, you will be carefully monitored for any signs of new or worsening GVHD. If you develop GVHD, we would perform all necessary evaluations and studies that are needed to make the diagnosis and provide you with approved treatment as soon as possible in an attempt to limit its severity. If you require and are a candidate for any experimental therapy for GVHD, the option would be discussed with you and you would be asked to sign a separate consent.

Other Risks or Discomforts Associated with Routine Procedures on this Study:

Side effects of a temporary I.V. in the vein of the groin (if you require it for apheresis) include bleeding, bruising, infection, blood clot, a hole in the vein or pain. If you require sedation (a type of mild anesthesia), the risks will be explained to you at that time. The I.V. will be put in by medical professionals with experience in this procedure. They will discuss the procedure and possible risks in further detail with you before the procedure. Should a temporary I.V. in the groin be required, you will be asked to sign a separate consent for I.V. placement and sedation (if necessary).

Blood Drawing: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When a large amount of blood is drawn, the red blood cell count may drop causing anemia. We will monitor your red blood cell count closely during the study.

Only small amounts of blood, cancer tissue, lymph node and/or bone marrow or other fluids will be collected during the sampling time points. The amount of blood and/or bone marrow collected will be restricted according to NIH safety standards below. Thus, there should be only a slight increase over minimal risk to you from participation in this study.

The maximum amount of blood taken from you is based on your age and will not be more than the strict blood volume limit set for research by the NIH. In adults that limit is 550 mL in an 8 week period. To reduce any risk from cancer tissue biopsies or bone marrow biopsy, no more than 2 (two) cancer tissue biopsies will be performed for research each month, and no more than 1 (one) bone marrow biopsy may be performed each month for research purposes.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aims of this study are to determine NIH treatment study options for patients who have progression of their cancer after an allotransplant, and to study blood and tissue from allotransplant recipients who may or may not have relapsed cancer to learn why some people respond to allotransplant and others do not. Analysis of blood and tissue will look for ways to make the allogeneic immune system more effective in fighting cancer, to prevent relapse or treat cancer progression if it does occur. We will catalogue the kinds of standard and experimental cancer therapies patients have received after allotransplant, which will be reviewed by experts to develop consistent guidelines for cancer doctors to use in making decisions for the best way to treat a patient's cancer after allotransplant.

It is possible that you as an individual will not receive any benefit from participation in this study. The screening evaluation includes testing to determine eligibility for several treatment studies, and results will be reviewed to determine your best treatment study option. This may shorten the time it takes for you to enroll on a study and begin cancer treatment. As a participant

of this study, you will receive evaluations of your cancer. You may receive individualized consultations with medical experts, to address your specific issues and/or concerns. We hope that you will get personal medical benefit from the individualized medical recommendations after each evaluation, including cancer treatment recommendations, but we cannot be certain. You may receive a standard treatment on this study, including donor cells, if they are available, which has the potential to shrink cancer or lessen symptoms, such as pain, that are caused by the cancer, and which may resolve a problem that would prevent your participation on a treatment study. The knowledge gained from studying your blood and tissue samples or your responses to treatments may help others in the future who have cancer and have not responded to allotransplant.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

To be eligible for this protocol, you must have already received an allogeneic stem cell transplant. Prior to this, you may have received other forms of treatment for your cancer. At this time you may consider other options such as:

- Taking part in a study using experimental therapies, either at the NIH or elsewhere;
- Getting treatment or care for your cancer without being in a study, such as approved forms of chemotherapy, radiation, surgery or immune therapies; or
- Electing not to try additional cancer treatments

None of these treatment options precludes your continuing to receive treatment for any symptoms you are experiencing. Sometimes called palliative care, it is focused on reducing your symptoms, such as pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but can be part of a comprehensive cancer treatment program.

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 study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the 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 if they are not covered by your insurance company.
- Medicines that are not part of the study treatment 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

Stopping Participation in this study

Your doctor may decide to stop your participation in this study for the following reasons:

- if he/she believes that it is in your best interest
- if you decide to withdraw
- if the study is closed
- if you lose your ability to provide informed consent

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

You can stop taking part in the study at any time. 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. Also, you may choose NOT to undergo specific tests or procedures requested during your participation in this study without affecting your participation in other studies or your care at NIH. Make your study team aware of those tests or procedures you do not want to undergo.

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.

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 they 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, Ronald Gress M.D., Building 10-CRC, Room 3E-3330, Telephone: 240-760-6167. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, 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 22, 2016 THROUGH AUGUST 21, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0125 PRINCIPAL INVESTIGATOR: Ronald Gress, M.D.

STUDY TITLE: Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/16/17 (E) Date Posted to Web: 03/04/17
Recipient-Subject in Remission

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 have previously received an allogeneic hematopoietic stem cell transplant (or "allotransplant") with the intention of curing your blood-system cancer (such as leukemia,

myelodysplastic syndrome, lymphoma, multiple myeloma). We are studying why some people's cancers continue to grow or spread after they have had an allotransplant, when for other people, like yourself, the allotransplant keeps the cancer from growing or coming back. We are asking for people who have had allotransplants for a cancer of the blood to participate, whether or not the cancer is in remission. If your cancer is in remission, the tests that are done on this study will help us study the biology of why the transplant worked. In the event that your cancer returns, we will determine that with the testing and will evaluate whether you would be able to participate in one of several NIH protocols that are testing cancer treatments for people whose cancer returns after an allotransplant.

Why is this study being done?

The main purposes of this study are to:

1. Study the biology and behavior of cancer when it comes back after allotransplant and when it does not.
2. Study changes in the immune system after allotransplant to better understand why some people's cancers keep growing or come back, while others may be cured.
3. Collect information about what kind of treatments people have received for relapse after allotransplant, how cancers have responded and how people have tolerated cancer therapies after an allotransplant. Cancer and transplant experts will study this information and develop guidelines to help doctors decide how to best treat an allotransplant recipient with cancer relapse.

Cancers are often well controlled (hopefully cured) after allotransplant, in part because the donor immune system is able to find and kill the cancer cells. However, sometimes after allotransplant, the cancer continues to grow ("progress") or goes away ("into remission") but then comes back ("relapses"). Unfortunately, when cancer grows after allotransplant there is no proven cure. We have several studies at the Clinical Center testing experimental treatments for cancer in people who have had an allotransplant. One goal of this study is to evaluate why some people's cancers are not controlled by the allotransplant. We will be examining cancer cells from samples taken from adults, with biopsies of old tumor sites, bone marrow biopsies, or abnormal fluid collections, and the immune system cells from samples taken during apheresis or blood draws, comparing people with cancer progression or relapse with people like you whose cancers are going away ("responding") or in remission. Our laboratory testing of tumor cells will include studying the specific immune cells present, the functioning of the cells in the area of old tumor, and whether the genetic make-up of your cells changes after treatment. If we have enough cells available we will also use them to study new treatments, including animal testing for cell treatments for conditions like yours. From blood samples (including apheresis procedures) we will examine the immune cells of both you and your donor (if available) to study

why some patients' cancer responds and other do not. We hope that by learning more about why allotransplant works for some people, we can find ways to treat relapse after an allotransplant and to prevent cancer relapse in the future.

You will have your medical history reviewed and a physical examination. You will have cancer staging studies, blood drawn, a bone marrow procedure, and, if you are an adult and it can be done safely, a biopsy of tissues in the area where your tumor used to be. This information and results will be part of a comparison between people whose cancer is not under control after allotransplant with people whose cancer is in remission or is responding. First, cancer experts will do a thorough evaluation of your medical history, particularly your cancer and transplant history, perform a physical examination, test your blood for how well your organs and immune system are working, examine your cancer cells, your immune cells, and if possible, immune cells from your allotransplant donor. You will be asked to return to the NIH at your six (+/-7 days), 12 (+/-7 days) and 24-month (+/-14 days) anniversaries from your allotransplant for a similar follow-up evaluation. We will contact you and/or your doctor's office at half-yearly intervals after the initial evaluation to get an update on how you are doing. If your cancer remains in remission, you will not be required to return to the NIH or provide six-month updates after your 24-month post-transplant visit. However, you may remain on the study indefinitely, and at any point during your participation in this study you may return to the NIH for evaluation if it appears that there are new studies of interest for which you may be eligible.

If you later need cancer treatment, you will have all the testing that is required to determine which treatment studies may be good options for you. If you are eligible for a treatment study at the NIH, this option will be discussed as well.

During your participation in this study, you will be asked to undergo many tests that are for research. Depending on whether you are an adult, the type of cancer you were treated for and where it was, these research tests may include blood sampling, biopsies (adults only), apheresis, and/or bone marrow biopsy. Everyone who agrees to participate in this study will have all of the research testing that can be done safely during the first study evaluation visit. How often the tests are repeated will depend upon how frequently you return to NIH, as detailed below.

How many people will take part in this study?

Up to 350 individuals who have had allotransplants and 150 allotransplant donors will participate in this study over the next 5 years.

Description of Research Study

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

Before you begin the study

Before you enter this study, we will help you arrange to have your medical records, radiology studies and previous cancer biopsy material sent to the NIH for review. We will discuss your medical history with you and, if you need treatment, with your physician. We will ask you to have a physical exam; this can be done at the NIH or with your local physician, who can send us the results. This will be done to make sure that you can safely travel to and from the NIH, and that that you will be able to enroll and undergo all study requirements. If the donor is available from your previous allotransplant, we will ask whether s/he would participate.

During the study

Initial Evaluation

Once you have signed the consent for this study, you will undergo a very thorough medical examination, depending upon the type and location of your cancer, which will include:

- History and physical examination.
- Routine laboratory tests of your blood and urine, to assess the function of your thyroid, liver, kidney, blood clotting, and immune system. They will also test your nutritional status, blood and tissue type, and for some infections you may have or have had (i.e., CMV, EBV, HSV 1 and 2, T. Cruzi (Chagas agent), Hepatitis A, B and C, HTLV-I and II, HHV-6, Toxoplasmosis, and varicella zoster (chicken pox). We will also test your immune status to common vaccines you may have received since allotransplant, including the pneumococcal (pneumonia) vaccine and the tetanus vaccine (either a tetanus shot or the DTaP vaccine). If you are female of childbearing potential, you will have a pregnancy test. As part of this study, you will be tested for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you have HIV infection, you would still able to participate in this study. If this is a new diagnosis, we would 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 anyone who may have been exposed or be at risk because of your HIV infection. These tests are similar to the tests that were done before your transplant.
- Cancer scans and x-rays. Depending on the details of your cancer history, these may include a computerized tomography ("CT") or magnetic resonance imaging ("MRI") scan of the brain; CT scans of neck, chest, abdomen, and pelvis; whole-body positron emission tomography (PET-CT) scan; and/or a lumbar puncture (or "spinal tap"). If you have had these tests performed recently at the NIH or the testing can be transferred for review at the NIH, it is possible that you may not need to have some studies repeated. A bone

marrow aspiration and biopsy may be part of the initial study evaluation depending on the type of cancer you had.

- Tissue evaluation. If you are an adult, depending on the type, location and status of your cancer, we may ask for a biopsy of a prior site of cancer, in order to study the cells around the area where your cancer went away. Your tissue samples will be evaluated by a medical specialist to test for any hidden cancer cells; if we can do so safely, we will obtain some extra tissue and/or use any tissue or fluid left that is left over after diagnostic testing to be used for research studies.

If you are pregnant you are not eligible to enroll on this research study, as it includes radiology studies that may not be safe for a fetus. If you are breastfeeding you are not eligible to enroll onto this research study as the protocol uses radiology tests that require injection of radioactive materials that might be secreted in the breast milk. If you are female, you will have a pregnancy test at the beginning of the initial and follow-up evaluation visits; if pregnant or breastfeeding, parts of the evaluation would not be performed. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Follow-up Evaluations

Since your cancer is responding or in remission after allotransplant, you will continue to receive routine care with your primary cancer or transplant physician. You will be asked to come back to the NIH at your six (+/-7 days), 12(+/-7 days) and 24-month (+/-14 days) anniversaries of your allotransplant. If you are on a transplant or treatment protocol at the NIH, we will coordinate this visit to coincide with other required restaging visits. Regardless of where you received your transplant, every effort will be made to use studies that you have had done recently, to minimize inconvenience and duplication of testing for you. In addition, the NIH doctors or nurses will contact you and/or your doctor's office for an update on how you are doing, so that we either see you or get an update every six months. After your 24-month anniversary evaluation, return visits and updates are no longer required. You may remain enrolled on this study indefinitely. If your cancer should come back after your 24-month transplant anniversary, we would like for you to let us know; we would offer to bring you to the NIH for further evaluation, including screening for treatment study options.

At each study follow-up evaluation, you will have a physical exam, blood work, and tests to make sure your cancer has not returned, such as scans, x-rays, bone marrow aspiration/biopsy. Which tests you will have done will depend on your particular cancer diagnosis and how recently they have been done prior to your visit. A bone marrow aspiration and biopsy may be repeated at follow-up visits, if necessary to assess your particular cancer. If you have had these tests performed recently at the NIH or if the films, slides, etc. can be transferred to the NIH for review, it is possible that you will not need to have some studies repeated.

In addition to testing for your clinical status, blood will be drawn at each visit for research studies of your immune system, including the types and numbers of different immune cells and the amounts of proteins these cells make when the immune system is activated. Some of the bone marrow would be used for research. We may ask you to undergo additional tests to obtain samples of your cells or fluid for research tests. These tests are optional and are described in detail later in this consent. Examples include apheresis, biopsy, or fluid sampling (e.g., spinal tap, abdominal tap, lung tap).

The maximum amount of blood taken from you for research will not exceed the strict limit set for research by the NIH. In adults that limit is 550 ml of blood in an 8-week period. The blood collections for research on this study are well below the NIH limit. However, if you are participating in more than one study at the NIH, we will monitor how much blood is being collected for research to make sure the total does not exceed the limit. Also, we will coordinate any other research collections with other protocols you may be on, to make sure that samples collected solely for research in any one-month period are no more than: 1 (one) bone marrow; or 2 (two) tumor biopsy procedures.

The Study Chart below outlines the assessments you will have while on this study.

Study Chart

Assessment	On-Study	6, 12and 24-Month + Anniversary Follow-up	6 Month+ Contact
Medical History Review	√	√	
Brief Medical Update			√
Physical Exam	√	√	
"Routine" Blood Tests	√	√	
Cancer Scans/Tests	√	√	
Research Blood Samples	√	√	
Biopsies of tissue adjacent to tumor	√		
Bone Marrow Procedure	Depending on type of cancer		
Apheresis	√		

+ visit dates can vary by 1-2 weeks

What does this study involve?

In addition to having a history and physical examination, blood drawn and standard scans and x-rays to evaluate you, the following procedures may also be done depending upon your type of cancer.

Bone marrow aspiration and biopsy:

You may be asked to have a bone marrow biopsy at the beginning of the study. A bone marrow biopsy is a procedure in which a needle is inserted into your bone marrow, usually in your hipbone, and one-to-two tablespoons of the liquid portion of your bone marrow is removed. Prior to putting the needle into your bone, the skin and bone are numbed with a medicine injected into the area.

Apheresis or Large-Volume Blood Draw:

Apheresis is a procedure that is used when only part of the cells or proteins in the blood are needed, to avoid having to take too much blood. It allows collection of the part that is needed, while the rest of the blood can be returned to the body. The procedure for obtaining blood cells through apheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells are removed from your blood stream with a serum-cell separator machine. The machine divides whole blood into red cells, plasma (the serum part) and lymphocytes (or white cells). This requires putting a needle into one of your arms to send blood into the machine and a second needle into the other arm to return the unused portion of the blood to your blood stream. In a lymphocyte collection, the lymphocytes are taken out, and the plasma and red cells returned to your blood stream, along with a small amount of salt solution (saline)

and blood thinning medication (anticoagulant). Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the procedure. A research lymphocyte collection takes approximately 1-to-2 hours to complete. Apheresis will be performed by trained personnel from the NIH Department of Transfusion Medicine (DTM). The I.V. tube(s) will be removed after the cells are collected.

As apheresis requires healthy, large veins, sometimes the arm veins cannot be used. While larger veins could be used, since the cells are for research only, apheresis would not be done. If your arm veins cannot be used, instead of apheresis, you would have several tubes of blood drawn for research ("large-volume blood draw"). Everyone will be asked to undergo an apheresis or research blood draw at the beginning of the study. Later, individuals who are being evaluated for an NIH treatment protocol may need to have it repeated if required for studies of interest.

Cancer Tissue Biopsy:

If you are in remission, biopsies will only be done on tissue from an area where you previously had tumor. These biopsies will be optional (you can refuse them) and will only be done if they will not cause you undue discomfort or put you at undue risk for complications.

If you have an area that used to have cancer cells that appears to be easy to sample, you will be evaluated by the Surgery Consult Service or Interventional Radiology to determine the safest and easiest way to take a sample of the tissue. The surgeon/radiologist, in consultation with your study doctor(s) will decide the exact procedure. Depending on the procedure that is required, you may have local anesthesia, where your skin is numbed and the sample is taken from your cancer tissue using a large needle or a small scalpel (knife). In some cases where the biopsy is done to determine whether there might be a recurrence for medical reasons, you may need to have general anesthesia and/or the procedure may be done in the operating room. The specific details of the procedure would be explained to you by the surgeon/radiologist before the biopsy takes place and you would be asked to sign a separate consent for the procedure.

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Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

The side effects or risks of participating in this study result from the procedures performed initially or during this study and are the same as the risks expected if these procedures were

performed by your local medical doctor. At no time will you be given an experimental treatment or procedure on this study.

Risks of Procedures During Evaluations

CT and/or FDG-PET-CT Scans

You will be receiving radiology tests, often including CT and/or PET-CT scans, as part of your evaluation. However, a major goal of this study is to learn how to monitor patients who might relapse. We and others have noticed that the way cancers behave if they grow or come back after an allotransplant can be different than usual patterns before transplant. Standard monitoring studies used for cancer before transplant may not be helpful to monitor cancer after allotransplant. Most radiologic procedures involve a low level exposure to radiation. While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence that any radiation exposure may not be completely safe. There may be a very slight increase in the risk of a new cancer from any radiologic procedure, depending on the dose of radiation it uses.

Bone marrow aspiration & biopsy:

This procedure usually causes temporary pain and bruising at the needle site. Pain can usually be managed with acetaminophen (Tylenol). Very rarely, infection or bleeding may occur at the needle site. Serious risks are very rare but include fat embolism (fat from the bone marrow enters the blood and goes to another part of the body, blocking the blood flow), and the risks of any sedation or anesthesia you require. You will be given these risks and asked to sign separate consent(s) for the bone marrow aspiration/biopsy (and for sedation, if required) before the procedure.

Apheresis:

The most common side effects of apheresis are pain and bruising at the IV needle sites. Mild side effects from the blood thinning medication citrate used in the apheresis procedure are common and include:

- Chills
- Numbness and tingling sensations ("pins and needles") especially around the mouth
- Anxiety
- Muscle cramps
- Nausea

These rapidly go away when the collection is slowed down or stopped. More serious side effects due to citrate-induced low calcium levels are uncommon and include:

- Low blood pressure
- Seizures
- Weakness
- Muscle stiffness or cramping

If this happens, the apheresis procedure will be stopped, in which case these side effects quickly go away. You will be watched closely for any side effects and the procedure will be stopped and appropriate treatment given if necessary. If you require calcium to be given through your I.V., there is a small risk of damage to your skin and veins around the I.V., slowed heart rate or changes in blood pressure. Some people have a low number of blood platelets for a short period of time after donation. Platelets help the blood to clot. However, low platelet counts from apheresis have not caused an increased risk of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure.

Tissue Biopsy:

The primary risks are from pain at the site of biopsy and a slight risk of infection, bleeding or injury to nearby tissue. This biopsy will only be done if you agree to it, and if it is relatively easy and safe to do. If you develop any complications you could require close monitoring, blood products, antibiotics or a surgical procedure to repair tissue injury. Specific risks of the procedure will be discussed with you during the consent process prior to undergoing the procedures. This biopsy is optional and you can decide not to have a biopsy and still participate in this research study. No matter what you decide to do, it will not affect your future care at the NIH. Even if you agree now to the biopsy, if you change your mind later, you can decline when we ask you to sign the separate procedure consent prior to undergoing the procedure.

Graft-Versus-Host Disease (GVHD):

Evaluation at study visits will include an assessment for GVHD. Any cancer treatment taken after an allotransplant may cause GVHD to occur or make it worse. Acute GVHD occurs in the first 100 days after transplantation. Mild acute GVHD (skin rash only) can be treated with steroid lotions that you can apply on your skin. More severe acute GVHD can cause blistering of the skin, abdominal pain and diarrhea, disturbances in liver function and jaundice (yellowing of the skin) and require stronger treatment including steroids, which are given intravenously (through the vein). Occasionally, severe acute GVHD does not respond to steroids or even more potent immune suppression, and can cause death. Sometimes GVHD can present with the kinds of problems that occur in acute GVHD, but it develops after Day 100. This is often called "Late-Acute GVHD." It tends to behave and respond to treatment much like acute GVHD.

Delayed or chronic GVHD may also occur. Typically, this occurs after the first 100 days following transplantation. The risk of chronic GVHD seems to be about the same as the risk for acute GVHD. Symptoms include dryness of the mouth and eyes, skin rash, joint stiffness, weight loss, liver damage (including jaundice), and/or lung damage leading to cough and shortness of breath. Sometimes chronic GVHD produces minor symptoms that require little, if any treatment. Other times, symptoms and damage can come and go over time; chronic GVHD can also be severe, with symptoms and damage getting worse over time. Chronic GVHD is treated with drugs that suppress the immune system, such as cyclosporine and/or steroids given by mouth. Chronic GVHD can persist to various degrees for the rest of your life. Both acute and chronic GVHD, and the drugs we use to treat them, can place patients at significant risk for infections. Infections can be severe, require hospitalization, and even cause death.
If you develop GVHD, we would perform all necessary evaluations and studies that are needed to make the diagnosis and provide you with approved treatment as soon as possible in an attempt

to limit its severity. If you require and are a candidate for any experimental therapy for GVHD, the option would be discussed with you and you would be asked to sign a separate consent.

Other Risks or Discomforts Associated with Routine Procedures on this Study:

Side effects of a temporary I.V. in the vein of the groin (if you require it for apheresis) include bleeding, bruising, infection, blood clot, a hole in the vein or pain. If you require sedation (a type of mild anesthesia), the risks will be explained to you at that time. The I.V. will be put in by medical professionals with experience in this procedure. They will discuss the procedure and possible risks in further detail with you before the procedure. Should a temporary I.V. in the groin be required, you will be asked to sign a separate consent for I.V. placement and sedation (if necessary).

Blood Drawing: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When a large amount of blood is drawn, the red blood cell count may drop causing anemia. We will monitor your red blood cell count closely during the study.

Only small amounts of blood, tissue, lymph node and/or bone marrow or other fluids will be collected during the sampling time points. The amount of blood and/or bone marrow collected will be restricted according to NIH safety standards.

To reduce any risk from cancer tissue biopsies or bone marrow biopsy, no more that 2 (two) cancer tissue biopsies will be performed for research each month, and no more than 1 (one) bone marrow biopsy may be performed each month for research purposes.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aims of this study are to study blood and tissue from allotransplant recipients who may or may not have relapsed cancer to learn why some people respond to allotransplant and others do not. Analysis of blood and tissue will look for ways to make the allogeneic immune system more

effective in fighting cancer, to prevent relapse or treat cancer progression if it does occur. We will catalogue the kinds of standard and experimental cancer therapies patients have received after allotransplant, which will be reviewed by experts to develop consistent guidelines for cancer doctors to use in making decisions for the best way to treat a patient's cancer after allotransplant.

It is possible that you as an individual will not receive any benefit from participation in this study. As a participant of this study, you will receive evaluations for your prior cancer. We hope that you will get personal medical benefit from the individualized medical recommendations

after each evaluation, if, for example, we identified a new medical condition or detected cancer recurrence at an early, treatable stage, but we cannot be certain. If your cancer were to recur, you might benefit from rapid evaluation, which could identify treatment studies and allow you to begin treatment faster that might otherwise be the case. It is possible that we might be able to use the information obtained while your cancer is in remission to identify a better treatment for you. The knowledge gained from studying your blood and tissue samples or your responses to treatments may help others in the future who have cancer and have not responded to allotransplant.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

To be eligible for this protocol, you must have already received an allogeneic stem cell transplant. Prior to this, you may have received other forms of treatment for your cancer. At this time you may consider other options such as:

- Getting evaluations at established intervals with your transplant physician, to see if your cancer recurs. If your cancer were to recur and this study is still accepting new patients, you would be able to reconsider enrollment to screen for potential treatment studies at that time.

Please talk to your doctor about this 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 study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the 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 if they are not covered by your insurance company.
- Medicines that are not part of the study treatment 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

Stopping Participation in this study:

Your doctor may decide to stop your participation in this study for the following reasons:

- if he/she believes that it is in your best interest
- if you decide to withdraw
- if the study is closed, in which case
- if you lose the ability to provide informed consent

In this case, you will be informed of the reason you are being removed from the study.

You can stop taking part in the study at any time. 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. Also, you may choose NOT to undergo specific tests or procedures requested during your participation in this study without affecting your participation in other studies or your care at NIH. Make your study team aware of those tests or procedures you do not want to undergo.

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 can**not** be recalled and destroyed.

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 they 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, Ronald Gress M.D., Building 10-CRC, Room 3E-3330, Telephone: 240-760-6167. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, 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 22, 2016 THROUGH AUGUST 21, 2017.

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

Print Name _____ Print Name _____

INSTITUTE: National Cancer Institute

STUDY NUMBER 11-C-0125 PRINCIPAL INVESTIGATOR: Ronald Gress, M.D.

STUDY TITLE: Study of the Biology and Natural History of Disease Outcomes in Patients Treated with Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/16/17 (E) Date Posted to Web: 03/04/17
Recipient-Subject Pre-Transplant

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 evaluated for treatment with an allogeneic hematopoietic stem cell transplant (or "allotransplant") with the intention of curing your blood-system cancer (such as leukemia, myelodysplastic syndrome, lymphoma, multiple myeloma). We are studying why some people's cancers continue to grow or spread after they have had an allotransplant, when for other people, the allotransplant keeps the cancer from growing or coming back. We are asking for people who

will have allotransplants for a blood-system cancer to participate. The tests that are done on this study will help us study the biology of the immune system and blood-system cancers before and after allotransplant. In the event that your cancer returns after allotransplant, we could evaluate whether you would be able to participate in one of several NIH protocols that are testing cancer treatments for people whose cancer returns after an allotransplant.

Why is this study being done?

The main purposes of this study are to:

1. Study the biology and behavior of cancer that is treated with allotransplant, to improve our understanding of how and why some cancers come back after allotransplant and some do not.
2. Study changes in the immune system before and after allotransplant to better understand why some people's cancers keep growing or come back, while others do not.
3. Collect information about what kind of cancer treatments people have received before and after allotransplant, how cancers have responded and how people have tolerated therapies given after allotransplant. Cancer and transplant experts will study this information and develop guidelines to help doctors decide how to best treat someone who has had an allotransplant for a blood-system cancer to prevent or treat a recurrence.

Cancers are often well controlled (hopefully cured) after allotransplant, in part because the donor immune system is able to find and kill the cancer cells. However, sometimes after allotransplant, the cancer continues to grow ("progress") or goes away ("into remission") but then comes back ("relapses"). Unfortunately, when cancer grows after allotransplant there is no proven cure. We have several studies at the Clinical Center testing experimental treatments for cancer in people who have had an allotransplant. One goal of this study is to evaluate why some people's cancers are not controlled by the allotransplant. We will be examining cancer cells using biopsies of old tumor sites, bone marrow biopsies, or abnormal fluid collections, and the immune system cells from samples taken during apheresis or blood draws, comparing samples from people before allotransplant with samples from those with cancer progression or relapse and with people whose cancers are going away ("responding") or in remission. Our laboratory testing of tumor cells will include studying the specific immune cells present, the functioning of the cells in the area of old tumor, and whether the genetic make-up of cancers cells change after allotransplant or later treatments. If we have enough cells available we will also use them to

study new treatments, including animal testing for cell treatments for conditions like yours. From blood samples (including apheresis procedures) we will examine the immune cells of both you and your donor (if available) to study why some patients' cancer responds and other do not. We hope that by learning more about why allotransplant works for some people, we can find better ways to treat relapse after an allotransplant and to prevent cancer relapse.

You will have your medical history reviewed and a physical examination. You will have cancer staging studies, blood drawn, a bone marrow procedure, and, if you have cancer in a location that can be safely removed, a biopsy of your tumor. This information and results will be part of a comparison between people with cancer before allotransplant with people whose cancer grows after allotransplant and with people whose cancer is in remission or is responding after allotransplant.

Your evaluation will take place as part of your evaluation for the allotransplant procedure, so that we can avoid having duplicate evaluations, tests and samples performed. First, cancer experts will do a thorough evaluation of your medical history, particularly your cancer and transplant history, perform a physical examination, test your blood for how well your organs and immune system are working, examine your immune cells, and if possible, your cancer cells and the immune cells from your allotransplant donor. You will be evaluated at the NIH at your 100 day (+/-7 days), six (+/-7 days), 12(+/-7 days) and 24-month (+/-14 days) anniversaries from your allotransplant, which, likewise, will take place during the routine evaluations done after allotransplant. We will contact you and/or your doctor's office 18 months after the initial evaluation to get an update on how you are doing. If your cancer remains in remission, you will not be required to return to the NIH or provide six-month updates after your 24-month post-transplant visit. However, you may remain on the study indefinitely, and at any point during your participation in this study you may return to the NIH for evaluation if it appears that there are new studies of interest for which you may be eligible.

If you later need cancer treatment, you may have all the testing that is required to determine which treatment studies may be good options for you. If you are eligible for a treatment study at the NIH, this option will be discussed as well.

During your participation in this study, you will be asked to undergo many tests that are for research. Depending on the type of cancer you were treated for and where it was, these research tests may include blood sampling, biopsies, apheresis, and/or bone marrow biopsy. Everyone who agrees to participate in this study will have all of the research testing that can be done safely during the first study evaluation visit. How often the tests are repeated will depend upon how frequently you return to NIH, as detailed below.

How many people will take part in this study?

Up to 350 individuals who have had allotransplants and 150 allotransplant donors will participate in this study over the next 5 years.

Description of Research Study

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

Before you begin the study

Before you enter this study, we will help you arrange to have your medical records, radiology studies and previous cancer biopsy material sent to the NIH for review. We will discuss your medical history with you and, if you need treatment, with your physician. We will ask you to have a physical exam; this can be done at the NIH or with your local physician, who can send us the results. This will be done to make sure that you can safely travel to and from the NIH, and that that you will be able to enroll and undergo all study requirements. If the donor is available from your previous allotransplant, we will ask whether s/he would participate.

During the study

Initial Evaluation

Once you have signed the consent for this study, you will undergo a very thorough medical examination. Most of the parts of the evaluation are required to determine whether allotransplant is a safe option for you, so that little additional testing is required for this study. Depending upon the type and location of your cancer, this evaluation may include:

- History and physical examination.
- Routine laboratory tests of your blood and urine, to assess the function of your thyroid, liver, kidney, blood clotting, and immune system. They will also test your nutritional status, blood and tissue type, and for some infections you may have or have had (i.e., CMV, EBV, HSV 1 and 2, T. Cruzi (Chagas agent), Hepatitis A, B and C, HTLV-I and II, HHV-6, Toxoplasmosis, and varicella zoster (chicken pox). We will also test your immune status to common vaccines you may have received since allotransplant, including the pneumococcal (pneumonia) vaccine and the tetanus vaccine (either a tetanus shot or the DTaP vaccine). If you are female of childbearing potential, you will have a pregnancy test. As part of this study, you will be tested for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you have HIV infection, you would still able to participate in this study. If this is a new diagnosis, we would 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 anyone who may have been exposed or be at risk because of your HIV infection.
- Cancer scans and x-rays. Depending on the details of your cancer history, these may include a computerized tomography ("CT") or magnetic resonance imaging ("MRI") scan of the brain; CT scans of neck, chest, abdomen, and pelvis; whole-body positron emission tomography (PET-CT) scan; and/or a lumbar puncture (or "spinal tap"). If you have had these tests performed recently at the NIH or the testing can be transferred for review at the NIH, it is possible that you may not need to have some studies repeated. A bone marrow aspiration and biopsy may be part of the initial study evaluation depending on the type of cancer you had.

- Tissue evaluation. If you have cancer in a location that can be safely removed, a biopsy of your tumor will be performed for diagnostic confirmation here at the NCI as well as for research. We may ask for a biopsy of an area of your body that used to have cancer in order to study the cells around the area where your cancer went away. Your tissue samples will be evaluated by medical specialists to test confirm the type of cancer or look for any hidden cancer cells. If we can do so safely, we will obtain some extra tissue and/or use any tissue or fluid left over after diagnostic testing to be used for research studies.

If you are pregnant you are not eligible to enroll on this research study, as it includes radiology studies that may not be safe for a fetus. If you are breastfeeding you are not eligible to enroll onto this research study as the protocol uses radiology tests that require injection of radioactive materials that might be secreted in the breast milk. If you are female, you will have a pregnancy test at the beginning of the initial and follow-up evaluation visits; if pregnant or breastfeeding, parts of the evaluation would not be performed. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Follow-up Evaluations

You will continue to receive routine care with your primary transplant physician. You will be asked to come back to the NIH at your 100 day (+/-7 days), six (+/-7 days), 12 (+/-7 days) and 24-month (+/-14 days) anniversaries of your allotransplant.

We will coordinate this visit to coincide with other required restaging visits at the NIH. Every effort will be made to use studies that you have had done recently, to minimize inconvenience and duplication of testing for you. In addition, the NIH doctors or nurses will contact you and/or your doctor's office for an update on how you are doing, so that we either see you or get an update every six months. After your 24-month allotransplant anniversary evaluation, return visits and updates are no longer required. You may remain enrolled on this study indefinitely. If your cancer should come back after your 24-month transplant anniversary, we would like for you to let us know; we would offer to bring you to the NIH for further evaluation, including screening for treatment study options.

At each study follow-up evaluation, you will have a physical exam, blood work, and tests to make sure your cancer has not returned, such as scans, x-rays, bone marrow aspiration/biopsy. Which tests you will have done will depend on your particular cancer diagnosis and how recently they have been done prior to your visit. A bone marrow aspiration and biopsy may be repeated at follow-up visits, if necessary to assess your particular cancer. If you have had these tests

performed recently at the NIH or if the films, slides, etc. can be transferred to the NIH for review, it is possible that you will not need to have some studies repeated. In addition to testing for your clinical status, blood will be drawn at each study visit for research studies of your

immune system, including the types and numbers of different immune cells and the amounts of proteins these cells make when the immune system is activated.

Some of the bone marrow would be used for research. We may ask you to undergo additional tests to obtain samples of your cells or fluid for research tests. These tests are optional and are described in detail later in this consent. Examples include apheresis, biopsy, or fluid sampling (e.g., spinal tap, abdominal tap, lung tap). The maximum amount of blood taken from you for research will not exceed the strict limit set for research by the NIH. In adults that limit is 550 ml of blood in an 8-week period. The blood collections for research on this study are well below the limit. However, if you are participating in more than one study at the NIH, we will monitor how much blood is being collected for research to make sure the total does not exceed the limit. Also, we will coordinate any other research collections with other protocols you may be on, to make

sure that samples collected solely for research in any one-month period are no more than: 1 (one) bone marrow; or 2 (two) tumor biopsy procedures.

The Study Chart below outlines the assessments you will have while on this study.

Study Chart

Assessment	On-Study	100 day, 6, 12 and 24-Month+ Anniversary Follow-up	6 Month+ Contact
Medical History Review	√	√	
Brief Medical Update			√
Physical Exam	√	√	
"Routine" Blood Tests	√	√	
Cancer Scans/Tests	√	√	
Research Blood Samples	√	√	
Biopsies of tumor tissue or sites of prior tumors	√		
Bone Marrow Procedure	Depending on type of cancer		
Apheresis	√		

+ visit dates my vary by 1-2 weeks

What does this study involve?

In addition to having a history and physical examination, blood drawn and standard scans and x-rays to evaluate you, the following procedures may also be done depending upon your type of cancer.

Bone marrow aspiration and biopsy:

You may be asked to have a bone marrow biopsy at the beginning of the study. If you are less than 18 years of age, this procedure would only be done if it is necessary for your medical care. A bone marrow biopsy is a procedure in which a needle is inserted into your bone marrow, usually in your hipbone, and one-to-two tablespoons of the liquid portion of your bone marrow is removed. Prior to putting the needle into your bone, the skin and bone are numbed with a medicine injected into the area.

Apheresis or Large-Volume Blood Draw:

Apheresis is a procedure that is used when only part of the cells or proteins in the blood are needed, to avoid having to take too much blood. It allows collection of the part that is needed, while the rest of the blood can be returned to the body. The procedure for obtaining blood cells through apheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells are removed from your blood stream with a serum-cell separator machine. The machine divides whole blood into red cells, plasma (the serum part) and lymphocytes (or white cells). This requires putting a needle into one of your arms to send blood into the machine and a second needle into the other arm to return the unused portion of the blood to your blood stream.

In a lymphocyte collection, the lymphocytes are taken out, and the plasma and red cells returned to your blood stream, along with a small amount of salt solution (saline) and blood thinning medication (anticoagulant).

Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the procedure. A research lymphocyte collection takes approximately 1-to-2 hours to complete. Apheresis will be performed by trained personnel from the NIH Department of Transfusion Medicine (DTM). The I.V. tube(s) will be removed after the cells are collected.

As apheresis requires healthy, large veins, sometimes the arm veins cannot be used. While larger veins could be used, since the cells are for research only, apheresis would not be done. If your arm veins cannot be used, instead of apheresis, you would have several tubes of blood drawn for research (large-volume blood draw). Everyone will be asked to undergo an apheresis or research blood draw at the beginning of the study. Later, individuals who are being evaluated for an NIH treatment protocol may need to have it repeated if required for studies of interest.

Cancer Tissue Biopsy:

If your cancer is active and it is safe to do so, a tumor biopsy will be done. If your cancer is in remission, biopsies will only be done on tissue from an area where you previously had tumor. If your cancer is in remission, these biopsies will be optional (you can refuse them) and will only be done if they will not cause you undue discomfort or put you at undue risk for complications.

If you have active cancer or there is an area of your body that used to have cancer cells that appears to be easy to sample, you will be evaluated by the Surgery Consult Service or Interventional Radiology to determine the safest and easiest way to take a sample of the tissue. The surgeon/radiologist, in consultation with your study doctor(s) will decide the exact procedure. Depending on the procedure that is required, you may have local anesthesia, where your skin is numbed and the sample is taken from your cancer tissue using a large needle or a small scalpel (knife).

In some cases where the biopsy is done to determine whether there might be a recurrence for medical reasons, you may need to have general anesthesia and/or the procedure may be done in the operating room. The specific details of the procedure would be explained to you by the surgeon/radiologist before the biopsy takes place and you would be asked to sign a separate consent for the procedure.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

The side effects or risks of participating in this study result from the procedures performed initially or during this study and are the same as the risks expected if these procedures were performed by your local medical doctor. At no time will you be given an experimental treatment or procedure on this study.

Risks of Procedures During Evaluations

CT and/or FDG-PET-CT Scans

You will be receiving radiology tests, often including CT and/or PET-CT scans, as part of your evaluation. However, a major goal of this study is to learn how to monitor patients who might relapse. We and others have noticed that the way cancers behave if they grow or come back after an allotransplant can be different than usual patterns before transplant. Standard monitoring studies used for cancer before transplant may not be helpful to monitor cancer after allotransplant. Most radiologic procedures involve a low level exposure to radiation. While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence that any radiation exposure may not be completely safe. There may be a very slight increase in the risk of a new cancer from any radiologic procedure, depending on the dose of radiation it uses.

Bone marrow aspiration & biopsy:
This procedure usually causes temporary pain and bruising at the needle site. Pain can usually be managed with acetaminophen (Tylenol). Very rarely, infection or bleeding may occur at the needle site. Serious risks are very rare but include fat embolism (fat from the bone marrow enters the blood and goes to another part of the body, blocking the blood flow), and the risks of any sedation or anesthesia you require. You will be given these risks and asked to sign separate consent(s) for the bone marrow aspiration/biopsy (and for sedation, if required) before the procedure.

Apheresis:
The most common side effects of apheresis are pain and bruising at the IV needle sites. Mild side effects from the blood thinning medication citrate used in the apheresis procedure are common and include:

- Chills
- Numbness and tingling sensations ("pins and needles") especially around the mouth
- Anxiety
- Muscle cramps
- Nausea

These rapidly go away when the collection is slowed down or stopped. More serious side effects due to citrate-induced low calcium levels are uncommon and include:

- Low blood pressure
- Seizures
- Weakness
- Muscle stiffness or cramping

If this happens, the apheresis procedure will be stopped, in which case these side effects quickly go away. You will be watched closely for any side effects and the procedure will be stopped and appropriate treatment given if necessary. If you require calcium to be given through your I.V., there is a small risk of damage to your skin and veins around the I.V., slowed heart rate or changes in blood pressure. Some people have a low number of blood platelets for a short period of time after donation. Platelets help the blood to clot. However, low platelet counts from apheresis have not caused an increased risk of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure.

Tissue Biopsy:
The primary risks are from pain at the site of biopsy and a slight risk of infection, bleeding or injury to nearby tissue. This biopsy will only be done if you agree to it, and if it is relatively easy and safe to do. If you develop any complications you could require close monitoring,

blood products, antibiotics or a surgical procedure to repair tissue injury. Specific risks of the procedure will be discussed with you during the consent process prior to undergoing the procedures. This biopsy is optional and you can decide not to have a biopsy and still participate in this research study. No matter what you decide to do, it will not affect your future care at the NIH. Even if you agree now to the biopsy, if you change your mind later, you can decline when we ask you to sign the separate procedure consent prior to undergoing the procedure.

Graft-Versus-Host Disease (GVHD):

Evaluation at study visits will include an assessment for GVHD. Any cancer treatment taken after an allotransplant may cause GVHD to occur or make it worse. Acute GVHD occurs in the first 100 days after transplantation. Mild acute GVHD (skin rash only) can be treated with steroid lotions that you can apply on your skin.

More severe acute GVHD can cause blistering of the skin, abdominal pain and diarrhea, disturbances in liver function and jaundice (yellowing of the skin) and require stronger treatment including steroids, which are given intravenously (through the vein). Occasionally, severe acute GVHD does not respond to steroids or even more potent immune suppression, and can cause death. Sometimes GVHD can present with the kinds of problems that occur in acute GVHD, but it develops after Day 100. This is often called "Late-Acute GVHD." It tends to behave and respond to treatment much like acute GVHD.
Delayed or chronic GVHD may also occur. Typically, this occurs after the first 100 days following transplantation.

The risk of chronic GVHD seems to be about the same as the risk for acute GVHD. Symptoms include dryness of the mouth and eyes, skin rash, joint stiffness, weight loss, liver damage (including jaundice), and/or lung damage leading to cough and shortness of breath. Sometimes chronic GVHD produces minor symptoms that require little, if any treatment. Other times, symptoms and damage can come and go over time; chronic GVHD can also be severe, with symptoms and damage getting worse over time. Chronic GVHD is treated with drugs that suppress the immune system, such as cyclosporine and/or steroids given by mouth.

Chronic GVHD can persist to various degrees for the rest of your life. Both acute and chronic GVHD, and the drugs we use to treat them, can place patients at significant risk for infections. Infections can be severe, require hospitalization, and even cause death.

If you develop GVHD, we would perform all necessary evaluations and studies that are needed to make the diagnosis and provide you with approved treatment as soon as possible in an attempt to limit its severity. If you require and are a candidate for any experimental therapy for GVHD, the option would be discussed with you and you would be asked to sign a separate consent.

Other Risks or Discomforts Associated with Routine Procedures on this Study:

Side effects of a temporary I.V. in the vein of the groin (if you require it for apheresis) include bleeding, bruising, infection, blood clot, a hole in the vein or pain. If you require sedation (a type of mild anesthesia), the risks will be explained to you at that time. The I.V. will be put in by medical professionals with experience in this procedure. They will discuss the procedure and possible risks in further detail with you before the procedure. Should a temporary I.V. in the groin be required, you will be asked to sign a separate consent for I.V. placement and sedation (if necessary).

Blood Drawing: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When a large amount of blood is drawn, the red blood cell count may drop causing anemia. We will monitor your red blood cell count closely during the study.

Only small amounts of blood, tissue, lymph node and/or bone marrow or other fluids will be collected during the sampling time points.

To reduce any risk from cancer tissue biopsies or bone marrow biopsy, no more that 2 (two) cancer tissue biopsies will be performed for research each month, and no more than 1 (one) bone marrow biopsy may be performed each month for research purposes.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aims of this study are to study blood and tissue from individuals who will be treated with allotransplant before and after allotransplant to learn why some people respond to allotransplant and others do not.

Analysis of blood and tissue will look for ways to make the allogeneic immune system more effective in fighting cancer, to prevent relapse or treat cancer progression if it does occur. We will catalogue the kinds of standard and experimental cancer therapies patients have received after allotransplant, which will be reviewed by experts to develop consistent guidelines for cancer doctors to use in making decisions for the best way to treat a patient's cancer after allotransplant.

It is possible that you as an individual will not receive any benefit from participation in this study. As a participant of this study, you will receive evaluations for your prior cancer. We hope that you will get personal medical benefit from the individualized medical recommendations after each evaluation, if, for example, we identified a new medical condition or detected cancer recurrence at an early, treatable stage, but we cannot be certain.

If your cancer were to recur, you might benefit from rapid evaluation, which could identify treatment studies and allow you to begin treatment faster that might otherwise be the case. It is

possible that we might be able to use the information obtained while your cancer is in remission to identify a better treatment for you. The knowledge gained from studying your blood and tissue samples or your responses to treatments may help others in the future who have cancer and have not responded to allotransplant.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

To be eligible for this protocol, you must be undergoing evaluation for an allogeneic stem cell transplant.

Prior to this, you may have received other forms of treatment for your cancer. At this time you may consider other options such as:

- Getting evaluations at established intervals with your transplant physician without participating on this research study. If your cancer were to recur and this study is still accepting new patients, you would be able to reconsider enrollment to screen for potential treatment studies at that time.

Please talk to your home doctor and transplant doctor about this 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 study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the 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 if they are not covered by your insurance company.
- Medicines that are not part of the study treatment 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

Stopping Participation in this study:

Your doctor may decide to stop your participation in this study for the following reasons:
- if he/she believes that it is in your best interest
- if you decide to withdraw
- if the study is closed
- if you lose your ability to provide informed consent

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

You can stop taking part in the study at any time. 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. Also, you may choose NOT to undergo specific tests or procedures requested during your participation in this study without affecting your participation in other studies or your care at NIH. Make your study team aware of those tests or procedures you do not want to undergo.

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 can**not** be recalled and destroyed.

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 they 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, Ronald Gress M.D., Building 10-CRC, Room 3E-3330, Telephone: 240-760-6167. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, 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 22, 2016 THROUGH AUGUST 21, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____