Children's Oncology Group

TO: Principal Investigators and CRAs at COG Member Transplant Centers

FROM: Judith Everett, Director, COG Study Development Office

DATE: December 31, 2007

SUBJECT: **Activation of ASCT0631 on December 31, 2007**

RE: *A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation*

ASCT0631 will be open for patient enrollment on **Monday, December 31, 2007**. Participation is limited to COG accredited Transplant Centers.

Patients and donors may be enrolled on the study once all eligibility requirements for the study have been met. **Only one patient ID will be assigned**. Institutions are reminded of the COG policy regarding eligibility waivers: No patient will be entered on a COG study unless the institutional investigator confirms the patient meets all the criteria for study entry as stated in the protocol at the time study entry is attempted. Eligibility criteria cannot be waived.

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Reference Number ***PASCT0631#R02PAPP01***
Notice of Protocol Approval

Date: JAN 2 3 2007
NCI Protocol #: ASCT0631
Local: ***ASCT0631***
Version Date: ***12/12/2006***
Principal Investigator: ***Stephan A. Grupp, M.D., Ph.D.***

Gregory H. Reaman, M.D.
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Dear ***Dr. Reaman:***

Your Protocol, ***"A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation"***, has been approved by the Protocol Review Committee (PRC) of the Cancer Therapy Evaluation Program (CTEP). Attached you will find the assigned monitoring mechanism for your protocol. Comments from the reviewers may be attached.

As the Principal Investigator, it is your responsibility to inform all co-investigators and personnel involved in the study (data management, pharmacy, nursing, statistics, etc.) of the approved status of this protocol. Please refer to the NCI Investigators Handbook (section 12) for a complete description of the role and responsibility of the Principal Investigator.

Notice of protocol activation (via the Protocol Status Update Form found on the CTEP home page (http://ctep.cancer.gov), an activation amendment, or a CDUS Submission) must be submitted to the Protocol and Information Office prior to opening this study for patient entry.

The NCI will not be supplying any agent(s) for this protocol.

All correspondence and review relevant to the protocol will be maintained in our files and made a matter of record for the next review of your group. A progress report on this study should appear in the minutes of every future meeting of your group until the study is completed and we have been notified of the completed status.

Should you have questions or comments regarding your protocol, please contact the PIO by telephone (301) 496-1367, fax (301) 496-9384 or e-mail (PIO@ctep.nci.nih.gov)

Sincerely,

Barry D. Anderson, M.D., Ph.D.
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Please note: Signature on file at CTEP. To request a signed document please contact PIO@CTEP.NCI.NIH.GOV.

MONITORING METHOD

Reporting of study results to the IND holder and/or study sponsor is a FDA requirement. Your study
ASCT0631, "***Gregory H. Reaman,***" has been assigned to the following reporting mechanism.

Please Note: Failure to submit clinical trial data on time may result in a suspension of your investigator privileges and/or study closure to further accrual.

CDUS

____ **CDUS Complete:** All CDUS data (e.g. protocol administrative and patient specific demographics, treatment, response and toxicity data) should be submitted quarterly.

_[X]_ **CDUS Abbreviated:** Protocol Administrative and Patient Demographic data.

CDUS data must be submitted quarterly to CTEP by electronic means. Paper reports will not be accepted. The instructions for the CDUS and the CDUS Smart Loader can be downloaded from the CTEP Home Page (http://ctep.cancer.gov). If you are unable to access the CTEP Home page please contact the **CDUS Help Line** by telephone (301) 840-8202, fax (301) 948-2242 or e-mail ncictephelp@CTEP.nci.nih.gov. The CDUS instructions identify the data required and provide specific instructions for each field. The specific file format and other details required for electronic submission are included in the CDUS Smart Loader instructions.

The due date for your quarterly report will be one month after the end of each quarter. Your first report is due on the date checked and each quarter thereafter as listed.

(_ April 30, _ July 31, _ October 31, _ January 31). (Check one)

CTMS

____ **CTMS**

This study has been assigned to be monitored by the Clinical Trials Monitoring Service (CTMS). Data is required to be submitted to CTMS at least once every two weeks, via the NCI/DCTD case report form or the electronic case report form (ACES). After CTEP approval, a CTMS representative will contact you with further instructions.

Other

____ **Other**

Activated: 12/31/07 Version Date: 10/29/07
Closed:

CHILDREN'S ONCOLOGY GROUP

COG ASCT0631
PBMTC STC051

A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation

Phase III Study

Limited to COG-accredited SCT Programs

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AGENTS

Filgrastim, G-CSF	NSC#614629
Tacrolimus	NSC # 717865
Methotrexate	NSC #000740
Thiotepa	NSC #6396
Cyclophosphamide	NSC #26271
Etoposide	NSC #141540
Busulfan	NSC #750
Cyclosporine	NSC #290193

FOR SPECIMEN SHIPPING, SEE SECTION 15.0

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

ABSTRACT

ASCT0631 is a Phase III trial comparing two graft sources for allogeneic transplantation using HLA-identical siblings as donors: bone marrow and filgrastim (G-CSF) stimulated bone marrow (G-BM) in children undergoing allogeneic transplantation for leukemias in which matched sibling donor transplantation is appropriate. The protocol is designed to implement a novel strategy to integrate transplant questions into treatment studies in the cooperative group setting, allowing patients on disease-specific treatment protocols co-enrollment on a study designed to investigate a transplant-specific question in a manner which does not adversely impact the primary, disease specific, treatment question. Thus, there will be two categories of leukemia patients enrolled on ASCT0631 – those for whom ASCT0631 is the only study enrollment, and those who are also enrolled on ASCT0431, AAML0532, or other leukemia treatment studies.

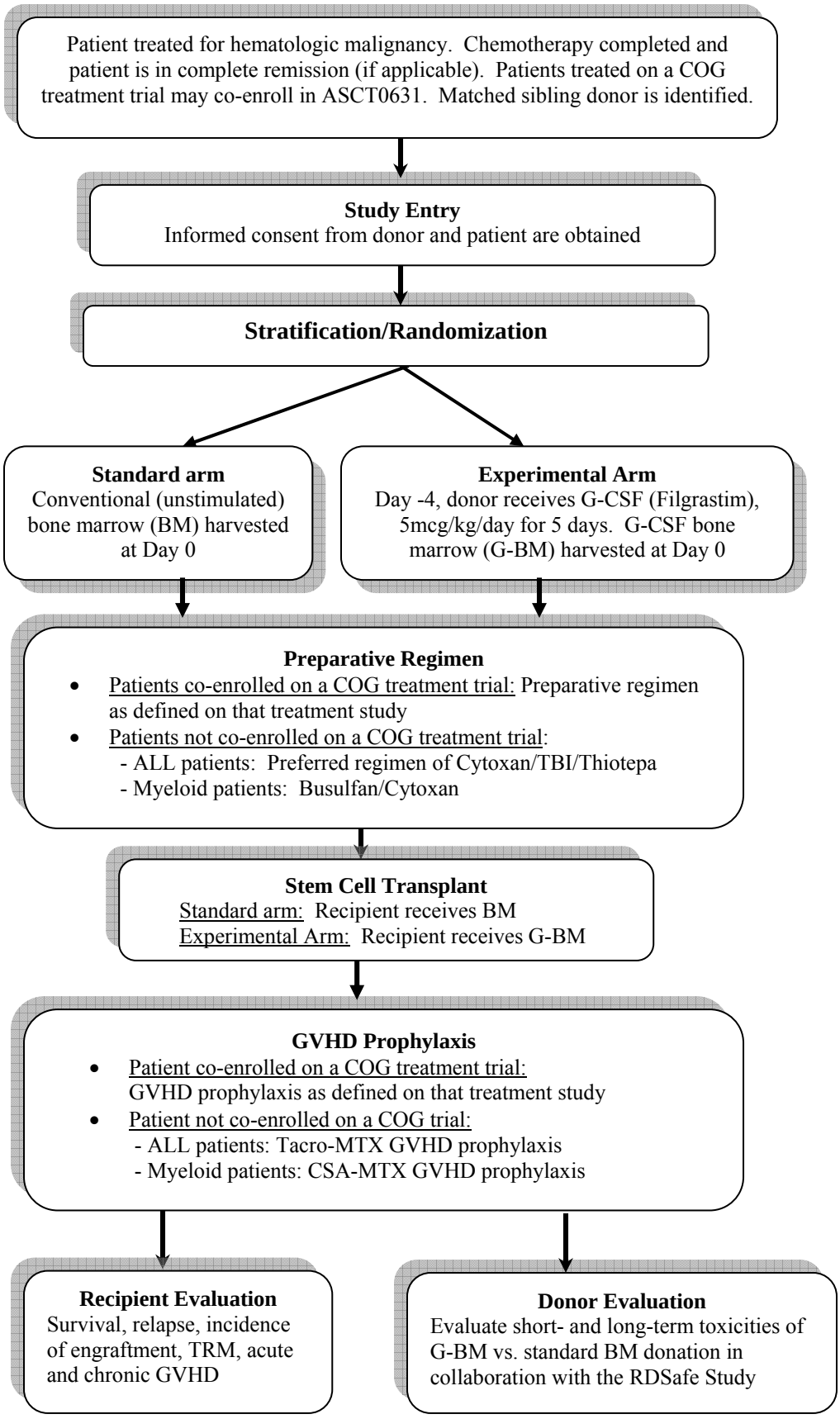
The major hypothesis of this protocol is that the increased bone marrow cell dose provided by the graft collected on the G-BM arm of this study will improve the event-free survival of these patients. We further hypothesize that patients on the G-BM arm will show more rapid engraftment kinetics with equivalent rates of acute and lower rates of chronic graft vs. host disease.

Any patient with acute or chronic leukemia or myelodysplasia needing bone marrow transplantation with a matched sibling donor available is eligible for this study. Eligible diseases include AML in CR1 or CR2; myelodysplastic syndrome; ALL in CR2 or high-risk CR1; CML in first or second chronic phase and JMML.

G-BM will be collected from donors on the experimental arm after five days of G-CSF treatment of the donor. Target volume for both BM and G-BM collections is 15 cc/kg of recipient weight, with a maximum of 20 cc/kg donor weight.

Biological studies will correlate graft characteristics with the incidence of GVHD and measure the rate of immunologic recovery of the patients. We will also assess the experience of the donor and family during participation on this protocol. There will be collection of acute adverse donor events and long-term donor experience using the national standard RDSafe approach pioneered by the NMDP and CIBMTR/NMDP.

EXPERIMENTAL DESIGN



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Hypotheses

1.1.1
The larger cell dose provided by G-CSF (filgrastim) stimulated bone marrow (G-BM) will improve event-free survival (EFS) in patients undergoing matched sibling donor bone marrow transplant (BMT).

1.1.2
Use of G-BM will provide more rapid engraftment kinetics compared to conventional BM.

1.1.3
Use of G-BM will result in similar rates of acute graft versus host disease (GVHD) and engraftment, and lower rates of chronic GVHD compared to conventional BM.

1.2 Primary Objective

1.2.1
Determine if the larger mononuclear cell dose provided by G-BM will improve EFS in patients undergoing myeloablative matched sibling donor BMT for hematologic malignancies.

1.3 Secondary Objectives

1.3.1
Evaluate the incidence and time to engraftment in subjects receiving G-BM as compared to conventional BM.

1.3.2
Evaluate rates of acute and chronic GVHD in subjects receiving G-BM as compared to conventional BM

1.3.3
Correlate incidence of acute and chronic GVHD with four parameters all assessed in the bone marrow harvests: i) absolute T cell numbers; ii) Th1 vs. Th2 profile of T cells; iii) Dendritic cell (DC) populations; and iv) T regulatory cell content.

1.3.4
Assess the impact of G-BM as a stem cell source on hospital stay, Day 100 TRM and reconstitution of cellular immunity.

1.3.5
Evaluate short- and long-term toxicities of G-BM vs. standard BM donation in collaboration with the RDSafe study.

2.0 BACKGROUND

Note: recombinant human granulocyte colony stimulating factor (G-CSF, filgrastim, Neupogen) will be referred to as G-CSF throughout this study protocol.

2.1 Study Rationale

Bone marrow transplantation is an important therapeutic intervention in pediatric and adult patients with malignant and non-malignant disorders. Although for many years the most commonly used hematopoietic stem cell source has been bone marrow, which is still the standard of care in pediatric allogeneic transplant. In recent years G-CSF mobilized peripheral blood stem cells (PBSC) have been shown to be an alternative source of hematopoietic stem cells. PBSC have now become the standard of care in adult allogeneic transplant (as well as being used almost universally in adult and pediatric autologous transplant). Although at least 20% of pediatric allogeneic transplants used PBSC in a recent survey, [1] there are risks and benefits associated with allogeneic PBSC that make its wider utilization in pediatrics potentially problematic. Some of these pediatric-specific issues are associated with the cell type (PBSC) and others are specific to the donor. Adult studies have shown that PBSC induce more rapid engraftment and are associated with improved outcome in patients with higher-risk leukemia. However, these benefits are obtained at a cost of significantly higher incidence of chronic graft versus host disease (cGVHD) as compared to harvested bone marrow. Additionally, in the setting of matched related transplantation of a pediatric patient, the donor is likely to be a child as well. This raises the issues of pheresis and potential need for catheter placement in smaller pediatric donors.

Treatment of the bone marrow donor with G-CSF prior to operative harvest has been shown to result in significant increases in marrow cellularity, resulting in a collected product with much high mononuclear cell concentrations and numbers of CD34+ progenitor cells. Studies in adults utilizing G-CSF stimulated bone marrow harvest (G-BM) have shown improved engraftment kinetics (similar to PBSC) compared to conventional marrow with no increase in the incidence of cGVHD (see below). Thus, G-BM may offer some or all of the benefits of PBSC compared to conventional bone marrow (BM), with fewer of the risks of PBSC. The potential benefits of G-BM, especially in the setting of pediatric matched sibling donor transplantation, include the following:

a) G-BM collection may be better tolerated than PBSC collection for pediatric donors.
   1. There will be no requirement for apheresis catheter placement as with PBSC collection in smaller children.
   2. A lower dose of G-CSF may be required, with the potential of less bone pain compared to the dose required for PBSC collection.

b) G-BM may offer benefit to recipients.
   1. Engraftment may be as rapid as PBSC and significantly more rapid than BM. This has the potential to reduce treatment-related mortality during BMT.
   2. A higher cell dose is associated with better outcome and improved leukemia-free survival in retrospective studies of BM transplantation. The PBMTC pilot experience and published studies of G-BM (summarized below) show that significantly higher cell doses are available with G-BM collection.
   3. The use of G-BM avoids the collection of large numbers of peripheral blood T cells, which are inherent in PBSC collection and which increases the risk of GVHD, especially cGVHD. Use of G-BM may therefore avoid the increased risk of cGVHD, a serious post-transplant complication.

These potential benefits can be assessed in the context of this randomized phase III trial, and have the potential to change the standard of care in pediatric transplantation.

2.2 G-CSF

G-CSF is a hematopoietic cytokine produced by monocytes, fibroblasts and endothelial cells. G-CSF is known to have multiple functions in normal, steady-state hematopoeisis, including the regulation of

neutrophil production and release from the bone marrow, neutrophil progenitor proliferation and differentiation, and the state of functional activation of neutrophils.[2] Genetically engineered recombinant human G-CSF was introduced in phase I trials in 1987.[3] At pharmacological doses, biological and clinical activity of G-CSF have been demonstrated in various settings such as treating chronic idiopathic neutropenia, neonatal sepsis, chemotherapy induced myelosuppression, aplastic anemia, recovery from aplasia after bone marrow transplant, and mobilization of CD34+ cells in the circulation with or without prior chemotherapy.[4]

The pharmacologic profile of G-CSF in normal donors is similar to that in cancer patients. G-CSF can be administered subcutaneously or intravenously, although subcutaneous administration is the preferred route. The maximum serum concentration after subcutaneous administration is reached within 2 to 8 hours.[5]

The side effects associated with G-CSF administration to normal individuals are similar to those seen in cancer patients. These include, bone pain, headache, fatigue, and nausea. More rarely reported side effects include anxiety, non-cardiac chest pain, myalgias, insomnia, night sweats, skin rashes and other local reactions and vomiting. These adverse events generally resolve quickly after discontinuation of G-CSF.[6]

2.3 Allogeneic BMT in Children

Hematopoietic stem cell transplantation using HLA matched sibling BM donors has been used successfully to treat pediatric patients since 1968. Standard indications for allogeneic bone marrow transplantation in children include the treatment of high-risk or relapsed hematologic malignancies, bone marrow failure syndromes, and hereditary immunodeficiency and metabolic disorders.[7]

2.4 Marrow Cell Dose and Outcome

Several studies have shown that a higher BM cell dose is associated with more rapid engraftment, less risk of fatal GVHD and improved survival in both related and unrelated marrow transplants.[8,9]

2.5 Allogeneic Transplantation using PBSC

A number of groups have recently reported on the outcome of patients who received G-CSF mobilized PBSC during HLA matched allogeneic transplantation.[10-14] These results have consistently shown that use of PBSC as a stem cell source led to more rapid engraftment of both neutrophil and platelets compared to BM as a stem cell source. In a recent randomized trial the Seattle group reported that allogeneic PBSC resulted in significantly faster neutrophil and platelet engraftment, and improved survival without increase in the incidence of acute or chronic GVHD with a relatively short follow-up of 1 year.[10,11] A particularly concerning report regarding the use of allogeneic PBSC comes from Brown et al, who reported the risk of cGVHD to be 87% at 2 years in 50 recipients of allogeneic PBSC with GVHD complications leading to death in 75% of the patients.[12] The European group for blood and marrow transplantation (EBMT) reported on 288 PBSC transplants from HLA-identical siblings as compared to a historic control of 536 HLA-identical sibling transplants using BM. Recipients of PBSC had more rapid neutrophil and platelet recovery (14 vs. 19 days) and (18 vs. 25 days) respectively. Although the incidence of aGVHD was not different there was significantly higher rate of cGVHD. The median time from transplantation to hospital discharge was 23 days after PBSC transplantation and 28 days after BM transplantation ($P = 0.003$). Treatment-related mortality rates were lower and leukemia-free survival rates were higher with blood stem cell transplants in patients with advanced leukemia.[13]

Levine et al. reported on 24 pediatric patients who received G-CSF mobilized PBSC transplants. 16 of 24 donors were children less than 18 years of age. The youngest donor was 8 years old. G-CSF was well tolerated and the main side effects reported were related to the G-CSF injections themselves. The study

showed more rapid neutrophil and platelet engraftment as compared to historic controls, but the incidence of chronic GVHD at one year was 75%; which is twice that typically observed in BM transplants.[14]

Recently, a retrospective analysis was performed by the International Bone Marrow Transplant Registry (IBMTR) of 143 PBSC and 630 BM transplants from HLA identical sibling donors in children aged 8 to 20 years with acute leukemia. This analysis revealed significantly higher rates of cGVHD (p=0.001) and transplant related mortality (p=0.001) in recipients of PBSC. Overall recipients of BM had significantly better survival (p=0.01). Clearly, the children receiving PBSC in this analysis had significantly higher-risk disease, which in turn reflects a considerable bias in the selection of PBSC over BM. However, this retrospective multivariate analysis has raised the possibility that the benefit conferred by a higher cell dose with PBSC may be offset by the morbidity of cGVHD.[15] Thus, this study suggests that a trial of G-BM may be particularly appropriate in the pediatric population.

In the aggregate, these studies suggest the following conclusions: allogeneic PBSC is associated with more rapid engraftment of neutrophils and platelets compared to unstimulated bone marrow. The incidence of chronic GVHD appears to be much higher than that seen after BM transplant. Though the data show a survival advantage for PBSC over BM for adult transplant recipients, there is potential concern as to whether allogeneic PBSC confers a survival advantage or disadvantage compared to allogeneic unstimulated bone marrow in pediatrics.

2.6 Experience with G-BM

There have been several small single arm and randomized studies of G-BM. In addition, the PBMTC has recently concluded a pilot study of G-BM in pediatric BMT patients which is summarized below. In a randomized trial of autologous G-BM transplantation versus G-CSF-mobilized PBSC transplantation in lymphoma patients, there was no significant difference in neutrophil recovery or duration of hospitalization.[16] Isola et al reported 10 patients who received G-CSF stimulated allogeneic bone marrow and compared their results to historic bone marrow recipient. The G-BM group attained an ANC of > or = 1×10^9/l nine days earlier and a platelet count of > or = 20×10^9/l six days earlier than historical controls receiving unstimulated HLA-identical sibling BM. Hospitalization was shortened by a mean of 10 days.[17] Couban reported on 29 allogeneic transplants using G-BM and showed that platelet and neutrophil engraftment was faster than historic controls with unstimulated marrow but both groups had similar length of hospital stay, febrile days, and days on antibiotics.[18] Mortin et al reported the results of a prospective randomized trial comparing G-BM versus G-CSF stimulated PBSC. There was no significant difference in neutrophil or platelet engraftment but there was significantly increased risk of acute (17 vs. 46%) and chronic (27 vs. 77%) GVHD in recipients of PBSC.[19] Similar results were reported by Serody et al showing that G-BM resulted in similar time to neutrophil engraftment but platelet engraftment was faster in recipients of PBSC. There was a trend towards increased risk of acute GVHD (27 vs. 60%, p=0.07) and significant increase in chronic GVHD (37 vs. 68%, p=0.049) in the PBSC group. The overall survival of the two groups in this study was similar.[20] None of these studies was powered to assess a survival difference between G-BM and the alternative cell source (BM or PBSC).

The data from G-BM studies to date suggest that use of G-BM may produce times to engraftment similar to that see with PBSC in the allogeneic setting, but the risk of cGVHD appears to be lower.

2.7 Experience with G-CSF in Pediatric Patients

There is extensive experience in using G-CSF in pediatric patients receiving intensive chemotherapy, post autologous or allogeneic stem cell transplant.[21] G-CSF in doses ranging from 10-12 mcg/kg has been well tolerated when administered either alone or following mobilizing chemotherapy regimens to collect PBSC for autologous transplantation in pediatric patients.[22,23] G-CSF has also been used in treating children with chronic neutropenia. A study of 44 patients with Kostmann syndrome who received G-CSF (0.8-50mcg/kg per day) for 4-6 years demonstrated a sustained neutrophil response following chronic

administration of G-CSF.[24] A number of patients with Kostmann syndrome have developed leukemia while receiving G-CSF. Though there exists the theoretical possibility that leukemia may develop following chronic G-CSF administration as a treatment-related adverse event, the consensus regarding MDS/AML in Kostmann patients is that Kostmann syndrome is itself a pre-leukemic condition and this is due to the natural progression of the disease in patients that are now surviving longer because the neutropenia is treated by G-CSF.[24] Two small studies involving 16 patients with cyclic neutropenia have shown G-CSF can be effective in maintaining neutrophil count for up to 6 years, and in this group of patients there is no evidence of increased leukemic risk.

Infectious diseases represent a significant cause of morbidity and mortality among neonates. In a placebo-controlled, randomized study of 42 pre-term infants with presumed sepsis, G-CSF at a dose of 1-20 µl/kg/day administered for 3 days led to dose dependent increase in their absolute neutrophil count, which was sustained for up to 96 hours after administration of the last dose. A long-term follow up of 21 infants in this study revealed no adverse events with 2-year follow-up.[25,26]

There is limited experience in administering G-CSF to mobilize PBSC in pediatric donors. Levine et al. reported on 24 pediatric recipients of G-CSF mobilized PBSC. Fourteen of the 24 donors were children: 8 adolescents and 6 preteens. The youngest donors were 8 years old. In most cases the donors were older and weighed more than the recipients and two of the donors required central access. Six donors complained of bone pain or headache that was relieved by acetaminophen.[14] Two PBMTC studies were then developed to lay the groundwork for this G-BM study. These data directly address some of the issues raised in terms of availability of pediatric data. The STC0212 study retrospectively reviewed 218 PBSC or donor leukocyte collections in 201 pediatric donors ranging from 8 months to 17 years in age, with 56% of the collections on children 12 and under and 17% on children under age 7. With an average G-CSF dose of 10 µg/kg/d for a mean of 4.4 days, less than 20% of children required pain medication, with a trend toward less pain with younger donors. No pain was reported in children under 7 and pain that did occur required at most acetaminophen, except for one teenage patient who required an oral narcotic (0.5%) for pain associated with line placement.[27] The second PBMTC study is the pilot trial leading to this study, and is detailed below.

2.8 Expected toxicities of G-BM donation

Toxicities that might be expected by donors given G-CSF followed by marrow harvest can be extrapolated from studies of donors undergoing either marrow harvest or PBSC donation. The Seattle group studied the experiences of a cohort of donors, ranging 22 to 63 years of age, who participated in the randomized trial of allogeneic marrow vs. peripheral blood stem cells.[28] Among 38 marrow donors, immediate adverse effects included pain (84%), nausea (26%), hypotension (34%), and hemorrhage (13%). Homologous blood was transfused in 1 patient (3%) and 3 (7%) were hospitalized overnight. Among the 30 PBSC donors, 4 patients (13%) developed complications (mostly minor) associated with the collection procedure. Physical status was reported to worsen in both groups; marrow donors reported a decrease in physical status on the day after donation, with gradual improvement over 2 week period, while PBSC donors reported a decrease in physical status through the duration of G-CSF administration. There were no significant differences in physical status, emotional status, duration or intensity of pain reported by the two donor groups. This study suggests that donors who are given G-CSF followed by marrow harvest will experience a period of discomfort that commences with G-CSF administration and resolves within 2 weeks of donation.

2.9 G-CSF Dosing

The G-CSF dose used to stimulate bone marrow from allogeneic donors ranges from 5-16 mcg/kg/dose for 1-5 days prior to marrow collection. All studies to date have shown prompt engraftment and increases in the total number of nucleated cells collected.[15-19] Chiang et al gave 5-10 mcg/kg/day of G-CSF for 5 days to normal volunteers and performed peripheral blood and bone marrow cell counts on Days 3, 6, 9 and 15. The

total nucleated cell count and CD34+ count per ml showed similar response in bone marrow and peripheral blood with peak around Day 6 that returned to normal on Day 15.[29,30] The absolute number of CD34+ cells in the bone marrow was higher using a dose of 5 mcg/kg as compared to 10 mcg/kg while the absolute number of CD34+ cells in the peripheral blood was higher with the 10 mcg/kg dosing (Figure 1). For the purpose of this study we will use G-CSF at 5 mcg/kg/dose daily for 5 days with bone marrow collection on the 5th day.[28]

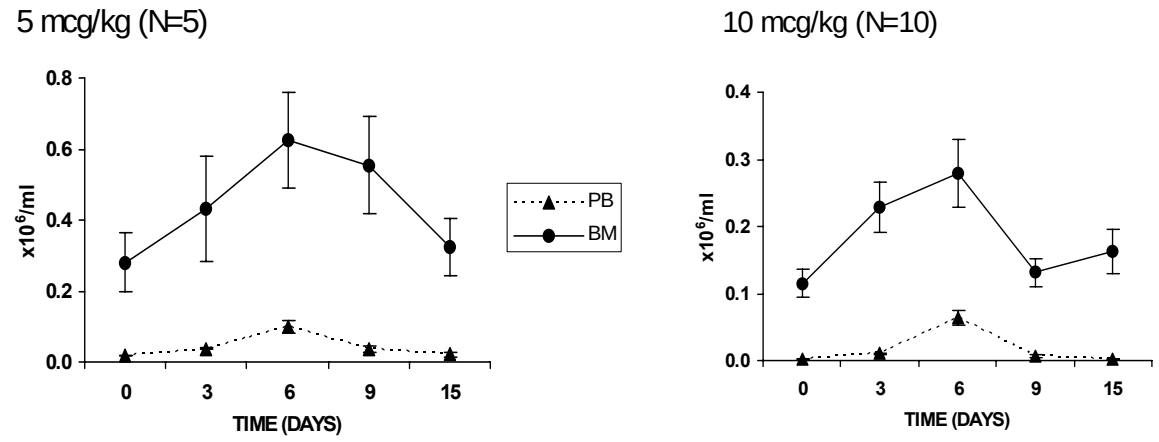


Figure 1. Absolute numbers of CD 34+ cells in bone marrow (BM) and peripheral blood (PB) during G-CSF treatment.[30]

2.10 G-BM in pediatric patients

PBMTC G-BM Pilot Study

A study has now been completed by the PBMTC to pilot use of G-BM in pediatric transplantation and to provide preliminary data to the study design of this trial. The PBMTC STC0233 prospective multi-center trial was conducted to evaluate the safety and feasibility of G-BM in children receiving HLA-identical sibling BMT. Thirty eight children at 9 different centers, 17 female and 21 male with a median age of 9.8 years (range 0.8-17) were enrolled between May 2003 and May 2005. Fifteen patients had high risk disease (ALL ≥CR2=4, AML≥ CR2/refractory=5, Advanced MDS=3, JMML=1, NHL=2) and 23 had standard risk disease (SAA=6, Red Cell Aplasia=1, Sickle cell disease=1, CML-CP=2, AML CR1=9, ALL CR1=2, MDS-RA=2). Five patients had undergone a prior allogeneic transplant. All patients received myeloablative preparative regimens (Cy/TBI±VP-16=12, BU/Cy±other=20 and Cy/ATG=6) and 32 (84%) received cyclosporine or tacrolimus with MTX as GVHD prophylaxis. Donors were HLA identical siblings (one donor was syngeneic). Donors with median age of 9.2 y (range 1.1-22) received 5 mcg/kg/day of G-CSF SQ for 5 consecutive days. Bone marrow was collected on the fifth day with a median volume of 14.5 cc/kg (range 5.2-25). No donor experienced any complications related to G-CSF administration or harvest, up to the time of last follow-up at one month after the harvest.

Graft Characteristics

The absolute CD34+ cell count at the day of the harvest was measured in 28 patients and it was significantly higher in bone marrow compared to peripheral blood, median of 513/µl (116-156) vs. 50/µl (8-247), respectively ($p < 0.0001$). Median nucleated and CD34+ cells infused was 8.4×10^8/kg (range 2.4-60.9) and 8.7×10^6/kg (range 2-27.6) respectively. Both the median and top range nucleated cell counts show that very high cell doses were collected and safely infused without severe GVHD (see below). This supports the use of a volume target, and not a cell dose target, for this trial. Another, related, potential concern in delivering high cell counts is that, using conventional BM collection, excessive numbers of peripheral blood T cells may be inadvertently collected with the graft. This was not the case on the

PBMTC pilot trial. The median CD3 count in the G-BM grafts (N=25 with available data) was 28 x 10^6/kg (range 1.5-74). This is similar to the T cell counts reported in the Bensinger et al report of BM vs. PBSC (24 x 10^6/kg in the BM group) and in the Morton G-BM vs. PBSC report (45 x 10^6/kg in G-BM). In both reports, the PBSC grafts contained approximately 10-fold higher T cell content than the respective marrow grafts. Thus, our pilot data show that high cell doses can be collected with similar absolute and lower relative numbers of CD3+ cells compared to conventional BM harvests.

No G-CSF was administered post-transplant to the pilot study patients. All patients had neutrophil engraftment, at a median of 19 days,[14-26,28-30] and all but one patient with early post-transplant relapse had platelet engraftment at a median of 20 days (range 9-44). Thirteen patients (35%) developed Grade 2 GVHD and 4 of 34 evaluable patients (12%) developed chronic GVHD (3 limited and 1 extensive). There was no transplant related mortality. Among 30 patients with malignant disorders 9 (30%) relapsed (6 with high risk and 3 with standard risk disease). The EFS and OS of patients with standard disease at 1 year is 84% (95% CI 68-100%) and 95% (95% CI 87-100%) respectively. With a median follow up of 1 year the estimated EFS and OS of all patients at one year is 76% (95% CI 62-93%) and 92% (95% CI 83-100%) respectively. No association between nucleated cell dose or CD34+ cell dose and EFS (p=0.17 and 0.44 respectively) or overall survival (p=0.55 and p=0.29 respectively) could be discerned in this group of patients who all received very high cell doses. We conclude from our pilot experience that G-BM collected from pediatric donors is safe and can result in high nucleated cell and CD34+ cell doses that facilitate engraftment after myeloablative BMT without a discernable increase in the risk of GVHD.[31]

2.11 Collaboration with the NMDP/CIBMTR Donor Safety Initiative, RDSafe

As outlined above, studies to date have yet to show significant short- or long-term toxicities from short-term G-CSF administration in the normal pediatric donor population. Whether toxicities already experienced by a normal donor are worsened by G-CSF will be prospectively assessed as part of this study to ensure protection of this donor population. The National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR) are jointly conducting a comprehensive national trial prospectively assessing donor safety with a specific focus on related, younger, and older donors, where published safety data is limited. The study is called RDSafe: A Multi-institutional Study of HSC Donor Safety and Quality of Life. This study looks at acute toxicities of the harvest procedure, short and long-term toxicities of G-CSF, and psychosocial aspects of the donor process. In ASCT0631, we will be collaborating with the RDSafe study effort on the following specific aims:

<u>RDSafe Specific Aim I</u>

Evaluate acute toxicities of donation in related donors with a focus on older and younger donors, comparing adverse events in these groups to toxicities of individuals donating for unrelated recipients through the National Marrow Donor Program.

A. Primary
   1. Compare the incidence of Grades III-IV Common Toxicity Criteria (CTC) adverse events in related versus unrelated hematopoietic stem cell donors between the ages of 18 and 60.
   2. Compare the incidence of Grades III-IV CTC adverse events of pediatric donors < age 18 and adult donors > age 60 with the younger adult related and unrelated donor groups in Specific Aim I.A.1.

B. Secondary
   1. Compare the incidence of serious and/or life-threatening toxicities in pediatric donors < age 18 and adult donors > age 60 with the younger adult related and unrelated groups in Specific Aim I.A.1.
   2. Compare the pre-donation risk factor profile of related and unrelated donors; assess whether donors with more risk factors have higher incidences of adverse events.

RDSafe Specific Aim II

Determine whether G-CSF is a risk to the normal donor.

A. Primary

1. Determine whether short-term administration of G-CSF causes an increase in the incidence of hematologic malignancies and/or myelodysplasia/myeloproliferative disorders in related and unrelated donors.

B. Secondary

1. Compare the incidence of vascular complications (stroke, MI, etc.), splenic rupture, and new onset or flares of autoimmune illnesses within six months of donation in related and unrelated donors treated with and without G-CSF prior to donation.

Data Gathering and Interaction between ASCT0631 and RDSafe

Through ASCT0631, donors will be assessed by standardized forms: a donor baseline form obtained prior to any treatment with G-CSF and BM donation, and a 2 week follow up form to assess any acute donor toxicities or exacerbation of baseline conditions. This data will be entered in the COG RDE system. Through the RDSafe study, further follow up at 1, 6, and 12 months after donation (and possibly yearly for up to 10 years thereafter) will be obtained by phone survey conducted through a call center at the NDMP for all patients who consent to this follow up on ASCT0631. Because the ASCT0631 and RDSafe are separate studies, opening at different times and possibly subject to regulatory closures, donors on ASCT0631 will not be automatically registered on the RDSafe study. The donors will be consented for long-term follow up and reported as a cohort to the RDSafe study. Many institutions will have both ASCT0631 and RDSafe open simultaneously. Those institutions have the option of registering donors on both studies. Data submission to COG is sufficient for the baseline forms required by the RDSafe study.

2.12 Outcomes for Matched Sibling Donor BMT for ALL and AML

In order to designate risk strata in this study, it is necessary to assess EFS likelihood after a matched sibling donors BMT. For the two most common diagnoses on the trial, ALL and AML, data are available from a number of pediatric trials.

Table 2.12.1 Matched Sibling BMT vs. Chemotherapy for Early Bone Marrow Relapse of ALL

Study	ALL Relapse Population	N (Chemo/ BMT)	Chemotherapy Outcome	Allo Transplant Outcome	p value
IBMTR/POG[32]	Remission <36m, MSD	179/179	10±3% (5yr LFS)	35±4% (5yr LFS)	<0.001
BFM[33]	Relapse<6m off therapy	115/51	22±4% (7yr EFS)	52±8% (7yr EFS)	<0.01
GITMO/AIEOP[34]	Remission<30m, MSD	142/29	16.1±4.5% (3yr DFS)	33.4±8.6% (3yr DFS)	0.002
CCG 1884[35]	Early Rel., mostly MSD	33/19	18±13% (2y EFS)	37±22% (2y EFS)	0.017
Spanish[36]	Remission<30m, MSD	30/14	6.9±4.7% (>10yr DFS)	36±12.8 (>10yr DFS)	0.01
MSKCC[37]	Relapse <24m, MSD	21/11	9±9% (5yr DFS)	48±11% (5yr DFS)	<0.01

Table 2.12.1 shows a series of studies performed by internationally recognized groups comparing matched sibling transplantation to chemotherapy in early ALL relapse. All outcomes are corrected for median time to transplantation and unanimously demonstrate superior outcome for matched sibling allogeneic transplant in this very high risk group. It is generally agreed that matched sibling

transplantation is the preferred therapy for this very high risk group. The Table is presented to give a sense of the range in outcomes that multi-institutional studies may detect in similar patients.

Thus, it is within the range of these studies to postulate a 40% 2 year LFS for ALL for the group that includes the "higher risk" ALL relapses – early marrow and relapsed T cell ALL.[33,38,39] Additionally, the outcome range in the literature for JMML is quite broad, from 33% to 43% to over 50%.[40-42] These patients form our High Risk stratum.

The group of "intermediate risk" patients with relapsed ALL include those with late BM relapses and those with early isolated extramedullary relapse.[43] Outcome of matched sibling donor BMT in the intermediate risk relapsed ALL group is in the range of 50% (data courtesy of CIBMTR) to 52-54%.[32-34]

Similarly, we identify three groups of patients in this outcome range in the 2000-2004 CIBMTR data: i) ALL in first complete remission (ie, those very high risk ALL patients for whom BMT in first remission is appropriate), where EFS is 51% +/- 6%, ii) AML in second complete remission, where EFS is 51 +/- 5%[44] and iii) MDS, where report outcome is again variable from 43% +/- 13% (North American CIBMTR data, 2000-2004) to over 60%.[41] Thus, we place these diagnoses in an Intermediate Risk stratum, where outcome is estimated to be 52%.

For patients with AML in their first CR (the large majority of the AML patients who will be enrolled on this trial), the outcome from the CIBMTR is around 60%. An outcome target in this range is supported by data from CCG 2891[45] and other studies,[46,47] although the induction approach taken in current studies will differ. Again, there is a range available in the literature, supporting outcome from 50% to 70% EFS. Similarly, the small number of children with CML fall into this range at 63%.[48] Thus, we will place these two disorders into a Standard Risk stratum, with an expected EFS of approximately 60%.

Standard Risk Disorders	Intermediate Risk Disorders	High Risk Disorders
AML CR1	ALL CR2 (late marrow relapse or early extramedullary relapse)	ALL CR2 (early BM relapse or T cell disease)
CML	ALL CR1	JMML
	AML CR2	
	MDS	

2.13 Preparative Regimens for BMT in Pediatric ALL

A panel of international experts reviewed HSCT approaches for ALL at the 2004 Tandem IBMTR/ABMTR annual meeting and concluded that the one element shown to improve outcome is the inclusion in the preparative regimen of a minimum of 1200cGy of fractionated total body irradiation (TBI).[49] Preparative regimens for ALL generally contain cyclophosphamide 60mg/kg/d x 2 plus at least 1200cGY of TBI.[50-52] Significantly higher doses of TBI (>1500 cGy) have been shown to result in less relapse with no benefit in survival due to excessive toxicity.[53,54] Several centers have added additional chemotherapy agents or a small fraction of additional radiation in order to decrease relapse without unduly increasing toxicity. Because centers are often invested in and/or more comfortable with a given preparative regimen, the bone marrow transplant Clinical Trials Network (CTN) has adopted an approach of allowing two or three groups of preparative regimens in phase III trials, as long as there is no clear evidence of significant differences in outcome between them. We have decided to adopt a similar approach in order to insure maximum participation. First, all patients will receive a common regimen consisting of a minimum of 1200cGy of fractionated TBI plus cyclophosphamide 60mg/kg/d x 2. All patients will receive therapy in addition to TBI 1200/Cy, with the preferred regimen consisting of the

addition of thiotepa 5mg/kg/d x 2 days.[55,56] We anticipate that 80% of our transplants will be performed using this "designated" regimen. If centers are unwilling to use the preferred thiotepa regimen, we will allow two other possible additions to the TBI 1200/Cy regimen, either VP-16 1500mg/m^2 x 1, or an additional 120-175cGy of TBI (total 1320-1375).[57-59] Each of these approaches has been used with a number of stem cell sources and is well established in the pediatric literature, and to date, there have been no significant differences noted between the regimens in outcome or toxicity. This will also allow us to preserve as much flexibility for the treating center as possible, while maintaining consistency with ASCT0431.

2.14 Preparative Regimens for BMT in Pediatric AML

In the CCG-2861 and 2891 protocols, busulfan and cyclophosphamide (Bu/Cy) were used as the cytoreduction transplant regimen. Outcomes using BuCy were similar to the CCG-213 and 251 protocols, both of which used cyclophosphamide and total body irradiation (Cy/TBI) as the transplant regimen. Although Cy/TBI was found to be significantly better in a randomized French study of adult patients, these results were not confirmed in a similar French pediatric study comparing Bu/Cy to Cy/TBI.[60,61] Children treated with Bu/Cy had an EFS of 80% compared to 42% following TBI. Finally, a comparison of the two regimens in patients with AML from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) could find no difference in leukemia free survival in 237 patients treated with Bu/Cy versus 237 patients treated with Cy/TBI.[62] Avoiding irradiation in pediatric patients is assumed to be desirable in order to prevent growth retardation and possible intellectual deficits. Wingard et al. have shown that growth impairment may be similar with the two cytoreductive regimens.[63] Two more comprehensive analyses have subsequently demonstrated that non-TBI containing regimens do not cause growth failure following BMT.[64,65] Thus, upon review of the relevant literature, Bu/Cy regimens appear to be at least equal to TBI regimens and will therefore be used as the standard cytoreductive regimen for patients undergoing BMT for myeloid diseases in this protocol. This also maintains consistency with the approach used in AAML03P1 and AAML0531.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to study enrollment, all patients must have been registered via the eRDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2 IRB Approval

Local IRB/REB approval of this study is to be entered into the Online IRB Submission System by each site. In addition, the official signed copy of the IRB approval document must be faxed to the Group Operations Center (GOC) at (626) 445-6715. Once IRB/REB approval documentation is received by COG, the institution will have access to the RDE enrollment screens within the next business day.

3.1.3 Study Enrollment

Patients and donors may be enrolled on the study once all eligibility requirements for the study have been met. During the informed consent process, institutions are encouraged to include donors between the ages of 14-17 years in the consent process. If appropriate, the local IRB may determine that donors in this age range may sign the consent form themselves. Alternatively, if the local IRB does not wish to require donors aged 14-17 to sign the consent form and they would like to participate, the parent must sign for them and institutions should document that the donor agreed to be a donor participant and was part of the consent process. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 Timing

There is an upfront randomization in this study and **patients must be enrolled before the BMT preparative regimen begins**. The date the transplant preparative regimen is projected to start must be no later than 28 calendar days after the date of study enrollment.

3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language where available.

3.1.6 Randomization

Randomization will take place at the time a patient is entered On Study via RDE. Patients and their donors will be assigned to either the unstimulated bone marrow arm (control) or the G-CSF stimulated bone marrow arm (experimental). Randomizations on the primary COG treatment study for the patient, if applicable, will occur prior to randomization on this study. Randomization will be stratified by disease risk (High Risk, Intermediate Risk or Standard Risk Disease).

3.2 Patient (Graft Recipient) and Graft Donor Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

The protocol is intended for patients with a hematologic malignancy (see Section 3.2.1.5 for eligible diseases) for whom a matched sibling donor BMT is appropriate therapy. Co-enrollment or prior enrollment on front line COG treatment studies such as AAML0531 and ASCT0431 is strongly encouraged.

3.2.1 Recipient Eligibility Criteria

3.2.1.1

Bone marrow recipients must be <22 years of age at time of study entry.

3.2.1.2 Disease Status

BM Status

Patients with acute leukemia must be in remission (bone marrow M1, <5% blasts by morphology, no evidence of CNS or other active extramedullary disease) prior to enrollment. This requirement does not apply to patients with MDS or JMML. Patients with CML should be in their first or second chronic phase.

Extramedullary Disease Status
No clinically evident extramedullary disease.

CNS Disease Status
No blasts seen on CSF cytospin.

Disease status must be documented by bone marrow and CNS assessment within 14 days of initiation of the preparative regimen.

3.2.1.3
All eligible patients should have completed reinduction therapy post-relapse, if applicable.

3.2.1.4 Reinduction Therapy for Relapsed ALL patients
Patients with **relapsed ALL** who are enrolled on the appropriate COG relapse trial are eligible for this study. Patient who are not on a COG relapsed ALL protocol are eligible to enroll in this study if they have received a minimum of one round of re-induction (4-6 weeks) and one round of intensive consolidation chemotherapy (3-6 weeks). Approaches similar to AALL01P2 are recommended.

3.2.1.5 Disease Eligibility

3.2.1.5.1
Patients with ALL in second complete remission after a bone marrow, extramedullary or combined bone marrow and extramedullary relapse

3.2.1.5.2
Patients with very high risk ALL in first complete remission. Very high risk criteria may include the following: i) Ph+ ALL; ii) hypodiploidy (<44 chromosomes); iii) MLL rearrangement; iv) induction failure.

3.2.1.5.3
Patients with AML who have completed appropriate induction therapy and are in their first or second complete remission.

3.2.1.5.4
Patients with juvenile myelomonocytic leukemia (JMML).

3.2.1.5.5
Patients with chronic myelogenous leukemia (CML) in first or second chronic phase.

3.2.1.5.6
Patients with myelodysplastic syndrome (MDS).

3.2.2 Recipient Exclusion Criteria

3.2.2.1 Patients with no matched sibling donor available.

3.2.2.2 Patients with Down syndrome are excluded.

3.2.2.3
Patients who have previously undergone allogeneic or autologous stem cell transplantation (SCT) are ineligible.

3.2.2.4
Pregnant or breast-feeding females are ineligible, as the medications used in this protocol could be harmful to unborn children and infants.

3.2.2.5
Performance Level (see Appendix I) Patients with Karnofsky or Lansky scores <60% are not eligible. Karnofsky scores must be used for patients >16 years of age and Lansky scores for patients ≤ 16 years of age.

3.2.2.6
Patients with known HIV or uncontrolled fungal, bacterial or viral infections are excluded. Patients acquiring fungal disease during induction therapy may proceed if they have a significant response to antifungal therapy with no or minimal evidence of disease remaining by CT evaluation.

3.2.2.7
No patient should be enrolled with the intent to i) deliver a reduced intensity conditioning regimen (see Section 4.0 for conditioning regimens) or ii) infuse a graft (BM or G-BM) that has undergone T cell depletion.

3.2.3 Recipient Organ Function Requirements

3.2.3.1 Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.2.3.2 Adequate liver function defined as:

- SGOT (AST) or SGPT (ALT) < 5 x upper limit of normal (ULN) for age.

- Total bilirubin <2.5 mg/dL unless the increase in bilirubin is attributable to Gilbert's Syndrome.

3.2.3.3 Adequate cardiac function defined as:

- Shortening fraction of ≥ 27% by echocardiogram, or

- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.3.4 Adequate pulmonary function defined as:

- FEV_1, FVC, and DLCO ≥ 60% by pulmonary function tests (PFTs).
- For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and not requiring supplemental oxygen therapy.

3.2.4 Donor Eligibility Criteria

3.2.4.1 Bone marrow donors must be > 6 months of age at time of planned harvest.

3.2.4.2 The matched sibling donor must be of adequate size relative to the recipient – ie, harvesting the maximum of 20cc/kg from the donor would result in a BM or G-BM graft that will provide an adequate cell and volume dose to the recipient, in the opinion of the treating physician. Donor exclusion criteria are listed below in 3.2.5.

3.2.4.3 The donor must undergo pre-harvest evaluation, consistent with applicable FDA requirements and FACT standards, including infectious disease testing.

3.2.5 Donor Exclusion Criteria

3.2.5.1 Donors who are HIV positive

3.2.5.2 Donors who have sickle cell trait

3.2.5.3 Donors who are found to be high risk for bone marrow donation due to a pre-existing medical condition

3.2.5.4 Female donors who are pregnant or lactating

3.2.5.5 Donors with uncontrolled infection

3.2.5.6 Donors with auto-immune disease

3.2.6 Regulatory

3.2.6.1
All patients and donors and/or their parent or legal guardian must sign a written informed consent.

3.2.6.2
All institutional, FDA, and NCI requirements for human studies must be met.

3.3 Definitions Relating to Relapse for Patients with ALL

Definitions of Relapse after Bone Marrow Transplant
Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of ALL consistent with pre-transplant features.

Minimal Residual Disease - Minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot, or Western blot, or polymerase chain reaction (PCR), or other techniques, in absence of morphological or cytogenetic evidence of disease in blood or marrow. **Evidence of minimal residual disease or rising host chimerism will not be sufficient to meet the definition of relapse in the context of this study, even if transplant physicians utilize the information to alter therapy**.

- **Bone Marrow Relapse after Transplant** is defined as:

  5% or more blasts by morphology, confirmed to be derived from the original leukemic clone by flow cytometry, PCR for antigen receptor loci or fusion genes, or cytogenetics/FISH

- **CNS Relapse after Transplant** is defined as:

  At least 5 WBC/µl in CSF with blasts present on cytospin, OR any number of WBC in CSF with immunophenotypic proof of leukemic relapse. Immunophenotypic proof of relapse is defined as identifiable blasts **plus** (for B-lineage ALL) TdT or CD-10 positivity on 2 consecutive CSF samples 2-4 weeks apart

- **Testicular Relapse after Transplant** is defined as:

  Unilateral or bilateral testiculomegaly with biopsy-proven testicular involvement
  OR
  Unilateral or bilateral testiculomegaly with concurrent relapse in the bone marrow and/or CNS

- **Combined Relapse after Transplant** is defined as relapse at 2 or more of the above sites

Bone Marrow Status

- **M1** Marrow

< 5% blasts in a bone marrow aspirate. True remission requires M1 status with normal marrow cellularity and the presence of all cell lines, and at least 200 cells counted.

- **M2** Marrow

5-25% blasts with at least 200 cells counted.

- **M3** Marrow

>25% blasts with at least 200 cells counted.

3.4 Definitions Relating to Relapse for Patients with myeloid diseases

3.4.1 Complete Remission (CR)

The bone marrow is regenerating normal hematopoietic cells and contains < 5% blast cells by morphology and no evidence of extramedullary disease.

3.4.2 Relapse

Morphologic relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. Should flow cytometric analyses suggest relapse (by

the reappearance of a similar immunophenotype to the original leukemia) in the presence of < 5% blasts, or ≥ 5% blasts in a regenerating marrow, a repeat bone marrow(s) performed at least a week later is necessary to confirm relapse by morphologic methods. In such instances the date of recurrence is defined as the first date that more than 5% blasts were observed in the marrow. The reappearance or development of cytologically proven extramedullary disease also indicates relapse. Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality.

For patients with CML, relapse is defined by the persistence of any Philadelphia chromosomes in metaphases after Day +50 on two occasions at least 1 month apart and after an attempt had been made to withdraw any immunosuppressive therapy, or by the presence of frank hematological relapse.

For patients with MDS relapse is defined morphologically as the detection of metaphases in the marrow that showed the same clonal marker(s) identified before transplantation, or as the reemergence of blasts or aberrant precursors identified by flow cytometry.

3.4.3 Inevaluable

Aplastic or severely hypocellular marrow with any blast percentage. In this instance, if there is a clinical concern of relapse, marrow evaluation should be repeated weekly until response determination can be made.

3.5 Definition of Engraftment and Graft Failure

Neutrophil engraftment is defined as the first of three consecutive days in which the absolute neutrophil count exceeded 500 per cubic millimeter. Platelet engraftment is defined as the first of seven consecutive days in which the platelet count exceeded 20,000 per cubic millimeter without platelet transfusions. The presence of donor cells is demonstrated by the detection of informative variable-number tandem-repeat polymorphisms or by fluorescent in situ hybridization with a Y-chromosome–specific probe in cases of sex-mismatched transplants.

The analysis of graft failure is limited to patients who survived at least 42 days without relapse of leukemia. Primary graft failure is defined as the failure to achieve an absolute neutrophil count of more than 500 per cubic millimeter for at least three consecutive days by Day +42. Secondary graft failure is defined as a decrease in the absolute neutrophil count to below 200 per cubic millimeter for at least three consecutive days after initial engraftment, or documentation of the loss of donor cells by testing with use of informative markers.

4.0 TREATMENT PLAN

4.1 Overview of Treatment Plan

Patients enrolling must have undergone an extensive pre-transplant evaluation to assess remission status, assure adequate organ system function, and document freedom from active viral, bacterial, and fungal infection (see Section 3.2.2 and 3.2.3 for exclusion criteria and organ system function requirements).

Patients should proceed to transplant as soon as possible after count recovery (guidelines for count recovery are ANC >1000/µL and platelets >50,000/µL – these are not eligibility criteria) following their final round of pre-BMT chemotherapy. Patients with delays in therapy due to toxicity should receive maintenance chemotherapy if possible.

At study entry, patients will be stratified by risk. This protocol will have two arms. Patients randomized to the standard arm will receive conventional bone marrow (BM) and patients randomized to the experimental arm will receive G-CSF stimulated bone marrow (G-BM).

Transplant preparative regimen and GVHD prophylaxis is dependent on the type of hematologic malignancy (lymphoid vs. myeloid). **If a patient is enrolled on a COG treatment trial such as ASCT0431 or AAML0531, the patient will receive a preparative regimen and GVHD prophylaxis as defined on that treatment study.**

4.2 Donor Considerations and Bone Marrow Collection

4.2.1 Donor Selection

- HLA, A, B, DRB1 identical or 1 antigen mismatched donor (ie, 5/6 or 6/6 antigen match).
- Donor must be a sibling.
- All first degree family members (eg, parents and siblings) should be HLA typed. High resolution typing may be necessary in some cases.

4.2.2 Details of Bone Marrow Collection

4.2.2.1 Experimental Arm: G-CSF Stimulated Bone Marrow (G-BM) Collection

Procedure/Treatment	Days	Important Notes
Start donor on G-CSF 5 mcg/kg/day	Day -4, -3, -2, -1, 0	Total 5 doses of G-CSF. AM dosing is recommended.
G-BM harvest of 15 cc/kg recipient weight	Day 0	**Collection target is a volume and not a cell dose**. Harvests outside the recommended volume ranges (see below) will be considered protocol violations.

Schedule the bone marrow harvest for Day 0 of the conditioning regimen. On Day -4 prior to G-BM harvest, start the DONOR on G-CSF 5 mcg/kg/d for 5 days, with the last injection on the day of harvest. This will allow G-BM to be collected from donors on the fifth day after initiation of G-CSF.

- Target volume is **15 cc/kg of recipient weight**.
  - NOTE that the collection target is a volume and not a cell dose. It is anticipated that G-BM harvests will have higher cell doses than most BM harvests.
- To protect the donor, the MAXIMUM collection is 20 cc/kg donor weight.
- A harvest of more than 20 cc/kg donor weight is a protocol violation.
- A harvest of less than 10 cc/kg recipient weight is also a protocol violation, unless this harvest would EXCEED 20 cc/kg donor weight (ie, small donor for a large recipient).
- Thus, most collections will be between 10 and 15 cc/kg of recipient weight.

The BM harvest will be infused, without the use of T cell depletion or cryopreservation, on Day 0 of the conditioning regimen. The only marrow manipulation allowed is red cell or plasma depletion as appropriate for ABO/red cell antibody match between donor and recipient.

Please see Appendix VI for the therapy delivery map for G-CSF administration. Use a copy of the map to record the actual dates, doses administered and details of the harvest, including actual volume of bone marrow collected.

4.2.2.2 Standard Arm: Conventional Bone Marrow (BM) Collection

Procedure/Treatment	Days	Important Notes
BM harvest of 15 cc/kg recipient weight	Day 0	**Collection target is a volume and not a cell dose**. Harvests outside the recommended volume ranges (see below) are protocol violations.

Schedule the bone marrow harvest for Day 0 of the conditioning regimen. G-CSF will NOT be used in the DONOR.

- Target volume is **15 cc/kg of recipient weight**.
  - NOTE that the collection target is a volume and not a cell dose.
- To protect the donor, the MAXIMUM collection is 20 cc/kg donor weight.
- A harvest of more than 20 cc/kg donor weight is a protocol violation.
- A harvest of less than 10 cc/kg recipient weight is also a protocol violation, unless this harvest would EXCEED 20 cc/kg donor weight (ie, small donor for a large recipient).
- Thus, most collections will be between 10 and 15 cc/kg of recipient weight.

The BM harvest will be infused, without the use of T cell depletion or cryopreservation, on Day 0 of the conditioning regimen. The only marrow manipulation allowed is red cell or plasma depletion as appropriate for ABO/red cell antibody match between donor and recipient.

Please see Appendix VII for the table to record details of standard bone marrow harvest. Use a copy of the table to record details of the harvest, including actual volume of bone marrow collected.

4.2.3 Donor Evaluation for Acute and Chronic Toxicity

4.2.3.1 Donor Background Health Information and Acute Toxicity Assessment
Two data forms (Baseline Donor Evaluation and Acute Donor Toxicity) will be submitted by individual COG institutions registered within 2 weeks of the donation procedure. The data forms are taken from the RDSafe study, but the data will be collected by centers and reported directly to COG to allow for appropriate acute toxicity monitoring in the donor population. The forms describe the donor's baseline health status. The forms also detail toxicities experienced by the donor through the process of the donation (from the start of G-CSF administration through the harvest procedure). This data submission will also include contact information for later phone follow up by the NMDP call center. Severe acute complications experienced by the donor (see Sections 7.4 and 12.5) will be reported through AdEERS.

4.2.3.2 Post-Harvest and Long-term Toxicity Assessment via the NMDP Call Center
The call center performing the RDSafe assessments, located at the National Marrow Donor Program (NMDP) office in Minneapolis, will contact donors and/or donor families at 1, 6, and 12 months after the donation. This may continue yearly for up to 10 years thereafter, depending on the status of the RDSafe study and data collection plan. These calls will address any acute toxicities discovered with the initial data form above and follow them to their resolution. The calls will also document any other toxicities experienced by the donor and describe the relationship of these toxicities to the donation process. Specifically, the interview will address issues of chronic pain, infection, or other complaints possibly related to the donation. The interview will also measure the incidence of new onset or recent flares of autoimmune illness, vascular events, or malignancies.

Families will need to give contact information and be willing (as indicated in the consent form) to accept calls from the NMDP call center in order to participate in this aspect of the study. Donors and/or their

families may opt out of receiving these follow up calls. Contact information on the donor families will be updated by the families and referring institutions by means of a toll-free contact hotline at the NMDP.

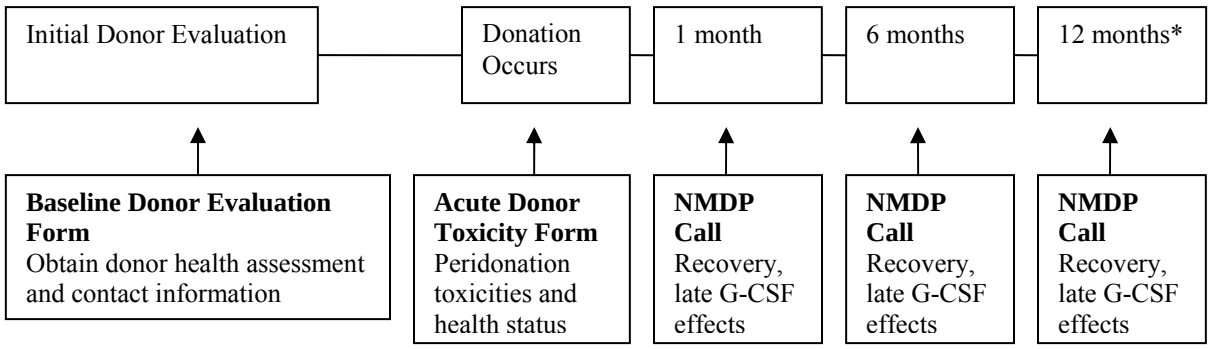


Figure 2. Outline of Donor Follow Up Assessments
Data Capture forms are bolded. Baseline donor evaluation form and acute donor toxicity form will be completed by COG SCT center. The acute donor toxicity form should be completed within 2 weeks of BM harvest. Health survey calls at 1, 6, and 12 months (*and possibly yearly for up to 10 years thereafter) will be made by the NMDP call center.

4.3 Preparative Regimen and GVHD Prophylaxis

4.3.1 Patients Co-enrolled on a COG Treatment Study

Patients who are co-enrolled on a COG treatment study such as ASCT0431 or AAML0531 will receive a conditioning regimen and GVHD prophylaxis as defined on that treatment study. For patients co-enrolled on ASCT0431, this will include GVHD prophylaxis as designated by the assigned arm of the study. All details of the primary treatment study should be followed, which supersede all conditioning regimens and GVHD prophylaxis regimens described below. In that case, ONLY the graft characteristics (volume and G-BM or BM) will be determined by this study.

4.3.2 Patient NOT Co-enrolled on a COG Treatment Study

For patients who are NOT co-enrolled on a COG treatment study that includes BMT, two types of regimens are provided.

- One regimen is for patients with ALL. Please see Sections 4.4 and 4.5 for ALL patients. This regimen is based on the condition regimen and standard arm GVHD prophylaxis as per ASCT0431. ALL patients will receive the preferred preparative regimen of Cy/TBI/Thiotepa. Institutions may choose Variation 1 or 2 (Section 4.4.1.6), but it is recommended that centers use the preferred regimen.
- The other regimen is for patients with myeloid malignancies. Please see Section 4.6 and 4.7 for patients with myeloid malignancies. For all patients with AML, JMML CML or MDS, a Busulfan/Cytoxan regimen with standard GVHD prophylaxis is provided as per AAML0531.
- NOTE on GVHD prophylaxis. In order to limit treatment variability, the GVHD prophylaxis defined below is based on the standard arm of ASCT0431 (for ALL) and AAML0531 (for myeloid malignancies). The GVHD prophylaxis for these 2 patient groups is therefore DIFFERENT, reflecting the need to be consistent with these two phase III studies. Please use the GVHD appropriate for the patient's disease (either ALL or a myeloid malignancy).

4.4 ALL Peri-transplant Therapies and Choice of Preparative Regimen

PLEASE NOTE: If the patient is enrolled on another, concurrent COG treatment trial such as ASCT0431, the conditioning regimens and GVHD prophylaxis will be prescribed as mandated on that study.

Prior to transplant, patients may receive intrathecal chemotherapy for prophylaxis according to institutional transplant practice, but this is not required. Patients will then receive the preferred preparative regimen of Cy/TBI/Thiotepa (Section 4.4.1.5). The regimens below are based on the COG ASCT0431 study for relapsed ALL and represent the consensus of the COG HSCT Discipline. Variations are provided so as to allow the treating center to approximate as closely as possible their "standard" regimen. Institutions may choose Variation 1 or 2 below, but we recommend that centers choose the preferred regimen. The preparative regimen is not part of the experimental question in this study. Although outcome with the three allowed variations is expected to be similar, choice of the preferred regimen will minimize variability. Aside from the three listed variations of the Cytoxan/TBI regimen outlined in Sections 4.4.15 and 4.4.1.6, no other preparative regimens will be allowed on this study.

4.4.1 ALL Preparative Regimen Administration

4.4.1.1 TBI Administration

Fractionated TBI will be administered according to protocol guidelines that include several fractionation and total dose regimens. The guidelines are summarized in this section and further detailed in Section 16.0.

4.4.1.2 Thiotepa Administration

Please see Section 5.1 for dose modification for patients whose weight exceeds 125% of IBW. Thiotepa will be administered intravenously. To minimize skin toxicity, frequent bathing (minimum 2-3x daily) is required on the days of thiotepa administration. Do not apply skin creams or large occlusive dressings during thiotepa or one day following. Bathing of the diaper area should be more frequent for children in diapers.

4.4.1.3 Cyclophosphamide Administration

Please see Section 5.1 for dose modification for patients whose weight exceeds 125% of IBW. Cyclophosphamide will be given as a dose of 60 mg/kg IV over one hour on Days -3 and -2. Patients should be given cyclophosphamide according to institutional chemotherapy standards. This should include infusion of a minimum of 3000 cc IV fluids/m2/day during the cyclophosphamide infusion days with careful attention to intake and output, electrolytes, body weight, and urinalysis.

During high-dose cyclophosphamide therapy, anticipate possible drug-induced SIADH, or hemorrhagic cystitis. Key elements in preventing and treating these complications include:

- Vigorous hydration with dextrose and normal saline along with supplemental potassium.
- Liberal use of diuretics to maintain a urine flow of 2 – 3 cc/kg/hr with balanced I/O and stable body weight, assessed twice daily during cyclophosphamide administration. Patient must void frequently to prevent hemorrhagic cystitis. Use of urinary catheters in young children is permissible to ensure prompt drainage of urine from the bladder.
- Mesna as a uroprotective may be used to prevent hemorrhagic cystitis. The recommended dose of mesna is a total of 60% of the cyclophosphamide dose divided into 3 doses and given prior to or with the cyclophosphamide then every 3 hours x 2 more doses.
- Careful attention to the patient's weight is necessary, and intensive forced diuresis should be used to prevent excess fluid retention.

4.4.1.4 Etoposide Administration

(For centers choosing the non-preferred regimen Variation 1 only) Please see Section 5.1 for dose modification for patients whose weight exceeds 125% of IBW. Patients should be given 1.5x maintenance fluids during etoposide administration to minimize the risk of hypotension. Etopophos substitution is allowed.

4.4.1.5 Preferred ALL Preparative Regimen

Treatment	Route	Dose	Days	Important Notes
TBI		150-200 cGy BID Total dose 1200 cGy	Day -8, -7, & -6	May deliver 1200 cGy fractionated TBI over 3 or 4 days per center preference
Thiotepa	IV	5 mg/kg/day	Day -5 & -4	
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic BM			Day 0	For patients on the standard arm
Infusion of allogeneic G-BM			Day 0	For patients on the experimental arm

4.4.1.6 Allowed Preparative Regimens for Patients with ALL

These variations are allowed, but not recommended. The preferred preparative regimen is listed above in Section 4.4.1.5.

Variation 1: TBI/Cy/VP-16

Drug/Treatment	Route	Dose	Days	Important Notes
TBI		150-200 cGy BID Total dose 1200 cGy	Day -7, -6, & -5	May deliver 1200 cGy fractionated TBI over 3 or 4 days per center preference
Etoposide	IV	1500 mg/m^2	Day -4	
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic BM			Day 0	For patients on the standard arm
Infusion of allogeneic G-BM			Day 0	For patients on the experimental arm

Variation 2: Higher Dose TBI/Cy

Treatment	Route	Dose	Days	Important Notes
TBI		165 cGy BID Total dose 1320 cGy	Day -7, -6, -5, & -4	TBI must be delivered over 4 days when using this dose
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic BM			Day 0	For patients on the standard arm
Infusion of allogeneic G-BM			Day 0	For patients on the experimental arm

Please see Appendix IV for ALL preparative regimen therapy delivery map. Use a copy of the map to track each patient's therapy by entering the actual dates and doses administered.

4.4.2 ALL Pre-transplant Intrathecal Prophylaxis

After count recovery from pre-transplant consolidation chemotherapy, patients may receive intrathecal chemotherapy according to institutional practice, but this is not required.

4.4.3 ALL Sanctuary Site Therapy (see Section 16)

Designated patients with a history of CNS or testicular involvement should receive supplemental irradiation preceding TBI.

4.4.3.1 Radiotherapy boost for patients with CNS leukemia:

The supplemental dose should be 600 cGy administered with a daily dose of 150 or 200 cGy. Supplemental cranial irradiation should precede fractionated TBI. Excluding weekends and holidays, supplemental cranial irradiation and fractionated TBI should be continuous.

The following patient category will receive the supplemental cranial irradiation:

- Patients with very high risk ALL in first complete remission, who had CNS leukemia at the time of their initial diagnosis, and who had not received cranial irradiation during their initial therapy
- Patients with CNS leukemia at relapse with or without a history of prior CNS leukemia and/or prior cranial radiotherapy

Exceptions to the use of supplemental cranial irradiation may include:

- Concerns about development because of patient age, history of prior cranial irradiation, and history or radiographic evidence of CNS toxicity (eg, leukoencephalopathy, necrosis, stroke).

4.4.3.2 Supplemental irradiation for patients with a history of testicular leukemia

The supplemental dose for testicular irradiation should be 600 cGy administered with a daily dose of 200 cGy. Supplemental testicular irradiation should precede fractionated TBI. Excluding weekends and holidays, supplemental testicular irradiation and fractionated TBI should be continuous.

The following patient category will receive the supplemental testicular irradiation:

- Patients presenting with testicular leukemia who have clinical evidence of persistent testicular disease after induction chemotherapy
- Patients with testicular leukemia at the time of relapse

Exceptions to the use of supplemental testicular irradiation may include:

- Prophylactic testicular irradiation (400 cGy administered in a single fraction or 200 cGy BID) is allowed but is not required.

4.4.4 Marrow Infusion (Day 0)

BM or G-BM for allogeneic BMT is infused within 36 to 48 hours after the last dose of cyclophosphamide over a recommended time of 3-4 hours (the marrow product should not be delivered at a rate that would exceed a 4 hour infusion time). All marrow collected at harvest will be infused.

4.5 GVHD Prophylaxis for Patients with ALL

Patients enrolled on ASCT0431 will receive GVHD prophylaxis as dictated by that study. The GVHD prophylaxis detailed below is based on the standard arm of ASCT0431. Patients will receive tacrolimus and "mini-dose" methotrexate.

Drug	Route	Dose	Days	Important Notes
Tacrolimus	IV, PO when able	0.02mg/kg/day continuous infusion	Begins Day -2	Target levels 5-12 ng/mL. Taper as per Section 4.5.4
Methotrexate	IV	5mg/m^2/dose	Days +1, +3, +6	Modify/hold for toxicity as per Section 5.5

4.5.1 Tacrolimus Administration, Monitoring and Dose Adjustments

Tacrolimus is STRONGLY RECOMMENDED for lymphoid leukemia (ALL) patients to reduce study variability. However, the use of cyclosporine as an alternative to tacrolimus during the period of continuous infusion as per institutional protocols is permitted. When the patient is switched to oral medication, tacrolimus should be used, regardless of what was used during the period of IV infusion. Tacrolimus should be administered by continuous IV infusion until patients are able to take PO. Levels should be drawn at least twice per week while hospitalized, then weekly or monthly thereafter unless a change in medication (eg, use of itraconazole) or renal function might result in an acute change in level. At that point levels will be measured as clinically indicated.

Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level. For levels < 5 ng/mL, it is suggested, that the dose of tacrolimus be increased by approximately 25% increments every 1-2 days, rounded to the nearest 0.5 milligram (when dosing is oral) until the target range is achieved. Conversely, for levels > 12-15 ng/mL, it is suggested, that the dose of tacrolimus be decreased by approximately 25% every 1-2 days until the target level is achieved. Alternatively, tacrolimus can be held entirely as long as serum levels are monitored and the drug is restarted when the level returns to the therapeutic range and the treating physician feels it is appropriate to restart the agent.

4.5.2 Methotrexate Administration, Monitoring and Dose Adjustments

"Mini-dose" methotrexate should be given at a dose of 5 mg/m^2 on Days +1, 3, and 6 after transplant. All doses of methotrexate should be administered as scheduled if possible, but centers may modify or hold methotrexate for significant toxicity (see Section 5.5 for methotrexate dose modification guidelines).

4.5.3 Leucovorin Administration

Leucovorin may be given at the physician's discretion for patients at risk for methotrexate toxicity. Patients at risk for methotrexate toxicity include those with extravascular fluid collections (ascites, pleural effusions) or with decreased renal function (see Section 5.5).

4.5.4 Tapering Immune Suppressive Medications

4.5.4.1 Tapering immune suppression in patients with GVHD

Patients who develop either acute or chronic GVHD will be treated according to institutional practice.

4.5.4.2 Tapering immune suppression in patients without GVHD

Start to taper tacrolimus on Day +42 and taper over 8 weeks, (~12%/wk), with a goal of being off by Day +98.

4.6 Conditioning Regimen and Treatment Considerations for Patients with Myeloid Malignancies

PLEASE NOTE: If the patient is enrolled on another, concurrent COG treatment trial such as AAML0531, the conditioning regimens and GVHD prophylaxis will be prescribed as mandated on that study.

4.6.1 Myeloid Preparative Regimen Administration

Treatment	Route	Dose	Days	Important Notes
Busulfan*	IV	Busulfan q 6 hours x 4 doses with 1st dose pharmacokinetics (See Section 5.6).	Day -9	See Section 4.6.3 for age-based dosing
Busulfan*	IV	Busulfan q 6 hours x 12 doses	Day -8 & -7 & -6	Targeted dose-adjustment based on PK results (see Section 5.6).
Cyclophosphamide	IV	50 mg/kg daily x 4 days	Day -5, -4, -3 & -2	
Begin cyclosporine infusion Rest			Day -1	
Infusion of allogeneic BM			Day 0	For patients on standard arm
Infusion of allogeneic G-BM			Day 0	For patients on the experimental arm

**Note: A total of 16 doses of Busulfan will be given during preparative regimen administration*
***Phenytoin should be administered as in 4.6.2 below, as supportive care for busulfan.*

Please see Appendix V for myeloid preparative regimen therapy delivery map. Use a copy of the map to track each patient's therapy by entering the actual dates and doses administered.

4.6.2 Administration of Phenytoin (Day -10)

Seizure prophylaxis with phenytoin is required for patients undergoing high-dose busulfan treatment. Institutions should follow clinical SOPs for such prophylaxis. In general, treatment with phenytoin or another anticonvulsant in intolerant patients should begin 12 hours prior to busulfan and continue for 48 hours after completion of busulfan. The dose of phenytoin should be 2.5 mg/kg/dose PO BID. Loading dose and therapeutic monitoring are not necessary. For patients with a known seizure disorder, consider IV dosing with loading and therapeutic monitoring.

Phenytoin interacts with busulfan causing reduced plasma levels. Therefore, failure to use phenytoin may result in elevated busulfan levels.

4.6.3 Administration of Busulfan (Day -9 to -6)

Busulfan should be administered **intravenously** via a central venous catheter as a two-hour infusion every six hours times four consecutive days for a total of sixteen doses.

Age-based dosing of intravenous busulfan (Busulfex™):
< 10 kg: 0.8 mg/kg/dose as a starting dose q 6 hours x 16 doses
≥ 10 kg but ≤ 4 years old: 1 mg/kg/dose as a starting dose q 6 hours x 16 doses
> 4 years: 0.8 mg/kg/dose as a starting dose q 6 hours x 16 doses
Note: DOSING SHOULD BE ADJUSTED BASED ON FIRST DOSE PHARMACOKINETICS (see Section 5.6).

4.6.4 Administration of Cyclophosphamide (Day -5 to Day -2)

Please see Section 5.1 for dose modification for patients whose weight exceeds 125% of IBW. Cyclophosphamide will be given as a dose of 50 mg/kg IV over one hour on Days -5, -4, -3, -2. Patients should be given cyclophosphamide according to institutional chemotherapy standards. This should include infusion of a minimum of 3000 cc IV fluids/m^2/day during the cyclophosphamide infusion days with careful attention to intake and output, electrolytes, body weight, and urinalysis.

During high-dose cyclophosphamide therapy, anticipate possible drug-induced SIADH, or hemorrhagic cystitis. Key elements in preventing and treating these complications include:

- Vigorous hydration with dextrose and normal saline along with supplemental potassium.
- Liberal use of diuretics to maintain a urine flow of 2 – 3 cc/kg/hr with balanced I/O and stable body weight, assessed twice daily during cyclophosphamide administration. Patient must void frequently to prevent hemorrhagic cystitis. Use of urinary catheters in young children is permissible to ensure prompt drainage of urine from the bladder.
- Mesna as a uroprotective may be used to prevent hemorrhagic cystitis. The recommended dose of mesna is a total of 60% of the cyclophosphamide dose divided into 3 doses and given prior to or with the cyclophosphamide then every 3 hours x 2 more doses.
- Careful attention to the patient's weight is necessary, and intensive forced diuresis should be used to prevent excess fluid retention.

4.6.5 Marrow Infusion (Day 0)

BM or G-BM for allogeneic BMT is infused within 36 to 48 hours after the last dose of cyclophosphamide over a recommended time of 3-4 hours (the marrow product should not be delivered at a rate that would exceed a 4 hour infusion time). All marrow collected at harvest will be infused.

4.7 GVHD Prophylaxis for Patients with Myeloid Malignancies

Patients enrolled on AAML0531 will receive GVHD prophylaxis as dictated by that study. The GVHD prophylaxis detailed below is based on AAML0531. Patients will receive cyclosporine and standard methotrexate.

Drug	Route	Dose	Days	Important Notes
Cyclosporine	IV, PO when able	3 mg/kg/day continuous infusion	Begins Day -1	Target levels 250-400 ng/mL. Taper as per Section 4.7.4
Methotrexate	IV	15mg/m^2/dose	Day +1	
Methotrexate	IV	10mg/m^2/dose	Days +3, +6, +11	Modify/hold for toxicity as per Section 5.5

4.7.1 Cyclosporine (CSA) Administration, Monitoring and Dose Adjustments

CSA is STRONGLY RECOMMENDED for myeloid disease patients to reduce study variability, however, use of tacrolimus as per institutional protocols is permitted for those patients who are not enrolled on AAML0531. CSA should be administered IV until patients are able to take PO. Levels should be drawn at least twice per week while hospitalized, then weekly or monthly thereafter unless a change in medication (eg, use of itraconazole) or renal function might result in an acute change in level. At that point levels will be measured as clinically indicated.

Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level. Patients will receive CSA starting on the day before marrow infusion (Day -1) for a total daily dose of 3 mg/kg/day IV divided into two doses (1.5 mg/kg each) infused over a period of 1-4 hours or given as a continuous infusion. The dose of CSA should be adjusted to achieve a serum level of 150-250 ng/mL (for patients on IV BID and oral CSA) or 250-400 ng/mL (for IV continuous infusion). IV CSA may be discontinued once the patient is able to consistently eat. At that time, the drug will be given orally at a starting dose equal to three times the IV dose.

For levels less than the recommended therapeutic range, it is suggested that the dose of CSA be increased by approximately 25% increments every 1-2 days until the target range is achieved. Conversely, for levels above the therapeutic range, it is suggested that the dose of CSA be decreased by approximately 25% every 1-2 days until the target level is achieved. Alternatively, CSA can be held entirely as long as serum levels are monitored and the drug is restarted when the level returns to the therapeutic range and the treating physician feels it is appropriate to restart the agent.

4.7.2 Methotrexate Administration, Monitoring and Dose Adjustments

Methotrexate should be given at a dose of 15 mg/m^2 on Day +1 and 10 mg/m^2 on Days +3, 6 and 11 after transplant. All doses of methotrexate should be administered as scheduled if possible, but centers may modify or hold methotrexate for significant toxicity (see Section 5.5 for methotrexate dose modification guidelines).

4.7.3 Leucovorin Administration

Leucovorin may be given at the physician's discretion for patients at risk for methotrexate toxicity. Patients at risk for methotrexate toxicity include those with extravascular fluid collections (ascites, pleural effusions) or with decreased renal function (see Section 5.5).

4.7.4 Tapering Immune Suppressive Medications

4.7.4.1 Tapering immune suppression in patients with GVHD
Patients who develop either acute or chronic GVHD will be treated according to institutional practice.

4.7.4.2 Tapering immune suppression in patients without GVHD
Start to taper immune suppression (cyclosporine or tacrolimus for those patients on tacrolimus) on Day +42-50. The taper can occur over a minimum of 8 weeks to a maximum of 16 weeks, (6-12% dose decrease/wk).

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Adjustment of Chemotherapy for Patients Whose Weight Exceeds >125% IBW

Chemotherapy given during the preparative regimen (thiotepa, cyclophosphamide, and etoposide) will be dosed based on actual weight for patients ≤125% IBW. Those >125% IBW will be dosed based upon adjusted ideal body weight as follows:

Adjusted ideal body weight = IBW + 0.25 (Actual weight – IBW).
The following formulas for pediatric and adult IBW calculations are recommended, but IBW may be calculated according to institutional SOPs.

5.1.1 Recommended Ideal Body Weight Calculation for Children Age 1- 17 years

$$\text{IBW} = \frac{\text{Height (cm)}^2 \times 1.65}{1000}$$

5.1.2 Recommended Ideal Body Weight Calculation for Adults

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg

IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

5.2 Adjustment of TBI/chemotherapy During the Preparative Regimen.

The full dose of preparative regimen TBI and chemotherapy agents will be administered unless patients have a life threatening reaction thought likely to occur again with continued administration and an appropriate substitution cannot be made (ie, etopophos for etoposide).

5.3 Neutropenia/non engraftment

If ANC<500 on Day +21, a thorough assessment should be made to rule out reasons for non-engraftment (assessment for infection, medications other than sirolimus contributing to cytopenias, etc.). Patients with no defined cause for low counts should receive G-CSF at 5-10µg/kg/d. If engraftment has not occurred by Day +28, a BM should be performed to assess morphology and chimerism. If patients do not have donor chimerism and have no evidence of recurrent disease, a subsequent second graft infusion should be considered according to institutional SOPs.

5.4 Tacrolimus and CSA

Tacrolimus and CSA commonly cause mild/moderate hypertension and less commonly kidney or liver dysfunction, thrombotic microangiopathy, or neurological changes associated with significant hypertension. When trough levels are kept in the therapeutic range and patients receive adequate hydration and magnesium replacement, most of these side effects can be minimized. Hypertension should

be managed with single or combination antihypertensive therapy. Tacrolimus or CSA should be held for severe toxicities thought to be related to its administration (significant neurological changes/malignant hypertension, thrombotic microangiopathy, kidney failure, etc.) Other immune suppressive medications may be substituted if tacrolimus is not tolerated (such as mycophenolate mofetil).

5.5 Methotrexate

The most common acute side-effects of methotrexate include delay of count recovery, worsened mucositis, and kidney and liver damage (can contribute to VOD). Toxicity is directly related to the length of exposure to the drug. While methotrexate is generally excreted rapidly, delayed excretion of methotrexate occurs with decreased renal function and in circumstances where patients have third-space fluid collections (pulmonary effusions, ascites, joint effusions, etc.). The attending transplant physician should assess each patient prior to delivery of each dose and decide whether full dose methotrexate should be administered. Guidelines for modification of methotrexate dosing are listed in Table 5.5.1 and Table 5.5.2 below.

Table 5.5.1 Methotrexate Dose Modification for Renal Impairment

	Mild	Moderate	Severe	Life-Threatening
Serum creatinine	**>1.5-2 x baseline**	**>2-2.5 x baseline**	**>2.5-3 x baseline**	**>3 x baseline or dialysis**
% Methotrexate Dose reduction (Day +1,3,6,11)	**0-50%**	**50-100%**	**100% (no drug)**	**100% (no drug)**

Table 5.5.2 Methotrexate Dose Modification for Significant Mucositis

Stomatitis, mucositis	**Painless ulcers, erythema, mild soreness or mild dysphagia**	**Painful erythema, edema, ulcers or moderate dysphagia, but can eat without narcotics**	**Cannot eat solids or requires narcotics to eat, requires parenteral or enteral support.**	**Complete obstruction or perforation**
% Methotrexate Dose reduction (Day +1,3,6,11)	**0%**	**0%**	**0-50%**	**50-100%**

For significant third spacing (ascites, effusions, significant edema or weight gain >5-10% above baseline) consider dose reductions of 50% and leucovorin rescue.

5.5.1 Guidelines for Leucovorin Rescue

Dose: Patients at risk for methotrexate toxicity should receive leucovorin at a dose of 5-10 mg/m^2 IV Q6H x 4 doses beginning 24 hours after administration of methotrexate. While most patients will need only 4 doses of leucovorin, if methotrexate levels are elevated due to renal dysfunction or other problems, leucovorin doses should be continued until serum methotrexate concentration is $< 1 \times 10^{-7}$M. If serum methotrexate concentration is $> 5 \times 10^{-6}$M, increase dose to 100 mg/m^2/dose IV Q3H until the serum methotrexate level is $< 1 \times 10^{-8}$M.

5.6 Pharmacokinetics for Busulfan dose adjustments

5.6.1 First Dose Pharmacokinetics

FIRST dose pharmacokinetics are recommended to achieve an AUC for busulfan of 900 to 1500 micromole/liter/minute. Note that busulfan levels may be expressed as AUC or steady state concentration (Css); the target in this study requires that results be expressed as AUC, and not Css.

Busulfan concentrations will be determined in plasma by collecting blood into a sodium heparin tube. Samples should be collected at the end of the first 2 hour infusion, 135 minutes after start of infusion, 150 minutes after start of infusion, and 3, 4, 5, and 6 hours after the start of the first infusion. Samples should not be drawn from the lumen used to infuse busulfan.

Institutional pharmacokinetic studies are acceptable. If pharmacokinetics cannot be performed at a local laboratory, samples can be shipped to the Fred Hutchinson Cancer Research Center in Seattle, WA (address below) or other regional laboratories experienced in this assay. Kits with complete instruction are available through the Pharmacokinetics Lab staff at phone # (206) 667-4572 (lab) or by e-mail at busulfan@fhcrc.org; kits should be requested at least one week before they will be needed. Results are usually available in time for adjusting doses 7 through 16. Brief instructions are as follows:

Collect 1-3 mL of blood into sodium heparin tubes (green top) according to the schedule above. Place labeled samples immediately on wet ice and refrigerate. Centrifuge samples as soon as possible at 4°C. Separate plasma from RBCs. Store plasma at –20°C. Plasma tubes must be labeled with the patient's name, medical records number, and the date and actual clock time that the sample was drawn.

Shipping

Samples must be shipped on a minimum of 3 kg of dry ice the day they were drawn using an urgent overnight carrier. Please use the IV Busulfan PK Requisition form located in the Specimen Shipping Forms link under the Data Collection/Specimen section of the ASCT0631 protocol home page. Send samples to:

Pharmacokinetics Lab
Fred Hutchinson Cancer Research Center
Room D2-245
1100 Fairview Avenue North
Seattle, Washington 98109

Note: Notify the lab staff of sample shipment at least 48 hours prior to arrival. Samples can be received Monday through Friday, or on Saturdays with at least 3 days advance notice. Coordinate the taking of samples so that delivery will occur Monday through Saturday and there will be time for a possible dose adjustment. Please provide the lab with a tracking number for the package at the phone or email listed above.

Provide fax and phone numbers for the attending physician so that results can be reported in time for targeted dose adjustment.

5.6.2 Guidelines for Adjusting Busulfan Dosing Based on Results of First Dose Pharmacokinetic Results

Once the results of the area under the curve (AUC) analysis of the first busulfan dose are available, subsequent doses should be adjusted to target an AUC of 900-1500 micromole/liter/minute. The amount by which the dose is increased or decreased should be decided by the patient's attending physician in

conjunction with the institutional toxicology laboratory director, or the Seattle Cancer Care Alliance Pharmacokinetics Laboratory (see above).

In cases where the pharmacokinetics are performed locally, a second AUC analysis is recommended after administration of the first modified dose, with further dose adjustments made accordingly.

6.0 DRUG INFORMATION

6.1 **FILGRASTIM** (Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®) NSC #614629 (032007)

Source and Pharmacology: Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subcutaneous):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain,	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability: Supplied as a clear solution in 300 mcg/ml 1 ml or 1.6 ml vials and prefilled syringes containing 300mcg/0.5mL or 480mcg/0.8mL. Vials are preservative free single use vials. Discard

unused portions of open vials. Store refrigerated at 2-8º C (36-46ºF). Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Avoid freezing and temperatures > 30ºC.

For IV use, dilute in D5W **only** to concentrations >15 mcg/ml. At concentrations between 5 and 15 mcg/ml, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/ml) in order to minimize the adsorption of filgrastim to infusion containers and equipment. Dilutions of 5mcg/ml or less are not recommended. Diluted filgrastim should be stored at 2-8º C (36-46ºF) and used within 24 hours. **Do not shake.**

Guidelines for Administration: See Treatment and Dose Modifications Sections of the protocol.
Filgrastim should not be administered within 24 hours of chemotherapy.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.2 **TACROLIMUS** (FK-506, Prograf®) NSC # 717865 (090205)

Source and Pharmacology: Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Tacrolimus is a potent immunosuppressive agent which prolongs the survival of the host and transplanted grafts in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (immunosuppression). Additionally, tacrolimus may inhibit cellular activities such as nitric oxide synthetase activation and apoptosis, and may potentiate the action of corticosteroids in these processes. Tacrolimus activity is primarily due to the parent drug. The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The t½ in adult patients ranges from 11-19 hours.

The pharmacokinetics of tacrolimus have been studied in pediatric liver transplant patients (0.7 to 13.2 years of age). Following the IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5 ± 3.8 hours, 2.6 ± 2.1 L/kg and 0.138 ± 0.071 L/hr/kg, respectively. Following oral administration to 9 pediatric patients, the absolute bioavailability was 31 ± 21%. Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations. Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A) in the liver and to a lesser extent in the intestinal mucosa. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. The main route of elimination is via the biliary tract and excretion in faeces. The mean clearance in renal dysfunction and mild hepatic dysfunction is the same as normal volunteers. Severe hepatic dysfunction (Pugh score >10) led to a substantially decreased clearance. A retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations; there were no gender-based differences. The absorption of tacrolimus from the gastrointestinal tract is incomplete and variable exhibiting large intra- and inter-patient variability. Administration with food significantly decreases the rate and extent of absorption Drugs that stimulate or inhibit hepatic p-450 enzymes will alter clearance of tacrolimus and close attention to potential drug interactions is crucial.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Headache (L), hypertension (L), nausea, vomiting, Anorexia Immunosuppression (L) Diarrhea, constipation, fever	Chest pain	Anaphylaxis with the injection, allergic reaction, hypotension, Asthma, dyspnea, Increased cough, flu like syndrome, pleural effusion, seizure (L), Tachycardia, angina
Prompt: Within 2-3 weeks, prior to the next course	Tremor (L),), renal dysfunction (acute with decrease in GFR, impaired urinary concentrating ability, and sodium retention), Elevated creatinine/BUN Anemia, insomnia, asthenia, Pain (abdominal, back, pain), Hyperglycemia, Hypomagnesemia (L), Hyper/hypokalemia (L), Hypophosphatemia Paresthesia,	Alopecia, dizziness, elevated LFT's, UTI, peripheral edema, Rash, pruritis, hyperlipidemia, Hypercholesteremia,	Dyspepsia, dysphagia, Gastritis, esophagitis, Flatulence, CNS abnormalities: (Confusion (L), somnolence (L), depression (L), Anxiety, anxiousness, abnormal dreams, emotional labiality, hallucinations, psychosis, hypertonia, incoordination, neuropathy, nervousness encephalopathy) Coagulation disorder, Leukopenia (L), Thrombocytopenia, Polycythemia, anemia, Leucocytosis, Infections (bacterial, fungal, viral – sepsis, cellulites, fungal dermatitis, herpes simplex, sinusitis, pharyngitis, abscess, pneumonia, bronchitis, peritonitis) Hyperbilirubinemia (L), Thrombosis, Phlebitis, Arthralgia, myalgia, Electrolyte abnormalities
Delayed: Any time later during therapy, excluding the above conditions			Acne, exfoliative dermatitis, skin discoloration, Photosensitivity reaction, skin ulcer, Delayed wound healing, hirsutism (Hypertrichosis) (L), Gingival hyperplasia, Abnormal vision, Amblyopia, ear pain, Otitis, tinnitus, GI Hemorrhage, GI perforation, Cholelithiasis, Cholestatic jaundice, Chronic renal dysfunction, renal failure, post transplant diabetes mellitus (L), Myocardial hypertrophy, elevated liver function tests, Liver damage, ascites
Late: Any time after completion of treatment			Lymphoproliferative disorders, skin malignancies
Unknown Frequency and Timing:	Fetal toxic effects of tacrolimus have been noted in animals. Tacrolimus is transported across the placenta and its use during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus is excreted in human milk, nursing should be avoided.		

(L) Toxicity may also occur later.

Formulation and Stability:

IV formulation:

Tacrolimus is available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Store between 5° C and 25° C (41° F and 77° F).

Oral formulations:
Tacrolimus is available for oral administration as capsules containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide. Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Guidelines for Administration: See Treatment and Dose Modifications Sections of the protocol.
Tacrolimus injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use to a concentration between 0.004 mg/mL and 0.02 mg/mL. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The polyoxyethylated castor oil contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC**. It is strongly recommended that glass bottles and non-PVC tubing be used to minimize patient exposure to DEHP**. Due to the chemical instability of tacrolimus in alkaline media, Tacrolimus injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir).

Monitor closely for an acute allergic reaction for the first 30 minutes and at frequent intervals thereafter.

Oral: Administer at a consistent time of day and at consistent intervals with regard to meals. Tacrolimus may be given with food as long as it is given the same way each time; however; administration with food significantly decreases the rate and extent of absorption

Supplier: Commercially available. See package insert for further information.

6.3 **METHOTREXATE** (MTX, amethopterin, Trexall®) NSC #000740 (102006)
Source and Pharmacology: A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses >30mg/m^2 absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12mg/m^2, the lumbar concentration of MTX is ~ 100 x's higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Transaminase elevations	Nausea, vomiting, anorexia,	Anaphylaxis, chills, fever, dizziness, Malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritis, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, Seizures[1], photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, Gingivitis, photosensitivity, Fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity[1] (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) Diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability[1] (L)	Pneumonitis, pulmonary fibrosis(L), Hepatic fibrosis (L), osteonecrosis (L), Leukoencephalopathy[1] (L), pericarditis, Pericardial effusions, hyperpigmentation of the nails,
Late: Any time after the completion of therapy			Progressive CNS deterioration[1]
Unknown Frequency and Timing:	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations.		

[1] ***May be enhanced by HDMTX and/or cranial irradiation.***
(L) Toxicity may also occur later.

Formulation & Stability: Methotrexate for Injection is available as a lyophilized powder for injection in 20 mg and 1 gm vials. The powder for injection contains approximately 0.14 mEq sodium in the 20 mg vial; 7 mEq sodium in the 1 g vial. Methotrexate for Injection is also available as a 25mg/mL solution in 2,4,8,10,20 and 40ml preservative free vials and 2 and 10ml vials with preservative. The 2, 4, 8, 10, 20, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, 4.3, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative and **must not be used for intrathecal or high dose therapy.**

Sterile methotrexate powder or solution is stable at 20 to 25 Cº (68 to 77 Fº); excursions permitted to 15 to 30 Cº (59 to 86 Fº). Protect from light

Guidelines for Administration: See Treatment and Dose Modifications Section of protocol.

For IV use: Powder for injection: Dilute 1 gm vial with 19.4 ml of non-preserved SWFI, Dextrose 5% or Saline 0.9% for a 50mg/ml concentration. Dilute the 20mg vial to a concentration ≤ 25mg/mL with above diluents. The powder for injection may be further diluted in Saline or dextrose containing solutions for IV use.

Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.4 **THIOTEPA** (Tespa, Thiophosphamide, Triethylenethiophosphoramide Tspa, WR-45312)
NSC #6396 (032006)

Source and Pharmacology: Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines. Thiotepa is desulfurated by cytochrome P-450 enzymes such as 2B1 and 2C11 which catalyze the conversion of thiotepa to tepa. Tepa is less toxic than thiotepa and has been demonstrated to produce alkali-labile sites in DNA, rather than cross-links. These findings indicate that tepa reacts differently from thiotepa and produces monofunctional alkylation of DNA. A second metabolite of thiotepa, a mercapturic acid conjugate, is formed via glutathione conjugation. Monochloro tepa is the third metabolite found in the urine.

Following short intravenous infusion (less than 5 minutes), peak concentrations of thiotepa were measured within 5 minutes. At steady state, the volume of distribution was independent of dose and ranged from 0.3 to 1.6 liters per kilogram (l/kg).

Approximately 4.2% of the original dose is eliminated in the urine within 24 hours as tepa. The elimination half-life of thiotepa ranges from 2.3 to 2.4 hours. The half-life of tepa ranged from 3.0 to 21.1 hours in one study.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia, fatigue, Weakness	Pain at the injection site, Dizziness, headache, blurred vision, abdominal pain, Contact dermatitis, rash	Anaphylaxis, laryngeal edema, wheezing, hives
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression; At higher doses in conditioning regimens for BMT: mucositis, esophagitis	At higher doses in conditioning regimens for BMT: inappropriate behavior, confusion, somnolence, increased liver transaminases, increased bilirubin, hyperpigmentation of the skin (bronzing effect)	Febrile reaction, Conjunctivitis, dysuria, urinary retention
Delayed: Anytime later during therapy, excluding the above conditions	gonadal dysfunction/infertility, azoospermia, amenorrhea		Alopecia, Secondary Malignancy

Unknown Frequency and Timing: **Fetal and teratogenic toxicities
**Carcinogenic and teratogenic effects of thiotepa have been noted in animal models at doses ≤ to those used in humans. It is not known if thiotepa is excreted into human breast milk.
(L) Toxicity may also occur later.

Formulation and Stability: Thiotepa for Injection USP, for single use only, is available in vials containing 15 mg of nonpyrogenic, sterile lyophilized powder. Store in a refrigerator at 2° to 8°C (36° to 46°F). **PROTECT FROM LIGHT AT ALL TIMES.**

Guidelines for Administration: See Treatment and Dose Modifications Sections of the protocol.

Reconstitute thiotepa for injection with 1.5 mL of Sterile Water for Injection resulting in a drug concentration of approximately 10 mg/mL**.** (As per manufacturer's information: Actual content per vial 15.6mg; withdrawable amount 14.7mg/1.4ml; approximate reconstituted concentration: 10.4mg/ml). When reconstituted with Sterile Water for Injection, solutions of thiotepa should be stored at refrigerated temperatures 2° to 8°C (36° to 46°F) and used within 8 hours. The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% NaCl) prior to use. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately.

In order to eliminate haze, filter solutions through a 0.22 micron filter [Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®-GSFilter Unit)] prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

When thiotepa is given in bone marrow transplant doses, bathe the patient frequently (≥ 2 baths/day) to avoid the contact dermatitis and discoloration of the skin that is seen with high dose.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.5 **CYCLOPHOSPHAMIDE** (Cytoxan) NSC #26271 (04162007)

Source and Pharmacology: Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P-450 isoenzymes (CYP2B6, CYP2C9 and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. Cyclophosphamide is well absorbed orally with a bioavailability greater than 75%. The plasma half-life ranges from 4.1 to 16 hours after IV administration and 1.3 to 6.8 hours after oral administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	abdominal discomfort, Diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, Immune suppression	Thrombocytopenia, Anemia, Hemorrhagic cystitis (L),	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, Infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction : azoospermia or oligospermia (prolonged or permanent)[1] (L)	amenorrhea[1]	gonadal dysfunction : ovarian failure[1] (L) Interstitial pneumonitis, pulmonary fibrosis[2](L),
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
[2] *Risk increased with pulmonary irradiation and higher doses.*
(L) Toxicity may also occur later.

Formulation and Stability: Available as 25mg and 50mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: acacia, calcium or magnesium stearate, starch, lactose, talc, stearic acid and various dyes.

Cyclophosphamide for Injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 gm and 2 gm vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30º C (86ºF).

Guidelines for Administration: See Treatment and Dose Modifications Sections of the protocol.

Cyclophosphamide for Injection: Reconstitute with sterile water or Bacteriostatic water for injection (paraben preserved only) to a concentration of 20 mg/ml. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/ml concentration, reconstitute with NS only to avoid a hypotonic solution.

Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.6 **ETOPOSIDE** (VePesid®, Etopophos®,VP-16) NSC #141540 (112005)

Source and Pharmacology: A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.
Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).
Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.			

Formulation and Stability:
Etoposide for Injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

Unopened vials of Etoposide are stable until expiration date on package at room temperature (25°C).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

Etoposide phosphate must be stored under refrigeration 2°-8°C (36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Etoposide:
Dilute Etoposide to a final concentration ≤0.4 mg/mL in Dextrose or Normal Saline containing IV solutions.
Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2mg/ml; stability is 24 hours at room temperature with concentrations of 0.4mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4mg/mL. Administer over 4 hours if diluted to this concentration for high dose etoposide. **Do not administer etoposide by rapid intravenous injection.**

To avoid leaching of DEHP from PVC bags and tubing, prepare the Etoposide solution as close as possible preferably within 4 hours to the time of administration or alternatively as per institutional policy, non-PVC containers and tubing may be used.

I.V. High Dose (usually associated with conditioning regimens involving hematopoietic stem cell support): Fluid volumes may be prohibitive at a 0.4 mg/ml concentration; an alternative dilution of 0.6 mg/ml (8 hour stability) may be used. Infusion of undiluted etoposide has been associated with cracking of hard plastic in chemotherapy venting pins and infusion lines. Infuse at a rate of 75-450 mg/m^2/hour. Use in-line filter during infusion secondary to precipitate risk.

Etoposide Phosphate:
Dilute the 100 mg vial with 5 or l0 mL of Sterile Water for Injection, USP; 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Bacteriostatic Water for Injection with Benzyl Alcohol; or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate) respectively.

When reconstituted with diluent containing a bacteriostat, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration at 2˚-8˚C (36˚-46˚F) for 7 days or at controlled room temperature 20˚-25˚C (68˚-77˚F) for 48 hours; following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride USP store at controlled room temperature 20˚-25˚C (68˚-77˚F) for 24 hours.
Following reconstitution, etoposide phosphate may be further diluted to concentrations as low as 0.1 mg/mL etoposide with Dextrose or Saline infusion solutions. Administer at same rate as etoposide above at a rate of 75-450 mg/m^2/hour or over 4 hours for high dose administration.

Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

6.7 **BUSULFAN INJECTION** (Busulfex®) NSC #750 (022005)

Source and pharmacology: Busulfan is a non-cell cycle specific bifunctional alkylating agent. In aqueous media, busulfan hydrolyzes to release methanesulfonate groups. This produces reactive carbonium ions that interact with cellular thiol groups and nucleic acids to form DNA cross-links. Busulfan injection is 100% bioavailable by definition of intravenous administration. It is approximately 30% bound to plasma proteins. The elimination half-life is 2 - 3 hours. It is rapidly distributed into tissue and crosses the blood-brain and the placental barriers. CSF concentrations are approximately equal to those in plasma.

Toxicities:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, electrolyte changes (hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia, and hyponatremia), hyperglycemia, dizziness, rash, pruritus, urticaria, injection site pain and inflammation, back pain, tachycardia, chest pain, edema, insomnia, anxiety, depression, headache, abdominal pain, diarrhea, (L) or constipation, anorexia, rectal discomfort, dyspnea, epistaxis	Weight gain, confusion	Seizures (rare with phenytoin prophylaxis), hematemesis, hyperuricemia, arrhythmias other than tachycardia, pleural effusion, alveolar hemorrhage
Prompt: Within 2-3 weeks	Myelosuppression, asthenia, immunosuppression, (L), mucositis, hyperbilirubinemia	Hepatotoxicity, veno-occlusive disease (L), mild alopecia (L), arthralgia, myalgia, hemorrhagic cystitis, hyperpigmentation (L), elevated creatinine and BUN	Reduced adrenal function (L), esophagitis, radiation recall reactions
Late: Any time after completion of treatment	Infertility, testicular atrophy and azoospermia, amenorrhea, ovarian failure		Secondary malignancy, breast enlargement, cataracts, idiopathic pulmonary syndrome (cough, dyspnea, pleural effusion, infiltrates, and hypoxemia), bronchopulmonary dysplasia with interstitial pulmonary fibrosis and pneumonitis, myocardial fibrosis, osteonecrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of busulfan and its solvent have been noted in animals. Toxicities include: multiple anomalies and low birth weight. It is unknown whether the drug or its solvent is excreted in breast milk.		

(L)Toxicity may also occur later

Formulation and Stability: Each ampoule of busulfan injection contains 60 mg (6 mg/mL) of busulfan, N,N-dimethylacetamide (DMA) 33% vol/vol and Polyethylene Glycol 400, 67% vol/vol. Store refrigerated at 2° to 8°C, (36° to 46°F).

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.
Dilute busulfan injection to a final concentration of approximately 0.5mg/mL with 0.9% sodium chloride or 5% dextrose in water. The drug should not be infused with any other drug or IV solution other than 0.9% sodium chloride or 5% dextrose. Only the 5 micron filter provided should be used to prepare the dose, using one filter per ampoule. (If using the enclosed syringe filter in the forward flow direction, the calculated volume of busulfan injection should allow for approximately 0.16 ml of residual busulfan in the filter.) Always add the busulfan to the diluent, not the diluent to the busulfan injection. Mix thoroughly by inverting several times. **Do not use polycarbonate syringes or filter needles with busulfan injection.** Busulfan injection diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is stable at room temperature (25° C) for up to 8 hours but the infusion must be completed within that time. Busulfan injection diluted in 0.9% Sodium Chloride Injection, USP is stable at refrigerated conditions 2°-8° C (36° to 46°F) for up to 12 hours but the infusion must be completed within that time.
Busulfan injection should be administered over 2 hours by IV infusion through a central venous catheter. In the bone marrow transplant setting ideal body weight must be used to calculate the dose. Patients receiving busulfan in a conditioning regimen for BMT should receive phenytoin prophylaxis to prevent seizures. Phenytoin should be given 12 hours prior to the start of busulfan, then daily during busulfan administration and for 48 hours after completion of busulfan. Phenytoin reduces busulfan plasma AUC by 15%. Use of other anticonvulsants may result in higher busulfan plasma AUCs, and an increased risk of VOD or seizures. After an initial dose of busulfan injection, blood levels are monitored with bone marrow transplant patients in order to achieve a target area-under-the-curve (AUC) plasma concentration.

Supplier: Commercially available injectable solution. See package insert for further information.

6.8 **CYCLOSPORINE A** (cyclosporine, CYA, Sandimmune®, Neoral®, Gengraf®) NSC #290193) (082006)

Source and Pharmacology: Cyclosporine (CSA) is a lipophilic fungal peptide consisting of 11 amino acids. CSA is a potent immunosuppressive agent which prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Current evidence suggests that cyclosporine selectively inhibits the transcription of IL-2; the action of which stimulates the proliferation of activated T-lymphocytes. CSA has been shown *in vitro* to be a potent inhibitor of P-glycoprotein, which has been postulated to be a factor in multi-drug resistance to various antineoplastic agents. The terminal half-life of CSA is approximately 19 hours (range 10-27 hours). Ninety-nine percent of CSA is metabolized. Elimination is primarily biliary with approximately 6% excreted in the urine. In the circulation, CSA is mainly bound to high, low, or very low density lipoproteins and to chylomicrons. Only a small fraction circulates unbound. The volume of distribution varies from 3.5 L/kg to 13 L/kg with higher concentrations of drug found in the liver, lymphocytes, kidney, heart, lung, pancreas, fat, neural and muscle cells. CSA clearance rates have been shown to be higher in pediatric patients and for patients <25 years old. The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable exhibiting large intra- and inter-patient variability. Drugs that stimulate or inhibit hepatic p-450 enzymes will alter clearance of CSA and close attention to potential drug interactions is crucial.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Hypertension (L), Immunosuppression (L)	Headache (L), nausea and vomiting, Diarrhea	Anaphylaxis, angioedema, Seizure (L), arrhythmia, chest pain, fever, facial flushing
Prompt: Within 2-3 weeks, prior to the next course	Tremor (L),), renal dysfunction (acute with decrease in GFR, impaired urinary concentrating ability, and sodium retention)	Hypomagnesemia (L), Hyperlipidemia (L)	Confusion (L), somnolence (L), Insomnia, depression (L), Anxiety, dizziness, rash, Urticaria, acne, hyperkalemia, Encephalopathy, hemolytic-uremic syndrome,cardiac failure, MI, leukopenia (L), Anemia, thrombocytopenia, Increased creatinine, infections, Hyperbilirubinemia (L), hepatic insufficiency
Delayed: Any time later during therapy, excluding the above conditions	Hirsutism (L)	Gingival hyperplasia (L)	Tinnitus, vestibular disorder, Cholelithiasis,cataracts (L), Gynecomastia, chronic renal dysfunction
Late: Any time after completion of treatment			Lymphoproliferative disorders, Skin malignancies
Unknown Frequency and Timing:	Fetal toxic effects of cyclosporine have been noted in animals. Of the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period, the only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Cyclosporine is excreted in human milk, nursing should be avoided.		

(L) Toxicity may also occur later.

Formulation and Stability:

IV formulation:

Cyclosporine (Sandimmune®) is available as a (50mg/mL) 5mL ampule use containing 650mg polyoxyethylated castor oil (cremophor) and 32.9% alcohol. Store at temperatures below 30°C (86°F) and protected from light.

Oral formulations:

Cyclosporine (Sandimmune®) 25mg, and 100mg capsule, 100mg/mL oral solution Inactive ingredients include: Sandimmune® Capsule = Dehydrated alcohol, sorbitol, glycerol, corn oil, gelatin, polyoxyethylated glycolysed glycerides; Sandimmune® Solution = Olive oil, dehydrated alcohol, polyoxyethylated glycolysed glycerides.

Cyclosporine USP modified (microemulsion) (Neoral®, Gengraf®) 25mg, 100mg capsule, 100mg/mL oral solution. Inactive ingredients include: Neoral® capsule and solution = dehydrated alcohol, corn oil, polyoxyl 40 hydrogenated castor oil, α tocopherol, gelatin, and propylene glycol. Gengraf® Capsule and solution = dehydrated alcohol, gelatin, polyethylene glycol, polyoxyl 35 castor oil, polysorbate 80, propylene glycol, and sorbitan monooleate.

Store capsules in the original unit-dose container at controlled room temperature 15°-30°C (59°-86°F). Store Oral solutions in the original container at controlled room temperature 68°-77°F (20°-25°C). Do not store in the refrigerator. Once opened, the contents must be used within two months. At temperatures below 68°F (20°C) the solution may gel; light flocculation or the formation of a light sediment may also occur. There is no impact on product performance or dosing using the syringe provided. Allow to warm to room temperature 77°F (25°C) to reverse these changes.

NOTE: Sandimmune®, Neoral® and Gengraf® ARE NOT BIOEQUIVALENT. Liquid formulations of each trade name are equivalent to capsules of that same trade name. Conversion from one trade name product to another is generally done at a 1:1 ratio, but requires close monitoring. Conversions from IV to PO are usually done at a 1:3 ratio, but should be monitored closely. Adjusting emulsion products to the same trough concentration as other oral products results in greater total exposure to the drug.

Guidelines for Administration: See Treatment and Dose Modifications Sections of the protocol.

Dilute I.V. concentrate 1 mL (50mg) of cyclosporine injection in 20 mL-100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection (0.5- 2.5 mg/mL). Diluted infusion solutions are stable for 24 hours at room temperature under fluorescent light.

The Cremophor ® EL (polyoxyethylated castor oil) contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC**. It is strongly recommended that glass bottles and non-PVC tubing be used to minimize patient exposure to DEHP**.

Monitor closely for an acute allergic reaction for the first 30 minutes and at frequent intervals thereafter. Note: cyclosporine absorbs into plastics and can give falsely high serum or blood concentrations if blood samples are collected from the same line through which cyclosporine was administered.

Oral: Administer at a consistent time of day and at consistent intervals with regard to meals. Do not use plastic or styrofoam cups. If diluted with juice or milk, use a glass container and rinse with additional diluent, and then consume to ensure that complete dose has been taken. Do not use water or cleaning agents on the dosing syringe. To improve palatability, mix Sandimmune® with milk, chocolate milk or orange juice; mix Neoral® or Gengraf® with orange juice or apple juice but NOT milk. After mixed, have patient consume immediately. **DO NOT MIX GRAPEFRUIT JUICE with any CSA product.**

Supplier: Commercially available from various manufacturers. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

All baseline studies must be performed prior to starting protocol therapy unless otherwise note below.

7.1 Required Clinical, Laboratory and Disease Evaluations.

Observation	Within 2 weeks prior to BMT	At BM or G-BM harvest	1-2 wks after ANC>500	3m after BMT	8m after BMT	1yr after BMT	2yrs after BMT	At Relapse
Bone Marrow aspiration	X							X
Sample from BM collection		X						
CSF counts/cytology	X							X
CBC with differential	X		X	X	X	X	X	X
BUN/Cr	X							
LFTs	X		X	X	X	X	X	
Immune reconstitution studies				X	X	X		
Disease status	X		X	X	X	X	X	X
Acute GVHD				X				
Chronic GVHD				X	X	X	X	
MUGA or ECHO	X							
Calculated GFR or Creatinine Clearance*	X							
Pulmonary Function Test	X							
Karnofsky or Lansky score	X		X	X	X	X	X	X

**Use the Schwartz formula (Section 3.2.3.1) for GFR and calculated Cr. Clearance only if serum creatinine is elevated for age*

7.2 Recommended Clinical, Laboratory and Disease Evaluations

Other studies as needed for good clinical care.

7.3 Follow-up

Follow up as needed for good clinical care. Required laboratory evaluations are needed within one to two weeks of engraftment, and at 3, 8, 12, and 24 months after transplant.

7.4 Events Related to Donor Safety

The side effects of BM donations are listed below in Table 7.4.1. The side effects of G-CSF are listed in Section 6.1. All toxicities experienced by donors will be reported via AdEERS (see Section 12.5 for reporting guidelines). The acute toxicities that will be monitored and reported for donor safety include: any toxicity which requires readmission to the hospital, life-threatening or incapacitating complications of BM harvest or G-CSF administration, thrombosis, splenic rupture, worsening of autoimmune disease, and Adult Respiratory Distress Syndrome (ARDS).

Table 7.4.1 Acute Side Effects Associated with Bone Marrow Donation

Common (20-85% of donations)	fatigue, collection site pain, back pain, pain upon sitting, nausea, sore throat, headache, emesis, iv site pain
Less Common (<20% of donations)	fever, bleeding, syncope, unexpected hospitalization, minor infections, hypotension, chipped teeth, urinary retention, post-spinal headache
Serious Complications (1% of donations)	seizure, bacteremia, abscess, prolonged pain or numbness, neuropathy, prolonged hospitalization
Life-threatening or Incapacitating Complications (All events combined = 0.29-0.4% of donations)	myocardial infarction, anaphylaxis, prolonged paralysis after anesthesia, pulmonary embolism, transfusion complications (anaphylaxis, acute renal failure, or hepatitis), malignant hyperthermia, pulmonary edema, significant arrhythmias, stroke, severe pain

8.0 SUPPORTIVE CARE GUIDELINES

These are provided for institutional consideration. Investigator discretion should be used, and individual considerations made for specific patient situations and institutional practices. Supportive care should be administered in a similar fashion to subjects randomized to either arm of the study.

8.1 Use of Growth Factors in Recipients of G-BM or BM

G-CSF is not generally recommended for patients undergoing matched sibling BMT. After engraftment, G-CSF may be given for severe neutropenia (ANC < 500/µL), or as necessary to keep ANC > 1000/µL. Other growth factors (GM-CSF, Erythropoietin) should also be given only if clinically indicated.

8.2 Prophylaxis Against Infections

Patients undergoing BMT on this protocol are at high risk for infection. This risk may be increased due to infections that occur during the intensive reinduction and consolidation chemotherapy many patients will receive prior to enrollment on this protocol. Centers should be especially mindful of this as they choose anti-bacterial, anti-fungal, anti-viral, and PCP prophylactic regimens. Aside from well established screening approaches for CMV, centers may wish to consider routine screening for other viral pathogens such as Adenovirus, EBV or HHV-6. Any prophylaxis regimen chosen must be the same for patients on both arms of the protocol. Special considerations should be given for antifungal prophylaxis (Section 8.3).

8.3 Anti-fungal Therapy

Prophylaxis with fluconazole or other antifungal agents can be given as per local institutional guidelines. **Fluconazole and other azoles are expected to increase serum tacrolimus (and sirolimus levels, if relevant). Therefore, dosages of sirolimus and tacrolimus should be adjusted accordingly. Due to extreme interactions with sirolimus, voriconazole is contraindicated during sirolimus therapy.**

8.4 Intravenous Immune Globulin (IVIG)

IVIG administration will be left to local institutional standard practice, however, we recommend that patients receive replacement IVIG (400-500 mg/kg) for severe hypogammaglobulinemia (IgG < 400 mg/dL).

8.5 Irradiation of Blood Products

Blood products should be irradiated following the current FDA guidelines found at: http://www.fda.gov/cber/gdlns/gamma.htm

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

a) Relapse. See Section 3.3 for definitions. Relapse is a key endpoint on this study. Patients must meet relapse criteria and be taken off protocol prior to the initiation of any non-study therapy (ie, DLI, imatinib).
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Completion of planned therapy.
d) Physician determines it is in patient's best interest.
e) Development of a 2nd malignancy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

9.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Entry onto another COG therapeutic study.
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of study closure to accrual

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Design

Patients will be randomized between BM and G-BM as their graft type. The primary objective is to compare two-year event-free survival between the two arms. An event is defined as relapse or TRM. Secondary endpoints are:

- Engraftment kinetics
- Rates of acute and chronic GVHD
- Graft Characteristics, including nucleated and CD34+ cell doses and T cell characterization
- Day 100 treatment-related mortality
- Length of Hospital Stay
- Immune reconstitution
- Short and long term safety in donors

The randomization will be stratified on disease risk (Standard Risk, Intermediate Risk and High Risk). For patients also enrolled on ASCT0431, the ASCT0631 randomization arms are separate ASCT0431 strata to ensure even allocation of BM and G-BM across the two arms of the ASCT0431 study (standard vs. experimental GVHD prophylaxis).

10.2 Patient Accrual and Expected Duration of Trial

A retrospective analysis by Gorin et al of the impact of cell dose on transplant outcome among patients undergoing matched sibling donor transplantation for AML showed the following differences between the high cell dose and low cell dose groups: 2 year LFS 72% vs. 54% (p=.0007); 2 year OS 74% vs. 58% (p not reported); TRM 17% vs. 27% (p=.02).[66] The difference in cell dose between the high cell dose and low cell dose group in this study was 1.7-fold. Our experience in the PBMTC phase II study has shown that the G-BM collections are very rich harvests, easily exceeding a 2-fold increase in cell dose as compared to conventional BM collections. Specifically, the median cell dose on STC0233 was 8.4 x 10^8/kg, and the median CD34 dose was 7.3x10^6/kg. Thus, we have already shown that use of G-BM will easily achieve the goal of significantly increasing the infused cell dose. The key will be the clinical impact of this cell dose. In the Gorin study, the RR for better leukemia-free survival was 1.64 for the high-dose BM patients compared to low dose BM patients; that is, subjects who received high-dose bone marrow were 1.64 times more likely to be alive and leukemia-free at 2 years post transplant.

Accrual estimates for the various diseases come from 2 sources. 1) Accrual estimates from COG studies (study number indicated). 2) CIBMTR data on the number of matched sibling donor transplants performed for various indications (other). We assume that we will enroll 50% of the transplant patients for each disease not enrolled on another COG study, and 70% of the patients co-enrolled on a COG study such as ASCT0431 or AAML0531. Based on accrual estimates in ASCT0431, we assume 50% of the ALL CR2 patients will fall into the High Risk stratum (early bone marrow relapse or T cell disease) and 50% of the ALL CR2 patients will fall into the Intermediate Risk stratum (late bone marrow relapse or early extramedullary relapse). All numbers presented are per year.

Table 10.2.1

Patient type	Pts/ year	risk status	Patient type	Pts/ year	risk status	Patient type	Pts/ year	risk status
ASCT0431 (ALL CR2 early BM and T cell)	9.5	H*	ASCT0431 (ALL CR2 early non-BM and late BM)	9.5	I*	AAML0531 (AML CR1)	30.1	S*
Other ALL CR2 early BM and T cell	8.8	H*	Other ALL CR2 early non-BM and late BM	8.8	I*	other AML CR1	14.7	S*
JMML	4	H[42]	ALL high-risk CR1	15.2	I^	CML	5.8	S[48]
			AML CR2	4.8	I[44]			
			MDS	5.8	I[41]			
	22.3			**44.1**			**50.6**	
			TOTALS					
			Overall TOTAL	**117**				

*see ASCT0431 and AAML0531 Concept and AALL0031 Protocol documents
^CIBMTR data 2000-2004
Risk status: H; High Risk, average expected EFS approximately 40% I; Intermediate Risk, average expected EFS approximately 52% S; Standard Risk, average expected EFS approximately 60%. See also Section 2.12 for data regarding risk assignment.

We will accrue patients for approximately 44 months. Based on the information in the table above, we expect to accrue 22 High Risk patients, 44 Intermediate Risk patients, and 50 Standard Risk patients each year, for a total of 425 patients. Randomization will be 1:1 between G-BM and BM arms. All patients will be followed for a minimum of 2 years.

10.3 Statistical Analysis Methods

10.3.1 Sample size justification

Testing at the 0.025 level, one-sided, 191 events will provide statistical power of 80% to detect a hazard ratio of 0.67.[67] In other words, patients randomized to G-BM will have a risk of an event that is one-third less than patients randomized to BM. For purposes of analysis and stratification, patients will be divided into three groups: High Risk, Intermediate Risk and Standard Risk disease. Among patients randomized to BM, the expected two-year event-free survival is assumed to be 40%, 52%, and 60% for high, intermediate, and standard risk, respectively. Forty-four months of accrual will yield 48 events in the High Risk group, 77 events in the Intermediate Risk group and 73 events in the Standard Risk group for a total of 198 events.

10.3.2 Study Interim Monitoring

10.3.2.1 Safety rule for recipients of grafts with volume < 10 cc/Kg recipient weight.

Due to concerns about potential graft failure in recipients of smaller volume BM infusions (<10 cc/kg of recipient weight), the graft failure rate will be formally monitored in this patient subset. These will be donor/recipient pairs in which the recipient is considerably larger than the donor, and the collection in the donor is capped at a maximum of 20 cc/kg of donor weight for donor safety. A four percent graft failure rate will be considered acceptable. Three interim analyses will be performed. We anticipate approximately 10% of the donors will yield a smaller volume BM collection, for a total of approximately 42, so the interim analyses will be performed after each 10th recipient of a BM collection <10 cc/kg recipient weight has reached day 42 post-infusion (i.e., after the 10th, 20th, and 30th recipient). At each interim analysis, the adjusted confidence interval for the non-engraftment rate will be calculated using the appropriate O'Brien-Fleming alpha as the significance level. Transplantation of patients with a graft volume < 10 cc/Kg recipient weight will be suspended, pending DSMC review, if the lower confidence limit is greater than 4% at any interim analysis.

10.3.2.2. Interim Monitoring for the Primary Endpoint

There will be four interim and one final analysis of event-free survival using the stratified log-rank test. The interim analyses will occur after 20%, 40%, 60%, and 80% of the expected number of events have been reported. The O'Brien-Fleming spending function, with early looks truncated to a Z-score of 3.0, will be used to define the stopping boundaries. The study will be monitored for futility using the approach of Friedlin and Korn with the lower boundaries based on testing the alternative hypothesis at the 0.005 level.

10.3.3. Statistical Considerations for Safety-Related Endpoints

10.3.3.1 Graft Failure

A one-sided Z-test of proportions will be used for the graft failure rate. The O'Brien-Fleming spending function, with early looks truncated to a Z-score of 3.0, will be used to define the stopping boundaries. Four interim analyses will be performed after 20%, 40%, 60%, and 80% of the recipients have reached day 42 post-infusion. We anticipate a 2% graft failure rate in patients randomized to receive un-stimulated grafts. Testing at the 0.05 level, we will have 80% power to detect a graft failure of 7% in patients randomized to receive G-CSF stimulated grafts.

10.3.3.2 Acute Graft-versus-Host Disease

A one-sided Z-test of proportions will be used for the incidence of Grade III-IV aGVHD. The O'Brien-Fleming spending function, with early looks truncated to a Z-score of 3.0, will be used to define the stopping boundaries. Four interim analyses will be performed after 20%, 40%, 60%, and 80% of the

recipients have become evaluable for aGVHD (day 120 post-infusion.) We anticipate the incidence of Grade III-IV aGVHD will be 17% in patients randomized to receive un-stimulated grafts. Testing at the 0.05 level, we will have 80% power to detect an incidence rate of 27% in patients randomized to receive G-CSF stimulated grafts.

10.3.3.3 Day 100 Treatment-Related Mortality

A one-sided Z-test of proportions will be used for the day 100 treatment-related mortality rate (TRM.) There will be no interim monitoring of TRM. We anticipate that the TRM will be 15% in patients randomized to receive un-stimulated grafts. Testing at the 0.05 level, we will have 80% power to detect a 25% rate in patients randomized to receive G-CSF stimulated grafts.

10.3.3.4 Monitoring for Donor Safety

10.3.3.4.1 *Monitoring Time Frame*

All patients will be monitored for peri-donation morbidity and mortality, which will be considered as any adverse event codeable using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) toxicity grading scale during the peri-donation period. For donors randomized not to receive G-CSF priming, the peri-donation period is defined as day of collection (Day 0) until 2 weeks after bone marrow donation (Day 14). For those randomized to receive G-CSF priming, the peri-donation period is defined as the day of the first dose of G-CSF (Day -4) until 2 weeks after bone marrow donation (Day 14). Planning for these outcomes was done assuming 202 patients will be randomized to non-primed donation and 203 patients will be randomized to primed donation.

10.3.3.4.2 *Monitoring for Death in the Peri-Donation Period*

Formal monitoring for this endpoint will be restricted to patients randomized to G-CSF priming, since non-primed donation is considered standard practice. Each institution will monitor for death during the peri-donation period for all patients randomized to non-priming using standard practices at their own institution and will take any action required on that account.

If any G-CSF primed donor dies from a cause other than accident during the peri-donation period, enrollment to the study will be suspended and identified to the DSMC for possible modification. If the true non-accidental death rate is 0.055%, the priming with G-CSF will be identified as having an *acceptable* non-accidental death rate with probability 0.89. If the true non-accidental death rate is 1.5%, the therapy will be identified as having an *unacceptably high* non-accidental death rate with probability 0.95.

10.3.3.4.3 *Monitoring for Unacceptable Non-Fatal Toxicity in the Peri-Donation Period*

This characteristic will be monitored by comparing the frequency of peri-donation complications for patients randomized to G-CSF priming with those observed for patients randomized to non-primed donation. Because it is known that patients randomized to G-CSF priming will experience pain, only the incidence of CTCAE Grade 4 pain will be monitored. We accept that the frequency of complications associated with G-CSF priming will be at least as great as donation without G-CSF priming, but that this is acceptable only for complications characterized by Grade 1 or 2 CTCAE toxicities. For non-fatal complications of Grade 3 other than pain or any of Grade 4, complications should occur at no greater rate for primed donation. We therefore will consider acceptable an increase of 25% in the relative risk of Grade 1 or 2 toxicity other than pain in the primed population when compared with the non-primed population, but evidence of an increase in the rate of any Grade 3 other than pain or any Grade 4 complication amongst the primed patients will cause the study committee to identify the primed therapy for possible modification. Because enrollment will require 2.67 years, we expect to monitor at Years 1 and 2 after enrollment which should correspond to information times of 0.44 and 0.89. The following test statistics will be used for the complication rate:

Grade 1 or 2 complication rate: The following test statistic will be compared with the Normal (0,1) distribution:

$$\frac{\ln\left(\frac{\hat{p}_G\left(1-\hat{p}_{NG}\right)}{\hat{p}_{NG}\left(1-\hat{p}_G\right)}\right)-\ln(1.25)}{\sqrt{\hat{V}\left[\ln\left(\frac{\hat{p}_G\left(1-\hat{p}_{NG}\right)}{\hat{p}_{NG}\left(1-\hat{p}_G\right)}\right)\right]}}$$

Grade 3 or 4 complication rate: The following test statistic will be compared with the Normal (0,1) distribution:

$$\frac{\ln\left(\frac{\hat{p}_G\left(1-\hat{p}_{NG}\right)}{\hat{p}_{NG}\left(1-\hat{p}_G\right)}\right)}{\sqrt{\hat{V}\left[\ln\left(\frac{\hat{p}_G\left(1-\hat{p}_{NG}\right)}{\hat{p}_{NG}\left(1-\hat{p}_G\right)}\right)\right]}}$$

For both complication rates, the O'Brien-Fleming spending function, with a nominal one-sided significance level of 0.05, will be used to define the stopping boundaries.

10.3.4 Statistical Considerations for Other Secondary Endpoints

10.3.4.1 Chronic Graft-versus-Host Disease

The cumulative incidence estimator will be used to estimate the incidence of chronic graft-versus-host disease (cGVHD) and we will a one-sided Z-test of proportion will be used to compare the cumulative incidence of cGVHD at 18 months post-transplant between randomization arms. We hypothesize that the rate of cGVHD may be lower in the experimental arm. Only patients who survive to day 100 will be included in the analysis of cGVHD. There will no interim monitoring of cGVHD. We anticipate that the cumulative incidence of cGVHD at 18 months post-transplant will be 20% in patients randomized to receive conventional BM. Testing at the 0.05 level, we will have 80% power to detect a cumulative incidence of 11% in patients randomized to receive G-CSF stimulated grafts.

10.3.4.2 Statistical Considerations for Neutrophil Engraftment

The log-rank test will be used to compare the time to neutrophil engraftment. There will be no interim monitoring of neutrophil engraftment. We anticipate that the median time to neutrophil engraftment will be 21 days in patients randomized to receive conventional BM. Testing at the 0.05 level, we will have 80% power to detect a median time to neutrophil engraftment of 16 days in patients randomized to receive G-CSF stimulated grafts, and 46% power to detect a median time to engraftment of 18 days.

10.3.4.3 Statistical Considerations for Hospital Stay

The median length of initial hospitalization for patients discharged alive will be estimated and compared between randomization arms using the Wilcoxon rank-sum test.

10.3.4.4 Statistical Considerations for Immune Reconstitution

For each measure (CD3+, CD4+, and CD8+ cell counts) of immune reconstitution, their levels over time (one month post, three months post, eight months post, one year post) will be summarized graphically. Generalized estimating equation will be used to model the levels as a function of time and randomization assignment (and their potential interaction) and to test the impact of G-CSF stimulation on immune reconstitution.

10.3.4.5 Statistical Considerations for Infused Cell Doses

The Wilcoxon rank-sum test will be used to compare the infused nucleated and CD34+ cell doses between randomization arms. Bensinger[9] reported a median nucleated cell dose of 2.3 x 10^8/Kg and a median CD34+ cell dose of 2.4 x 10^6/Kg in patients receiving conventional BM. Based on our pilot experience, we hypothesize a doubling of the nucleated cell dose in patients receiving stimulated BM. Testing at the 0.05 level, one-sided, we will have 80% power to detect this difference as long the standard deviation of the nucleated cell dose is less than 9.5. Since Bensinger reported a range of 0.2 to 14.6 for the nucleated cell dose, we anticipate our standard deviation will be much less than 9.5 and we will therefore have power in excess of 80%. Since we hypothesize a larger increase in CD34+ cell dose with stimulated BM based on our pilot experience, we will also have power in excess of 80% for this comparison.

10.3.4.6 Statistical Considerations for Graft Characteristics

As described in Section 15.0, six graft characteristics will be examined: absolute and relative T cell numbers, cytokine profile, plasmacytoid DC numbers and function, and T regulatory cell number. Continuous graft characteristics will be summarized using their median and interquartile range. Dichtomous graft characteristics will be summarized using their proportion and 95% confidence interval. The Wilcoxon rank-sum test will be used to compare continuous graft characteristics between the randomization arms and the chi-square test will be used to compare dichotomous graft characteristics (eg, proportion with Th1-type profile) between the randomization arms. The Wilcoxon rank-sum test will also be to compare the levels of continuous graft characteristics between patients who do and do not develop Grade III-IV aGVHD. The chi-square test will be used to compare dichotomous graft characteristics between patients who do and do not develop Grade III-IV aGVHD. The log rank test will be used to assess the relationship between graft characteristics and the time to cGVHD.

11.0 EVALUATION CRITERIA

11.1 Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the current version of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/). Additionally, toxicities are to be reported on the appropriate data collection forms.

11.2 Response Criteria for ALL

See definitions in Section 3.3

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using

similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol).

12.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current NCI Agent-Specific Adverse Event List (provided in the Drug Information Section of this protocol); or***
- ***the drug package insert (for treatments with commercially available agents).***

12.3 Reporting of Adverse Events for Commercial Agents - AdEERS

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the Drug Information Section of this protocol.

Table B Expedited reporting requirements for AEs experienced by patients on study.

Attribution	Grade 4		Grade 5[a]		Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See the data submission packet for additional toxicity reporting requirements.
Unrelated or Unlikely			AdEERS		
Possible, Probable, Definite	AdEERS		AdEERS	AdEERS	

a **This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.**

12.4 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the following information within two weeks of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials:

a completed NCI/CTEP Secondary AML/MDS Report Form *(do not use AdEERS);*

- a copy of the pathology report confirming the AML/MDS; and
- a copy of the cytogenetics report (if available).

Submit the information via fax to:

NCI (fax # 301-230-0159) and

COG (fax # 626-445-4334; attention AER Coordinator)

Note: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report Form must be submitted for the most recent trial. The COG must also be provided with a copy of the report even if the study was not the patient's most recent trial.

12.5 Donor-Related Adverse Event Reporting Requirements

Because the use of filgrastim (G-CSF) with normal pediatric bone marrow donors is experimental, increased attention is required for toxicities related to use of this agent with donors enrolled in this study. Thus, adverse events experienced by donors must be reported in an expedited manner to allow for timely monitoring of safety and care. As such, acute donor toxicities will be reported in the same manner as for investigational agents.

G-CSF is a commercially available drug. However, this agent is being tested for an indication not included in the approved package label. The use of G-CSF in this setting meets the criteria for an exemption from IND filing.

Table A USE IN REPORTING ADVERSE EVENTS EXPERIENCED IN DONORS RECEIVING FILGRASTIM (G-CSF)

Phase 2 and 3 Trials and COG Group-wide Pilot Studies: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4[3] & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	**24-Hour**; 5 Calendar Days	5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:**

AdEERS 24-hour notification (via e-mail to COG AE Coordinator) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Please see exceptions below under section entitled "Additional Instructions or Exceptions."

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Note: **All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via e-mail to COG AE Coordinator within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete AdEERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the AdEERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials:

- **Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent.**

  The following are of special concern in the donors receiving filgrastim and are required to be reported via AdEERS

- Any toxicity which requires readmission to the hospital;
- Life-threatening or incapacitating complications of BM harvest or G-CSF administration;
- Thrombosis, splenic rupture, and worsening of autoimmune disease; and
- Adult Respiratory Distress Syndrome (ARDS).

13.0 RECORDS AND REPORTING

13.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Pathology Narrative Reports and Surgical Reports. These forms are faxed to the Statistics and Data Center at (626) 445-4334.

2. Reference Labs' required reports, and QARC data: These data accompany submissions to these centers, which forward their review data electronically to the COG Statistics and Data Center.

Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes submission schedule.

13.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

See Section 3.0 for definitions and Section 7.0 for study requirements.

14.1 Bone Marrow Analysis

Bone marrow aspiration and CSF assessment to confirm complete remission after relapse is required for study entry. Morphologic, immunophenotypic, & cytogenetic analysis should be performed by the local institution.

14.2 Cytogenetics Central Review for ALL patients

Patients entered on AALL0433 and possibly other COG lymphoid leukemia relapse studies will have undergone central review of relapse cytogenetics prior to entering this study. For patients who have not had slides sent for central review on COG relapse studies, cases will be reviewed by the COG Cytogenetics Committee. Each laboratory submits the cytogenetic materials on each case for central review, and these are reviewed by members of the Cytogenetics Review committee. This process encompasses detailed evaluations of parameters such as type of specimen, culture methods, duration of cell culture, quality of chromosome banding, karyotypes of each clone, identification of chromosomes, interpretation and chromosome nomenclature. Any changes made by the reviewers or any discrepancies noted are recorded. At times, the reviewers ask local laboratories to submit additional materials or recommend FISH studies to determine the final interpretation. The submitting laboratory receives a copy of the changes made on their original interpretation. The final interpretation is that of the Review Committee, and any changes are a consensus of at least two (experienced cancer cytogeneticist) reviewers. The review committee invites feedback from the local laboratories if they disagree with the changes.

If there are discrepancies between the cytogenetics data and the molecular data, the laboratory will be contacted to ascertain if there was any mix-up of samples or asked to repeat the procedure on left-over/stored specimens. The Cytogenetics Review Committee's experience (from on-going protocols on diagnostic samples) demonstrates that 20-30% of the cases reviewed centrally require some degree of reinterpretation of the karyotypes.

Required Material:

a) Two **original** karyotypes of different cells from each abnormal clone or of two normal cells when no abnormalities are found; full-size metaphase images of the karyotypes cells.

b) A completed COG Cytogenetics Reporting Form and FISH Form. These reporting forms are available on the COG Web site. Electronic submission of the karyotypes/FISH images is required.

Shipping:

The materials on each case should be sent to the COG ALL Cytogenetic Coordinators within 8 weeks of study entry. If the laboratory is west of the Mississippi River, send these materials to Dr. Andrew Carroll (University of Alabama). If the laboratory is east of Mississippi River (except Minnesota and Wisconsin, which go to Dr. Carroll), send all materials to Dr. Nyla Heerema (The Ohio State University).

Western Laboratory – Shipping Address:
Dr. Andrew Carroll, Ph.D.
Department of Genetics
University of Alabama at Birmingham
Phone: 205 934-0665
Fax: 205 934-1078
Email: acarroll@genetics.uab.edu
Regular U.S. Mailing Address: Street Address and Courier Delivery:
Kaul Bldg., Room 314B Hugh Kaul Human Genetics Building, Room 314B
1530 3rd Ave South 720 20th Street South
Birmingham, AL 35294-0024 Birmingham, AL 35205

Eastern Laboratory – Shipping Address:
Dr. Nyla Heerema, Ph.D.
Professor and Director of Cytogenetics
The Ohio State University
Division of Clinical Pathology
Department of Pathology
Hamilton Hall, Room 167
1645 Neil Ave.
Columbus, OH 43210
Phone: 614-292-7815
Fax: 614-292-7072
Email: heerema-1@medctr.osu.edu

15.0 CORRELATIVE BIOLOGY STUDIES & SPECIMEN REQUIREMENTS

15.1 Primary Biology Hypothesis

Measurable differences in the numbers and functional properties of immunological cells in the donor graft will explain and predict differences in the in vivo development of GVHD in recipients of allografts of unstimulated BM vs. BM cells from G-CSF pretreated donors.

Thus, we hypothesize that use of G-BM to support matched sibling donor transplantation will have several potential impacts on transplant outcomes:

1. We hypothesize an improvement in EFS in the G-BM arm. This will be tested in the primary aim of the study (Section 1.1.1).
2. We hypothesize that use of G-BM will improve time to ANC>500 compared to BM (1.1.2), as well as time to discharge (1.3.3). This will be reflected in a greater stem/progenitor cell content in the G-BM grafts.
3. The PBMTC G-BM pilot study showed encouragingly low rates of GVHD, especially chronic GVHD. We hypothesize that rate of cGVHD in the G-BM arm may be lower (1.1.3), and that, if so, this may occur because of a number of shifts in the cellular makeup of the graft. These include:
    i. Differing absolute or relative numbers of CD4 and CD8 T cells within the grafts
    ii. A change in cytokine profile in the G-BM graft from a Th1-type profile to a Th2-type profile
    iii. Altered numbers and function of plasmacytoid dendritic cells
    iv. Increased number of T regulatory cells in G-BM

15.2 Rationale

Immunological Studies: Focused immune characterization of the BM grafts from each arm of the study will be performed in the laboratories of Kirk Schultz and Megan Levings on samples obtained from each enrolled donor and correlated with development of GVHD. The focused studies will be based on studies performed by the Schultz laboratory and on observations from three sources: a) the pilot CBMTG studies comparing PBSC versus G-BM; b) immune populations identified in an NCI funded chronic GVHD study, COG ASCT0031; and c) the NIH Chronic GVHD Consensus Biomarkers Working Group document (K. Schultz, Chair). The CBMTG performed pilot studies to immunologically characterize G-BM versus PBSC.[68] These studies show the feasibility of this work, comparing graft types that, in initial studies, clearly have differing rates of GVHD. These data demonstrated an increase in naive B cells and plasmacytoid dendritic cells (CD123+) in G-BM compared to PBSC, suggesting a potential role in cGVHD. Moreover, the Schultz laboratory (analyzing samples from the GVHD study ASCT0031) characterized immune populations in patients who had had chronic GVHD and those who had not. These

studies suggest that cGVHD is associated with activated B cell populations that express TLR9, and also have unpublished data that demonstrates an increase in TLR9 expressing B cells in PBSC compared G-BM (samples from the CBMTG G-BM versus PBSC study). These data further support a potential role for these B cells in cGVHD development.

In addition to TLR responses in antigen presenting cell populations, the NIH Chronic GVHD Consensus Biomarkers Working Group has identified that regulatory T cells may be a major mechanism for cGVHD. In collaboration with Megan Levings' laboratory, the Schultz laboratory will also evaluate for the presence of Treg and TR1 cells in the donor products. General characterization of T cells focused on Th1/Tc1 and Th2/Tc1 phenotype will also be performed.

The biological reasons underlying the apparent lower rate of cGVHD associated with infusion of G-BM compared to PBSC are not known.[19] Our preliminary studies on a small number of individuals presented two primary observations of an increase in two cell populations (plasmacytoid DCs and B cells) in G-BM compared to PBSC. These are therefore studies that could be applied to a comparative analysis of BM vs. G-BM in the context of the ASCT0631 study. We also observed several other potential immune population differences that require further delineation in larger studies. One deficiency of previous studies was that the populations evaluated were undiluted BM and peripheral blood, which will differ from BM and G-BM harvests as actually collect in the operating room. Inadvertent collection of at least some peripheral blood, with large numbers of T cells, is part of operative BM collection. Because of the great cellularity of G-BM collections and the greater ease with which G-BM "pulls" are obtained that was observed in the G-BM pilot, we postulate that a difference in peripheral blood contamination may also be a relevant difference between G-BM and BM. Based on prior data, we hypothesize that G-BM donor cells may have an increased capacity to induce T cell hyporeactivity or immune tolerance.

15.3 Cellular Evaluations of the BM and G-BM grafts

i. Enumeration of nucleated cells, mononuclear cells, CD34+ stem and progenitor cells and CD3+/4+ and CD3+/8+ T cells in the graft (done at the transplant center)
ii. Assessment of cytokine profile, looking for a shift to a Th2/Tc2 profile in G-BM compared to BM (Schultz laboratory)
iii. Increased number and function of plasmacytoid DCs in G-BM compared to BM (Schultz laboratory)
iv. Increased number of T regulatory cells in G-BM compared to BM (Levings laboratory)

Two aliquots of each of the BM harvests will be cryopreserved and banked at the Biopathology Center. This bank will provide a unique resource to later studies, including potential analyses of specific stem and progenitor cell content of the grafts related to patient outcome, that subsequent funding may allow. See Section 15.5.1 for submission instructions for the BM harvest aliquots.

15.4 Studies of Immune Reconstitution

Because of the greater cellularity of the G-BM grafts, we hypothesize that there may be more rapid immune reconstitution observed in patients in the G-BM arm. In order to assess this, we will enumerate CD3+, CD4+ and CD8+ T cells at the treating center at the following time points: 1, 3, 8 and 12 months post-BMT. These time points match the points at which studies are being performed on recipient peripheral blood on the ASCT0431 study. For patients co-enrolled on ASCT0431, samples of peripheral blood will also be shipped to the BPC at those time points, for analysis according to that study. For those patients not co-enrolled on ASCT0431, samples of peripheral blood will be collected, shipped to BPC, ficolled and cryopreserved for subsequent analysis. See Section 15.5.2 for submission instructions for the peripheral blood.

15.5 Specimen Submission for Correlative Studies

Label specimens with the patient's BPC Number, collection date and specimen type. Include a completed specimen transmittal form with each shipment of specimens to the BPC.

15.5.1 Bone Marrow

10 ml of donor bone marrow from bone marrow harvest should be collected and put into two CPT tubes. Place 5 ml of bone marrow into each collection tube. Store the tube upright at room temperature until centrifugation. The bone marrow should be centrifuged within 2 hours of collection. Gently invert the tube 8 to 10 times immediately prior to centrifugation. Centrifuge at room temperature in a horizontal rotor for a minimum of 15 minutes at 1500 x g. Mononuclear cells and platelets will be in a whitish layer just under the plasma layer. Aspirate about half of the plasma without disturbing the cell layer. Collect cell layer with a pipette and transfer into cryotubes. Add freezing media. Ninety percent fetal calf serum with 10% DMSO is preferred, but 20% serum with 70% RPMI and 10% DMSO is an acceptable alternative. Store samples at -70°C until shipment. Samples should be sent to the BPC in the same shipment as the batched blood specimen. Include at least 4-5 lbs of dry ice with the shipment.

15.5.2 Peripheral Blood for Immune Reconstitution (Patients Not Enrolled on ASCT0431)

Peripheral blood samples are to be collected in two 10 ml Cell Preparation Tubes (CPTs) at 3, 8 and 12 months post-BMT. Draw at least 6 ml of blood into each collection tube. Store the tube upright at room temperature until centrifugation. The blood should be centrifuged within 2 hours of collection. Gently invert the tube 8 to 10 times immediately prior to centrifugation. Centrifuge at room temperature in a horizontal rotor for a minimum of 15 minutes at 1500 x g. Mononuclear cells and platelets will be in a whitish layer just under the plasma layer. Aspirate about half of the plasma without disturbing the cell layer. Collect cell layer with a pipette and transfer into cryotubes. Add freezing media. Ninety percent fetal calf serum with 10% DMSO is preferred, but 20% serum with 70% RPMI and 10% DMSO is an acceptable alternative. Store blood samples at -70°C until shipment. Blood can be batched and sent in one shipment. Include at least 4-5 lbs of dry ice with the shipment.

15.5.3 Shipping Instructions

Ship the specimens via Federal Express Priority Overnight using the BPC Federal Express Account number (**1290-2562-0).** Arrange for Federal Express pick-up per your usual institutional procedure or by calling (800)-238-5355. When requesting pickup, be sure to give the appropriate FedEx account number, but stress that pickup is at your institutional address.

Specimens may be shipped to the BPC on Monday-Thursday for Tuesday-Friday delivery. Saturday delivery is not available. Specimens must be packaged in accordance with IATA packing instruction 650. Place specimens in secondary packaging materials with absorbent material before packaging in shipping container.

Biopathology Center
Columbus Children's Hospital
700 Children's Drive, WA1300*
Columbus, OH 43205
Phone: (614) 722-2810

For questions please call (800) 347-2486

*** Be sure to include the room number. Packages received without the room number may be returned to the sender.**

16.0 RADIATION THERAPY GUIDELINES FOR ALL PATIENTS

16.1 Protocol Summary for Radiation Oncologists and Indications for Radiation Therapy

The objective of this protocol is to compare the benefits and risks of G-CSF stimulated bone marrow transplant and conventional bone marrow transplant in patients undergoing matched sibling donor bone marrow transplant. Patients eligible for this study include those with very high risk ALL in first complete remission, relapsed ALL in second complete remission, AML in first or second complete remission, JMML, CML in first or second chronic phase and myelodysplastic syndrome. This protocol will enroll patients who are already enrolled on a COG stem cell transplant or other treatment protocol. Those patients will follow the treatment or transplant regimen and radiation therapy guidelines for their primary protocol. Patients not already enrolled on a COG stem cell transplant protocol or other treatment protocol will receive their transplant conditioning according to one of the regimens included in this study. Among these patients, only those with ALL require radiation therapy and will use the guidelines defined in this section. Because there is no consensus on fractionated TBI or supplemental irradiation regimens, the radiation therapy guidelines for this study were designed to promote protocol participation and match guidelines used at the majority of approved transplant institutions and guidelines developed for other COG protocols. Questions about these guidelines should be directed at the radiation therapy coordinator or principal investigator.

Total body irradiation is indicated as part of the preparative regimen for allogeneic matched sibling donor transplantation in patients with ALL. Supplemental cranial irradiation is indicated for patients with a history of CNS leukemia. Supplemental testicular irradiation is indicated for patients with a history of testicular leukemia or may be used prophylactically as a boost treatment according to institutional preferences. Definitions of CNS leukemia and testicular leukemia are given in Section 3.3. Supplemental irradiation may be indicated for patients who present with ocular, brain, spinal cord or extramedullary involvement. For these rare events, questions should be directed at the radiation therapy coordinator.

16.2 Total Body Irradiation

TBI shall be administered as part of the preparative regimen for allogeneic transplantation for patients with ALL. For the preferred and variation 1 preparative regimens, TBI will include a total dose of 1200 cGy given over three consecutive treatment days (Days -7, -6, -5) at 200cGy BID or a total dose of 1200 cGy given over four consecutive treatment days (Days -8, -7, -6, -5) at 150cGy BID. The interfraction interval shall be no less than 6 hours. For the variation 2 regimen, TBI will include a total dose of 1320cGy given over four consecutive treatment days (Days -8, -7, -6, -5) at 165 cGy BID. Treatment centers may propose a different fractionated TBI regimen but are required to contact the radiation therapy coordinator and receive written permission. All efforts should be made to not to have any delay or interruption in TBI administration.

16.2.1 Modality

High-energy photons with energy ≥ 4MV photons should be utilized. Co-60 may be used.

16.2.2 Calibration

The calibrations of therapy units used in this protocol shall be verified by the Radiological Physics Center.

16.2.3 Target Volume

The entire body will be treated including the head and feet in one field.

16.2.4 Prescription Point

The prescription point is defined as the point along the longitudinal axis of the patient at the midline and at the level of the umbilicus. No tissue inhomogeneity correction will be made in the calculation of dose to the prescription point.

16.2.5 Dose Rate

A mid-plane dose rate of between 6 and 15 cGy per minute is required.

16.2.6 Dose Uniformity

The variation in dose throughout the body shall be within 10% of the prescription dose.

16.2.7 Treatment Technique

Treatment centers are allowed to use institutional guidelines for treatment techniques (eg, AP/PA or lateral). Any treatment technique and patient position that meet the criteria on dose, dose rate, and dose uniformity is acceptable. Institutions must complete the QARC TBI benchmark prior to any patient receiving TBI on this protocol. A new benchmark must be completed and approved if the institutional technique differs from that used to satisfy the benchmark requirement. The benchmark is available from the QARC website (www.QARC.org).

16.2.8 Lung Shielding

Lung shielding is optional. Treatment centers are encouraged to use lung shielding with partial transmission blocks to reduce the total midplane lung dose to 1000 cGy. Lung dose between 1100 and 1200 cGy will be considered as a minor deviation and >1200 cGy as a major deviation. No compensatory chest wall electron boost is required. Tissue heterogeneity calculations shall be used in the calculation of dose to lung.

Lung blocks will confirm to the following guidelines: The lateral edges will be 1.0 – 1.5 cm from the inner border of the ribs; the inferior edges will be 1.0 – 1.5 cm from the dome of the apex of the diaphragm; the superior borders will be 1.0 – 1.5 cm below the clavicles; the medial border 2.0 – 2.5 cm from the lateral edges of the thoracic vertebral bodies. No contouring of the lung shields will be done around the hilum unless there is a residual abnormal hilar adenopathy, in which case the margins around the hilar mass will be 1.0 – 1.5 cm.

16.3 Supplemental Cranial Irradiation

Patients with very high risk ALL in first complete remission and a history of CNS leukemia at the time of presentation and patients with CNS leukemia at the time of relapse should receive supplemental cranial irradiation (as defined in Section 4.4.3.1). Exceptions to the use of supplemental cranial irradiation may include concerns about development because of patient age, history of prior cranial irradiation, and history or radiographic evidence of CNS toxicity (*e.g.,* leukoencephalopathy, necrosis, stroke).

16.3.1 Dose and Fractionation

The supplemental dose for cranial irradiation should be 600 cGy. The daily dose to the prescription point for the cranial volume shall be 150 or 200 cGy. All fields should be treated each day.

16.3.2 Timing

Supplemental cranial irradiation should precede fractionated TBI. Excluding weekends and holidays, supplemental cranial irradiation and fractionated TBI should be continuous. All efforts should be made not to have treatment delay or interruption.

16.3.3 Modality

High-energy photons with a nominal energy of 4 or 6 MV. Co-60 may be used.

16.3.4 Cranial Target Volume

The target volume consists of the entire brain and intracranial subarachnoid volume as well as the posterior halves of the optic globes and the optic nerves. The caudal border shall be the C2/3 vertebral interspace.

16.3.5 Localization

The target volume should be defined by means of a CT simulator or conventional fluoroscopic simulator.

16.3.6 Prescription Point

The dose should be prescribed at the midplane along the central axis or at an off-axis point which corresponds to the center of the cranial volume.

16.3.7 Tissue heterogeneity

There shall be no correction for tissue heterogeneity.

16.3.8 Dose Uniformity

The dose variation in the target volume should be within +7% and -5% of the prescription-point dose.

16.3.9 Treatment Technique

16.3.9.1 Patient Position:

Supine treatment is recommended with immobilization appropriate for the age of the child..

16.3.9.2 Beam Configuration:

Two opposed-lateral, equally weighted photon beams are preferred. The fields shall extend at least 1 cm beyond the periphery of the scalp.

16.3.9.3 Field Shaping and Normal Tissue Sparing:

Customized field-shaping is required with cerrobend blocks that are at least 5 HVL thick. Alternatively, a multileaf collimator may be used provided the leaf width is less than or equal to 5mm. Lens sparing techniques with anteriorly angulated lateral fields (RAO/LAO) are encouraged but not required.

16.4 Supplemental and Prophylactic Testicular Irradiation

Patients with a history of testicular leukemia at the time of relapse should receive supplemental testicular irradiation (as defined in Section 4.4.3.2). Exceptions to the use of supplemental testicular irradiation may include prior testicular irradiation. Prophylactic testicular irradiation (400 cGy administered in a single fraction or 200 cGy BID) is allowed but is not required. Administration of prophylactic irradiation will be concurrent with TBI.

16.4.1 Dose and Fractionation

The supplemental dose should be 600 cGy. The daily dose to the prescription point for the testicular volume shall be 200 cGy.

16.4.2 Timing

Supplemental testicular irradiation should immediately precede fractionated TBI. Excluding weekends and holidays, supplemental cranial irradiation and fractionated TBI should be continuous. All efforts should be made to not to have treatment delay or interruption.

16.4.3 Modality

High-energy photon or electron beams. Co-60 may be used. The selection of energy is determined by the dose uniformity criterion, and with electrons, the lowest possible energy should be used to spare tissues outside the target volume.

16.4.4 Target Volume

The targeted volume consists of the testes; however, the entire scrotum is generally targeted.

16.4.5 Prescription Point

The prescription point is at or near the center of the planning target volume.

16.4.6 Dose Uniformity

The variation of dose within the planning target volume shall be within +7%, -5% of the dose to the prescription point. When using electrons, bolus is not required.

16.4.7 Treatment Technique

16.4.7.1 Patient Position:

The patient shall be treated in the supine position.

16.4.7.2 Field-shaping and Normal Tissue Sparing:

Field shaping can be done with blocks of at least 5 HVL thick for photon beams. Multileaf collimation is permitted. When using electron fields, customized or standard sized and shaped cerrobend apertures should be used. The penis should be excluded from the treatment volume.

16.5 Treatment Deviations

Minor Deviation:
The dose to the prescription point differs from that in the protocol by between 6% and 10%.
Major Deviation:
The dose to the prescription point differs from that in the protocol by more than 10%.

16.6 Quality Assurance Documentation

16.6.1
There is no on-treatment review in this study. QARC will conduct Post Treatment Review for the patients receiving radiotherapy on this study. There are no film submission requirements.

The following documentations shall be submitted within one week of the completion of radiotherapy:

- The “TBI Summary Form” for Total Body Irradiation with the indication of treatment techniques and delivered dose to the prescription point at the level of the umbilicus. The midline lung dose should also be recorded.
- The "RT-2 Radiotherapy Total Dose Record" forms must be completed for TBI, cranial and testicular irradiation.

- A copy of the patient's radiotherapy records for each portion of the treatment that was delivered (TBI, cranial and testicular) including the prescription describing treatment techniques, daily and cumulative doses

These data should be sent to:
T.J. Fitzgerald, MD Director
Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rl 02903-1025
Telephone: (401)454-4301
Fax: (401)454-4683
e-mail: tjfitzgerald@qarc.org

16.6.2 Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rl 02903-1025
Telephone: (401)454-4301
Fax: (401)454-4683

16.6.3
Questions regarding the radiotherapy section of this protocol should be directed to the radiation therapy study coordinator:

Natia Esiashvili, MD
Emory University
Department of Radiation Oncology
1365 Clifton Road, NE
Atlanta, GA, 30322
Work: (404)778-5782
Fax: (404)778-4139
Email: natia@radonc.emory.org

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
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	60	Required occasional assistance but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II: ORGAN STAGING OF GVHD

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dl (< 34 µmol/L)	Adult: < 500 ml/day Child: < 10 ml/kg/day
1	Maculopapular rash < 25% BSA	2-3 mg/dl (34.1 – 51 µmol/L)	Adult: 500–999 ml/day Child: 10 -19.9 ml/kg/day Or persistent nausea, vomiting, or anorexia, with a positive EGD biopsy.
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dl (51 – 102 µmol/L)	Adult: 1000-1500 ml/day Child: 20 – 30 ml/kg/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dl (102.1-255 µmol/L)	Adult: >1500 ml/day Child: > 30 ml/kg/day
4	Generalized erythroderma with bullous formation and desquamation > 5% BSA	>15 mg/dl (> 255 µmol/L)	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

- For GI staging: The "adult" stool output values should be used for patients ≥ 50 kg in weight.
- Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is estimated to be 50% of total stool / urine mix.
- For stage 4 GI: the term "severe abdominal pain" will be defined as:
  (a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
  (b) Pain that significantly impacts performance status, as determined by the treating MD.
- If colonic or rectal biopsy is +, but stool output is < 500 ml / day (< 10ml/kg/day), then consider as GI stage 0.
- There is no modification of liver staging for other causes of hyperbilirubinemia.

Overall Clinical Grade:

Grade 0	No stage 1-4 of any organ
Grade I	Stage 1-2 rash and no liver or gut involvement
Grade II	Stage 3 rash, or Stage 1 liver involvement, or Stage 1 GI
Grade III	Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
Grade IV	Stage 4 skin, liver or GI involvement

APPENDIX III: DEFINING CHRONIC GRAFT VS. HOST DISEASE (FROM BMT CTN MOP SEPT. 2005)

Chronic Graft-vs-Host Disease (GVHD) is a specific syndrome involving, for example, scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolits obliterans, vanishing bile ducts, or weight loss. It is to be diagnosed specifically rather than diagnosed when acute GVHD-like syndromes develop late (beyond Day+100) after any transplant or donor leukocyte infusion.

Definite and Possible Manifestations of Chronic GVHD

Organ System	**Definite Manifestations of Chronic GVHD**	**Possible Manifestations of Chronic GVHD**
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
GU	Vaginal structure, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculo-skeletal/Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis

1. At any time point post-transplant, if there are ANY definite symptoms (column 2) then the symptoms should be identified as chronic GVHD.
2. At any time post-transplant, if there are any possible symptoms (column 3) but no definite symptoms, then it is at the physician's discretion to identify as either acute or chronic GVHD.
3. Acute and chronic GVHD cannot be present at the same time. Thus if #1 is fulfilled then all manifestations of GVHD should be identified as chronic GVHD.

APPENDIX IV: ALL PREPARATIVE REGIMEN THERAPY DELIVERY MAP

Reg # _____ Accession # _____ Reporting Period _____ Page 1 of 4

Preferred ALL Preparative Regimen (TBI/Cy/Thiotepa) Administration

Treatment	Route	Dose	Days	Important Notes
TBI		200 cGy BID	Day -8, -7, & -6	May deliver 1200 cGy fractionated TBI over 4 days per center's preference
Thiotepa	IV	5 mg/kg/day	Day -5 & -4	
Cyclophosphamide	IV	60mg/kg/day	Day -3 & -2	
Tacrolimus	IV, PO when able	0.02mg/kg/day continuous infusion	Begin Day -2	This is part of GVHD prophylaxis therapy for ALL patients
Infusion of allogeneic BM			Day 0	For patients on standard arm
Infusion of allogeneic G-BM			Day 0	For patients on experimental arm

Preferred Preparative Regimen (TBI/Cy/Thiotepa) Delivery Map

Use a copy of this page to track each patient's therapy by entering the actual dates and doses administered below.

Day -8 - -1 **Note Patient's: Wgt _____kg Hgt_____cm BSA _____m^2**									
DATE									
DAY	-9*	-8	-7	-6	-5	-4	-3	-2	-1
Total Dose of TBI									
Thiotepa									
Cyclophosphamide									
Tacrolimus									

Use only if your center prefers to deliver 1200 cGy fractionated TBI over 4 days.

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy)

Variations to the Preferred Preparative Regimen

These variations are allowed, but not recommended. The preferred preparative regimen is listed above.

Variation 1: TBI/Cy/VP-16 Administration

Drug/Treatment	Route	Dose	Days	Important Notes
TBI		200 cGy BID	Day -7, -6, & -5	May use 150 cGy BID x 4 days per center preference
Etoposide	IV	1500 mg/m^2	Day -4	
Cyclophosphamide	IV	60mg/kg/day	Day -3 & -2	
Tacrolimus	IV, PO when able	0.02mg/kg/day continuous infusion	Begin Day -2	This is part of GVHD prophylaxis therapy for ALL patients
Infusion of allogeneic BM			Day 0	For patients on standard arm
Infusion of allogeneic G-BM			Day 0	For patients on experimental arm

Variation 1: TBI/Cy/VP-16 Delivery Map

Use a copy of this page to track each patient's therapy by entering the actual dates and doses administered below.

Day -7- -1 **Note Patient's: Wgt _____kg Hgt_____cm BSA _____m^2**								
DATE								
DAY	-8*	-7	-6	-5	-4	-3	-2	-1
Total Dose of TBI								
Etoposide								
Cyclophosphamide								
Tacrolimus								

Use only if your center prefers to deliver 1200 cGy fractionated TBI over 4 days.

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

Variation 2: Higher Dose TBI/Cy Administration

Treatment	Route	Dose	Days	Important Notes
TBI		165 cGy BID	Day -7, -6, -5, & -4	Fractionation scheme may differ, total dose must be 1320 cCy
Cyclophosphamide	IV	60mg/kg/day	Day -3 & -2	
Tacrolimus	IV, PO when able	0.02mg/kg/day continuous infusion	Begin Day -2	This is part of GVHD prophylaxis therapy for ALL patients
Infusion of allogeneic BM			Day 0	For patients on standard arm
Infusion of allogeneic G-BM			Day 0	For patients on experimental arm

Variation 2: Higher Dose TBI/Cy Delivery Map

Use a copy of this page to track each patient's therapy by entering the actual dates and doses administered below.

Day -7 - -1 **Note Patient's: Wgt _____kg Hgt_____cm BSA _____m^2**							
DATE							
DAY	-7	-6	-5	-4	-3	-2	-1
Total Dose of TBI							
Cyclophosphamide							
Tacrolimus							

Use only if your center prefers to deliver 1200 cGy fractionated TBI over 4 days.

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

Required Clinical, Laboratory and Disease Evaluations for Recipients

Observation	Within 2 weeks prior to BMT	At BM or G-BM harvest	1-2 wks after ANC>500	3m after BMT	8m after BMT	1yr after BMT	2yrs after BMT	At Relapse
Bone Marrow aspiration	X							X
CSF counts/cytology	X							X
CBC with differential	X		X	X	X	X	X	X
BUN/Cr	X							
LFTs	X		X	X	X	X	X	
Immune reconstitution studies				X	X	X		
Disease status	X		X	X	X	X	X	X
Acute GVHD				X				
Chronic GVHD				X	X	X	X	
MUGA or ECHO	X							
Calculated GFR or Creatinine Clearance*	X							
Pulmonary Function Test	X							
Karnofsky or Lansky score	X		X	X	X	X	X	X

Use the Schwartz formula (Section 3.2.3.1) for GFR and calculated Cr. Clearance only if serum creatinine is elevated for age

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

Reg # _____ Accession # _____ Reporting Period _____ Page 1 of 2

APPENDIX V: MYELOID PREPARATIVE REGIMEN THERAPY DELIVERY MAP

Myeloid Preparative Regimen Administration: Busulfan/Cyclosporine

Treatment	Route	Dose	Days	Important Notes
Phenytoin		2.5 mg/kg/dose PO BID	Start Day -10	Begin 12 hours prior to and continue for 48 hours after completion of busulfan
Busulfan*	IV	Busulfan q 6 hours x 4 doses with 1st dose pharmacokinetics (See Section 6.7).	Day -9	See Section 4.6.3 for age-based dosing
Busulfan*	IV	Busulfan q 6 hours x 12 doses	Day -8 & -7 & -6	Targeted dose- adjustment based on PK results at participating institutions (see Section 5.6).
Cyclophosphamide	IV	50 mg/kg daily x 4 days	Day -5, -4, -3 & -2	
Begin cyclosporine infusion	IV, PO when able	3 mg/kg/day continuous infusion	Day -1	This is part of GVHD prophylaxis therapy for myeloid patients
Infusion of allogeneic BM			Day 0	For patients on standard arm
Infusion of allogeneic G-BM			Day 0	For patients on experimental arm

**Note: A total of 16 doses of Busulfan will be given during preparative regimen administration*

Myeloid Preparative Regimen (Busulfan/Cytoxan) Therapy Delivery Map

Use a copy of this page to track each patient's therapy by entering the actual dates and doses administered below.

Day -8 - -1 **Note Patient's: Wgt _____kg Hgt_____cm BSA _____m^2**										
DATE										
DAY	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Phenytoin										
Busulfan										
Cyclophosphamide										
Cyclosporine										

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

Reg # _____ Accession # _____ Reporting Period _____ Page 2 of 2

Required Clinical, Laboratory and Disease Evaluations for Recipients

Observation	Within 2 weeks prior to BMT	At BM or G-BM harvest	1-2 wks after ANC>500	3m after BMT	8m after BMT	1yr after BMT	2yrs after BMT	At Relapse
Bone Marrow aspiration	X							X
CSF counts/cytology	X							X
CBC with differential	X		X	X	X	X	X	X
BUN/Cr	X							
LFTs	X		X	X	X	X	X	
Immune reconstitution studies				X	X	X		
Disease status	X		X	X	X	X	X	X
Acute GVHD				X				
Chronic GVHD				X	X	X	X	
MUGA or ECHO	X							
Calculated GFR or Creatinine Clearance*	X							
Pulmonary Function Test	X							
Karnofsky or Lansky score	X		X	X	X	X	X	X

Use the Schwartz formula (Section 3.2.3.1) for GFR and calculated Cr. Clearance only if serum creatinine is elevated for age

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

APPENDIX VI: DONOR G-CSF AND BONE MARROW COLLECTION

Donor G-CSF Administration and Bone Marrow Collection

Treatment	Days	Important Notes
Start donor on G-CSF 5 mcg/kg/day	Day -4, -3, -2, -1, 0	Total 5 doses of G-CSF. AM dosing is recommended.
G-BM harvest of 15 cc/kg recipient weight	Day 0	**Collection target is a volume and not a cell dose**. Harvests outside the recommended volume ranges will be considered protocol violations. See Section 4.2.2 for details regarding bone marrow collection.

Donor G-CSF Administration and Bone Marrow Collection Therapy Delivery Map
Use a copy of the map to record the actual dates, doses administered and details of the harvest, including actual volume of bone marrow collected.

Day -4-0 **Donor's Weight _____kg Recipient's Weight _____kg**					
DATE					
DAY	-4	-3	-2	-1	0**
G-CSF					
Bone Marrow Collection*					

Actual volume of bone marrow collected should be recorded on Day 0.
****Bone marrow sample should be collected for patients who consented to cellular evaluation studies.***

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

APPENDIX VII: STANDARD BONE MARROW COLLECTION

Standard Bone Marrow Collection

Procedure	Days	Important Notes
G-BM harvest of 15 cc/kg recipient weight	Day 0	**Collection target is a volume and not a cell dose**. Harvests outside the recommended volume ranges will be considered protocol violations. See Section 4.2.2 for details regarding bone marrow collection.

Standard Bone Marrow Collection
Use a copy of the map to record details of the harvest, including actual volume of bone marrow collected.

Day 0 **Donor's Weight _____kg** **Recipient's Weight _____kg**					
DATE					
DAY	0**				
Bone Marrow Collection*					

Actual volume of bone marrow collection should be recorded on Day 0.
****Bone marrow sample should be collected for patients who consented to cellular evaluation studies.***

For Institutional Use:
COMMENTS (Must be dated; document any change from required therapy):

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SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

This model informed consent form has been reviewed by COG. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

COG ASCT0631
PBMTC SCT051
"A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation"
Recipient Informed Consent Form

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by the Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 240 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You have been treated for a cancer of the blood cells called leukemia. You have received chemotherapy treatment for your cancer and now have no visible signs of leukemia. This is called remission. Your doctor has recommended that you have a stem cell transplant. Stem cell transplant (SCT) is a method of replacing blood-forming cells that were destroyed by cancer treatment. The stem cells are given after treatment to help the bone marrow recover and continue producing healthy blood cells.

We are studying the effect of a growth factor drug given to your donor that can help increase the number of stem cells that we collect from your donor's bone marrow. This drug is called G-CSF or filgrastim or Neupogen. Throughout the rest of the consent form we will call it G-CSF. You are being asked to take part in this study to test if G-CSF bone marrow transplantation will keep more patients in remission. In addition, we would like to find out if the new treatment may improve how quickly you recover from the transplant. We also want to know if the stem cells from these donors make it more or less likely that patients get graft-versus-host disease (GVHD). GVHD is a disease that may occur following transplant, when the donated cells attack your body's cells because they are different. When GVHD occurs, donor cells target the skin, liver, and intestines; which may cause you to develop a rash, stomach pains, vomiting, or diarrhea.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part.

Many different treatment programs have been used for children with leukemia. You have a choice between other treatments for your type of cancer or this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part.

WHAT IS THE CURRENT STANDARD TREATMENT FOR THIS DISEASE?

Children with leukemia usually receive chemotherapy to put them into remission *(disappearance off all signs and symptoms of leukemia).*

After chemotherapy treatment, many doctors recommend high dose chemotherapy followed by a transplant of bone marrow cells from a donor, or SCT, for children and adolescents with high risk or relapsed leukemia. This is because SCT may be a better therapy than chemotherapy alone for most patients. This use of stem cell transplant is considered to be an accepted, standard treatment for children with leukemia who are in remission.

WHY IS THIS STUDY BEING DONE?

Bone marrow transplant is recommended by many physicians for children with leukemia that have a high chance of relapse with chemotherapy alone. Bone marrow transplant is not recommended for all types of leukemia. This is a phase III study of bone marrow transplant using donated bone marrow that has been treated with G-CSF. A phase III study is done to compare the effects, good and/or bad of an experimental treatment against a standard treatment.

G-CSF has been approved by the Food and Drug Administration. It is a white cell growth factor that is often given to people with cancer. When G-CSF is given to a donor, it can help increase the number of stem cells in the donor's bone marrow. This treatment has been previously used in a clinical trial for patients receiving transplants from related donors. The main purpose of this study is to determine if G-CSF will increase the number of stem cells donated by your donor for transplant, and if those increased numbers of stem cells might provide a benefit to you in terms of improved survival.

The goals of this study are:

- **To compare the effects, good and/or bad, of an experimental treatment (G-CSF given to the bone marrow donor) against standard treatment (no G-CSF given to the bone marrow donor) for patients during their stem cell transplant (SCT).**
- **To compare the speed of cell recovery in patients receiving the experimental G-CSF bone marrow with those receiving standard treatment bone marrow.**
- **To evaluate and compare the occurrence of GVHD in patients receiving G-CSF bone marrow with those receiving standard bone marrow.**
- **To evaluate how the immune system *(body system that helps fight infections)* is restored in patients transplanted with G-CSF bone marrow.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of patients enrolled on this study is expected to be 425.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Random Assignment
You will go on 1 of the 2 different arms of the treatment plan. The arm you are assigned to is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer to make sure that there are about the same number of people on each treatment arm of the study. The randomization process is described in your COG Family Handbook for Children with Cancer.

Treatment Plan
Prior to your transplant, it is standard to receive chemotherapy or radiation therapy to prepare you for your transplant. The type of preparative treatment you receive will depend on the type of leukemia you have. Your doctor determines this treatment and will discuss this with you. Information about the different preparative treatments can be found in Attachment #1. These treatments are different, based on the kind of leukemia you have. Patients with acute lymphoblastic leukemia (ALL) get one kind of treatment. Patients with acute myeloid leukemia (AML), or related diseases like chronic myelocytic leukemia (CML), juvenile myelomonocytic leukemia (JMML) and myelodysplastic syndrome (MDS) get a different kind of treatment. These treatments are not experimental, but are standard for your type of disease. It is also standard to have an extensive evaluation of your health and disease status, including a bone marrow test and tests of the function of specific organs such as heart, liver and kidneys.

The donor bone marrow will be given to you, through your central venous line (CVL). This is considered “Day 0” or “transplant day”. These cells will be given to restore normal bone marrow function. The bone marrow will be given in a small transfusion bag through your CVL, much like a blood transfusion.

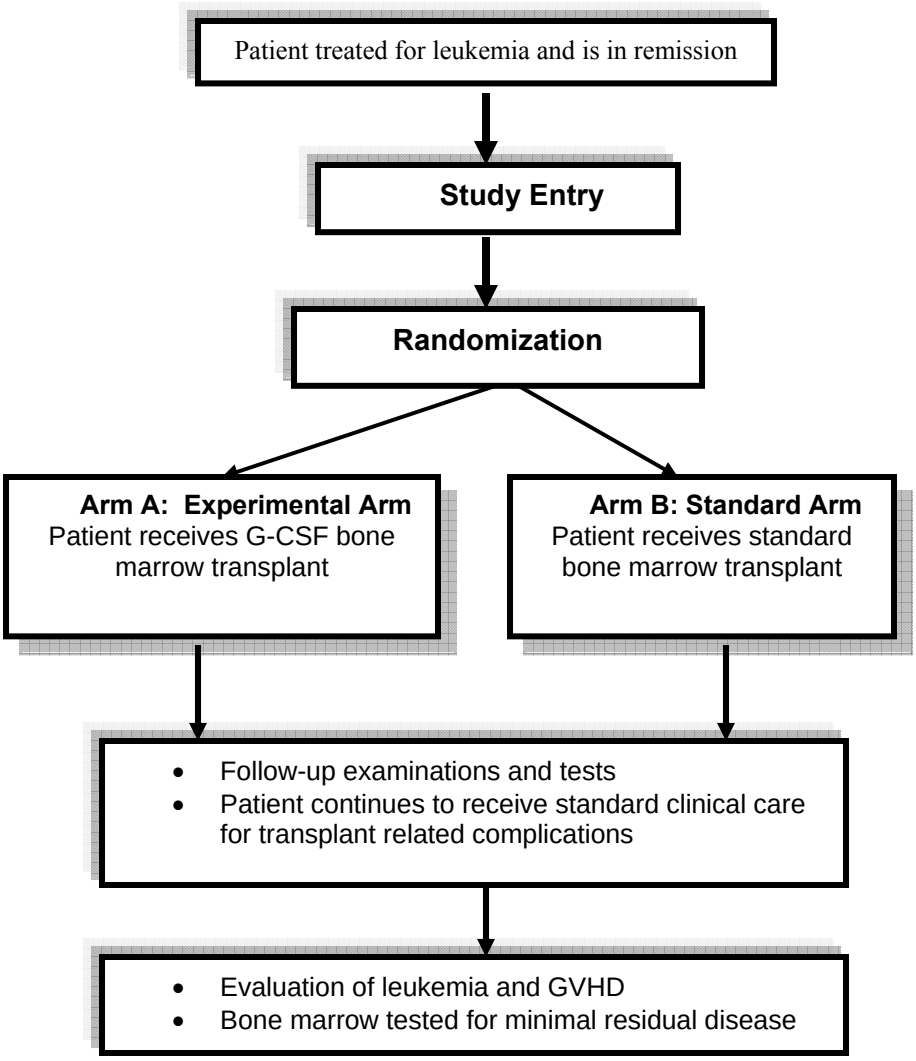
The two treatment arms are called A and B as follows:

- Arm A: Experimental Treatment Arm (G-CSF bone marrow from your donor will be transplanted)
- Arm B: Standard Treatment Arm (standard bone marrow from your donor will be transplanted)

Randomization
Some participants will be randomized to receive the Standard Treatment arm. Others will get the Experimental Treatment arm. If you consent to take part in the study, randomization will be done before the stem cell transplant.

Diagram of treatment

A diagram of treatment can be seen below.



Treatment Plan Tables
The following tables show the difference in how treatment will be given to subjects on Arm A and Arm B of this study. Day 0 means the day when the pre-transplant treatment (Attachment #1) is complete and the marrow is infused.

Arm A: Experimental Arm (G-CSF Bone Marrow Transplant)

Drug	***How the marrow will be given***	***Days***
G-CSF Bone Marrow Transplant	*Given by CVL over about 3-4 hours*	*Day 0*

Arm B: Standard Arm (Standard Bone Marrow Transplant)

Drug	***How the marrow will be given***	***Days***
Standard Bone Marrow Transplant	*Given by CVL over about 3-4 hours*	*Day 0*

If you are on Arm A, you will receive a standard transplant preparative treatment and will be transplanted with donated G-CSF bone marrow.

If you are on Arm B, you will receive a standard transplant preparative treatment and will be transplanted with standard donated bone marrow.

Optional Research Study Tests and Procedures
We would like to collect an additional amount of blood for optional research tests.

You can choose to take part in this clinical trial without taking part in the following tests. The results will not be used to make any treatment decisions on this study and will not be given to you or your doctor. The results may help to improve treatments for leukemia in the future. No matter what you decide, your care will not be affected. A check box for your decision about taking part in this test is provided at the end of this consent form.

Immune Reconstitution Studies
During your treatment we will collect blood to monitor your response to treatment at certain time points. Immune reconstitution is how the immune system *(body system that helps fight infections)* is restored**.** If you agree to take part in the Immune Reconstitution Studies, we would like to take about 2 teaspoons of extra blood at 3 time points (month 3, 8, and 12 after bone marrow transplant).

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study through the day of their transplant (Day 0). After study treatment, subjects will have follow-up examinations and will continue to receive standard clinical care for transplant related complications. We will continue to collect some medical information about how you are doing for up to 10 years after the bone marrow is given.

Your doctor or the research doctors running the study may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks

Patients who receive stem cell transplants are at risk of having significant side effects. Some of the common side effects include infection and graft-versus-host disease (GVHD). More serious side effects can include problems with organ function or possibly death. The risks of transplants are listed in Attachment #3.

There is a risk that the treatment plan will not get rid of the cancer or that the cancer can go away after the treatment and then come back at a later date.

Risks of Study

It is possible that this study treatment may be less effective than other therapy options. It is also possible that the study treatment may cause more side effects than other therapies. Since receiving G-CSF bone marrow might result in receiving a higher stem cell dose, there is the possibility of an increased risk of GVHD.

GVHD is a risk of any bone marrow or stem cell transplant where the cells come from another person (the donor). GVHD occurs when the donor's white blood cells recognize the patient's body as "foreign". In acute graft-versus-host disease, which occurs within 3 months of transplant, the skin, liver, or intestine may be affected. This may result in a rash, yellowness of the skin (jaundice) or very watery diarrhea. Medications will be given to help prevent GVHD. However, mild to severe GVHD may still occur due to the transplant. If GVHD should develop, it will be treated with steroids, which are successful in eliminating or controlling symptoms in many patients. We are often successful in controlling acute graft-versus-host disease with medicines, but not always, and fatal complications may arise.

Chronic graft-versus-host disease occurs most commonly in patients who have had acute graft-versus-host disease, but may occur in patients who did not have any acute symptoms. Patients can have problems with skin, liver, intestine, joints, mucous membranes, eyes, or other organs. Chronic scarring may result. Medicines can help, but may not completely eliminate all the symptoms. Chronic GVHD may have lingering symptoms for years, or may go away completely. Infection is a major risk in patients with chronic GVHD, as the immune system takes a very long time to recover and some cases might not be completely normal again.

We do not know for certain whether the use of G-CSF bone marrow might increase the risk of either acute or chronic GVHD, although other studies have not shown any such risk.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. The potential benefit could include a quicker recovery from the low blood counts after transplant or a better chance of a getting rid of cancer for a long time.

We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

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

- **Receiving a standard stem cell transplant. The therapy is described on page 1. It is Arm B of this study.**
- **Receiving a transplant where your doctor decides to use G-CSF bone marrow. This is not a standard stem cell transplant, and is Arm A of the study.**
- **You may choose a chemotherapy approach and not undergo transplantation.**
- **You may take part in another study.**
- **You may decide not to receive treatment at this time.**

Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government which will help us protect the privacy of our research subjects. A copy of the certificate is in Attachment #4 of this consent.

It is very unlikely that the research testing might uncover important information about your current or future health. If this unlikely even occurs, the researchers may contact your doctor through COG's Data Center about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. It will remain confidential. Your doctor may discuss this unexpected finding with you. Your doctor may recommend consultation with a genetic counselor or repeat testing in a clinical (not research) laboratory if needed. It is possible that your doctor may recommend that no additional action is necessary.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), and the Food and Drug Administration (FDA)**
- **Other US and international governmental regulatory agencies involved in keeping research safe for people**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The Institutional Review Board of this hospital**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

You will receive no payment or money for taking part in this study. If this study included providing tissue specimens to the researcher, you will not profit from any new products developed from research done on your specimens.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You may stop being in the study at any time. If you stop being in the study, you will not be penalized and you will not lose any benefits to which you are entitled. Physicians and hospital personnel will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related problem or you are injured, contact Dr. XXXX or your doctor at XXXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at (XXXX

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX

WHERE CAN I GET MORE INFORMATION?

The *COG Family Handbook for Children with Cancer* has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources.

You may call the NCI's *Cancer Information Service* at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

Visit the *COG Web site* at http://www.curesearch.org

Information about long term follow-up after cancer treatment can be found at http://www.survivorshipguidelines.org/

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

OPTIONAL RESEARCH QUESTIONS

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

1. My blood may be collected and sent to a COG laboratory to be kept for testing in the Immune Reconstitution Studies.

   #1: Yes_____ No_____ _____ / _____
   Initials Date

2. My blood may be kept for use in future research to learn about, treat or prevent cancer or other serious diseases.

   #2: Yes_____ No_____ _____ / _____
   Initials Date

3. Someone from the Children's Oncology Group may contact me in the future to ask me to take part in more research.

#3: Yes_____ No_____ _____ / _____
Initials Date

SIGNATURE

I have been given a copy of all XX pages of this form. The form includes four (4) attachments.

I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____
IRB# IRB Approved:

Attachment #1
Preparative Treatments, Procedures, and Treatments to Prevent GVHD

Central Line (CVL)
For drugs to be given by vein, your doctor will likely recommend that you (your child has) have a CVL placed. A description of the types of central lines is in your Oncology Family Notebook.

Methods for Giving Drugs
Various methods will be used to give drugs to patients.

- PO - Drug is given by tablet or liquid swallowed through the mouth (PO).
- IV - Drug is given using the CVL. It can be given by IV push over several minute or by infusion over minutes or hours.

Transplant Preparative Treatment:
You have received chemotherapy for your leukemia and are in remission. Treatment with chemotherapy or radiation as part of the transplant step is needed to restore your bone marrow. The type of preparative treatment you receive will depend on the type of leukemia you have. Below is a list of the possible preparative treatments that may be given. The type of therapy you receive will be determined by your study doctor and will be indicated on the study form.

Radiation (only for ALL patients) If you will be receiving radiation, the form of radiation used is called total body irradiation, or TBI. It is given to the entire body either before or after chemotherapy and prior to your transplant. The radiation treatment destroys the tumor cells and controls the function of the stem cells in preparation for the transplant. TBI helps your body begin producing new blood cells (engraft). If your disease involves the brain or testes, you will also have radiation therapy in these organs prior to having TBI.

The following tables show the possible therapy that you may receive. The type of therapy you receive will be determined by your study doctor. The days listed are all related to the day of the marrow transplant, which occurs on Day 0. Therefore, Day -7 is a week before the day of the transplant.

The type of treatment your doctor has chosen for you is: Treatment #_____

Possible Preparative Therapy #1:

Treatment	How the drug will be given	Days
TBI	Radiation given two times a day	Days -8, -7, and -6 or Day -9, -8 -7, and -6
Cyclophosphamide	Given by IV	Days -3 and -2
Thiotepa	Given by IV	Days -5, and -4

Possible Preparative Therapy #2:

Treatment	How the drug will be given	Days
TBI	Radiation given two times a day	Days -7, -6, -5 and -4
Cyclophosphamide	Given by IV	Days -3 and -2

Possible Preparative Therapy #3:

Treatment	How the drug will be given	Days
TBI	Radiation given two times a day	Days -7, -6, and -5 or Day -8, -7 -6, and -5
Etoposide	Given by IV	Day -4
Cyclophosphamide	Given by IV	Days -3 and -2

Possible Preparative Therapy #4:

Treatment	How the drug will be given	Days
Busulfan	Given by IV	Days -9, -8, -7, -6
Cyclophosphamide	Given by IV	Days -5, -4, -3 & -2

In addition, the anti-seizure medicine pheytoin (Dilantin) is given during the period when the busulfan is given.

Standard tests and procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- To help reduce the risk of GVHD, you will receive either cyclosporine A or tacrolimus. These will be given by IV initially and then PO later for at least several months.
- Physical exams
- Frequent labs to monitor blood counts and blood chemistries
- Urine tests to measure how the kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins
- X-rays and scans to monitor the patient's response to treatment.
- Tests to monitor heart and lung functioning
- Bone Marrow Aspirations to see if the leukemia is responding to treatment. The bone marrow procedure is described in your Family Handbook for Children with Cancer.
- Spinal Taps to check for leukemia cells in the spinal fluid and to give chemotherapy into the spinal fluid prior to transplant. This is described in your Family Handbook for Children with Cancer.

Attachment #2
About Using Tissue for Research (Banking)

During your diagnosis and treatment your doctor will remove some body tissue (blood and bone marrow) to do some tests. We would like to take extra blood or bone marrow samples for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research?" to learn more about tissue research.
[Note to Local Investigator: This information sheet is available on the COG web site at: https://members.childrensoncologygroup.org/prot/reference_materials.asp *under* **CONSENTS AND IRB FORMS***]*

The research that may be done with your tissue is not designed only to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About
The choice to let us keep the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While this institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits
The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them. Subjects will not profit from any new product developed from research done on their specimens.

Risks
The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice
If you have any questions, please talk to the study doctor or nurse, or call our research review board at IRB's phone number. No matter what you decide to do, it will not affect your care.

Attachment #3
Chemotherapy, Radiation Therapy and Stem Cell Transplant Risks

Radiation Risks

Radiation therapy may produce the following side effects: nausea, vomiting, diarrhea, generalized redness or dryness of the skin, bone marrow failure (absent blood counts resulting in increased risk of infection, weakness and bleeding), loss of hair (which may take 6 months or more for full re-growth), parotitis (swelling of salivary glands) causing jaw pain and swelling, damage to major body organs which may include the brain, eyes, heart, lung, liver and kidneys, and reddening of the skin. There is also the risk of temporary worsening of neurological symptoms such as weakness or loss of sensation. Some children experience a week or two of low grade temperature and extreme sleepiness six to eight weeks after radiation therapy has been completed. Both total body radiation and testicular radiation will cause sterility.

Possible late effects may include: shortened height, back bone change of shape (vertebral deformities), difficulty with vision (cataracts), changes in endocrine function (low hormones), learning disabilities or brain damage, and increased risk of developing another cancer.

Your radiation therapy doctor will discuss these issues with you and have you sign a separate consent for that part of the treatment.

Risks of the Preparative Treatments and the SCT

1. Loss of Bone Marrow Function: The preparative treatments are designed to remove all bone marrow cells, including leukemia cells. Loss of bone marrow function means decreased blood counts, including red blood cells, white blood cells and platelets. Until the new bone marrow cells begin to grow, you are at risk of developing infections or bleeding. Infections can be treated with antibiotics. Bleeding can be corrected, at least in part, by transfusions. The effect of receiving G-CSF stimulated bone marrow on the duration of bone marrow depression is not known.

2. Infection: The immune system will be not be normal for many months, and the white blood cells that fight infection will be very low until the new cells grow. You will be taking antibiotics by mouth to help decrease the possibility of infection, and will probably be receiving intravenous gammaglobulin to help decrease the possibility of a serious viral infection. If you should have a fever, intravenous antibiotics would be started. Usually, we are successful in treating a bacterial infection with antibiotics, but infection can be life-threatening, and some patients may die as a result of an infection. Other types of infections that can occur are from fungi or viruses. Viral infections can, in particular, be dangerous, as there are few antibiotics against most viruses.

3. Graft-versus-host disease (GVHD): GVHD is described above and is a risk of any bone marrow transplant where the cells come from another person.

4. Graft Rejection: This occurs when the patient's body does not accept the transfused bone marrow. If this occurs, it is sometimes possible to infuse additional cells, but the risk of infection or bleeding may be higher due to the delay in engraftment.

5. Bleeding: as the platelets which help blood clot will be low until the new bone marrow grows, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the

platelet count remains low. Usually, we are successful in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets, and may be at serious risk for bleeding.

6. Veno-Occlusive Disease (VOD): This can occur as a result of chemotherapy, radiation therapy (if given), or both. Symptoms include jaundice (yellowness of the skin and eyes), with liver dysfunction, weight gain, and extra fluid in the abdominal cavity. It may often be managed successfully, and completely resolve. However, complications can arise that can be fatal.

7. Mucositis and diarrhea: The large doses of medicines and radiation cause damage to the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. Pain medicine like morphine is almost always required, because the mucositis is often severe. Mucositis gets better when the white blood count starts to rise.

8. Capillary leak syndrome: This may occur as a result of chemotherapy and radiation therapy. The blood vessels may become "leaky" and fluid may enter the abdominal cavity and tissues. A patient may gain water weight and the urine output may fall. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. Patients may die if there is continued fluid collections in the lungs.

9. Unexpected organ damage: Although your major organs function well, it is possible that unexpected, life-threatening heart, lung, kidney, or liver damage may occur as a result of this therapy. If problems arise, you will be informed of the measures being taken to help you. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal despite intensive care management.

10. Late Effects: The treatments will cause sterility. Other late effects may include gland problems resulting in poor growth. There may be poor function of the thyroid gland, requiring thyroid hormone supplementation. Cataracts may occur as a result of radiation, and may require treatment. In some patients, the kidneys may be affected, causing anemia or high blood pressure. There is also a risk of second cancers as a result of the chemotherapy, radiation and/or underlying disease. This risk is felt to be outweighed by the risk of you dying from the return of the leukemia. The long term effects upon heart, lung, and brain are unknown.

Treatment Risks

For Women:

The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your regular doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid nursing.

For Men:
The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your regular doctor immediately.

Listed below are drugs which are given as part of the transplant and to control GVHD. Your doctor will tell you which of these drugs you will be given. No one will be receiving all of these drugs, only some.

Risks and side effects related to the thiotepa include those which are:

Likely	Less Likely	Rare But Serious

• **Nausea**
• **Vomiting**
• **Loss of appetite**
• **A feeling of extreme tiredness or weakness**
• **Fewer white blood cells, red blood cells and platelets in the blood.**
  ○ **A low number of red blood cells can make you feel tired and weak.**
  ○ **A low number of white blood cells can make it easier to get infections.**
  ○ **A low number of platelets causes you to bruise and bleed**
• **Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children**
• **Absence or decrease in monthly periods and could affect your ability to become pregnant**
 	
With High Doses used before marrow transplants:
• **Inflammation and/or sores in the mouth, throat and/or esophagus (the passage between the throat and stomach)**
	• **Pain at the injection site**
	• **Dizziness**
	• **Headache**
	• **Blurred vision**
	• **Hives, skin rash**
	• **Wheezing**
	• **Sudden high fever**
	• **Pain in the abdomen**
	• **Difficulty emptying the bladder**
	• **Feeling the urgency to urinate or pain on urination**
	• **Hair loss**
	• **Inflammation and reddening of the eye**
	• **Inflammation of the skin where the drug comes into contact with the skin**
	
	With High Doses used before marrow transplants:
	• **inappropriate behavior**
	• **confusion**
	• **drowsiness**
	• **Elevation in the blood of certain enzymes and/or bilirubin found in the liver**
	• **Bronze discoloration or darkening of the skin**
		• **Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate**
		• **Swelling and tightening of the throat which can cause difficulty with breathing**
		• **A new cancer or leukemia resulting from this treatment**

Risks and side effects related to <u>methotrexate (when given by vein)</u> include those which are:

Likely	Less Likely	Rare But Serious

• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea
	• Vomiting
	• Loss of appetite
	• Diarrhea
	• Chills and/or fever
	• Inflammation and/or sores in the mouth, gums, throat and/or esophagus
	• Inflammation of the intestines which may cause bleeding
	• Sensitivity to sunlight and increased risk of sunburn
	• Fewer white blood cells, red blood cells and platelets in the blood.
	  ○ A low number of red blood cells can make you feel tired and weak.
	  ○ A low number of white blood cells can make it easier to get infections.
	  ○ A low number of platelets causes you to bruise and bleed
	• Learning disability
	• Dizziness
	• Sense of not feeling well or tiredness
	• Drowsiness
	• Blurred vision
	• Rashes with itching and hives
	• Hair loss, inflammation of the hair follicles
	• Acne
	• Tearing and inflammation of the eyes
	• Darkening of the fingernails
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys.
		• Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet
		• Damage, inflammation and/or scarring of lung tissue which may make you short of breath and cough
		• Seizures
		• Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes
		• Temporary loss of function or feeling in the lower part of the body (partial paralysis)
		• Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or could lead to a coma.
		• Inflammation and scarring of the liver
		• Damage to the bone which could lead to arthritis pain and weakness of the bone
		• Inflammation of the heart
		• Fluid buildup around the heart
		• Damage to the kidney

Risks and side effects related to Tacrolimus include those which are:

Likely	Less Likely	Rare But Serious

• Headache
• Nausea and vomiting
• High Blood Pressure
• Loss of desire to eat or appetite
• Reduced ability of the body to fight infection
• Diarrhea or Constipation
• Fever
• Tremor (shakiness usually of the hands)
• Increases in the levels of certain chemicals in the blood because the kidney is not working as well as normal which may require lowering the dose
• Fewer red blood cells in the blood
  o a low number of red blood cells can make you feel tired and weak
• Difficulty sleeping or falling asleep
• A feeling of weakness and/or tiredness
• Pain which may be in the abdomen (belly), back and/or other parts of your body
• High levels of sugar in the blood that may require treatment
• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or vein
• Low (*or High*) levels of certain salts in the body like potassium and phosphate which may require treatment
• Numbness and tingling in the fingers and toes
	• Chest pain
	• Hair loss
	• Dizziness
	• Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean the liver is not working as well
	• Bladder or kidney infection
	• Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight
	• Rash that may itch
	• An increase in the levels of lipids (fats) and cholesterol in your blood which if prolonged could lead to heart problems later in life
	• Acid or upset Stomach (heartburn)
	• Difficulty or discomfort on swallowing
	• Inflammation of the stomach or esophagus (the tube that leads from the mouth to the stomach)
	• Too much gas produced in the intestines
	• Shortness of breath and/or a tight feeling in the chest with wheezing and shortness of breath (asthma)
	• Increased cough
	• Flu type symptoms with fever, tiredness, aches and pains
	• Changes in your brain function such that you have difficulty in thinking clearly, are sleepy, depressed, anxious, have strange dreams, are nervous, have changes in your mood which may include severe depression, feelings of suicide, feelings of aggressiveness and violent behavior or see or hear things that are not there
	• Fewer white blood cells and platelets in the blood
	  o a low number of white blood cells can make it easier to get infections
	  o a low number of platelets causes you to bruise and bleed more easily
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever (usually only with the IV form)
		• Allergic reactions
		• Fluid build-up in the lungs that can make you feel short of breath
		• Convulsions
		• A fast heartbeat which may cause pain in the chest
		• Chest pain or discomfort that occurs when your heart muscle does not get enough blood
		• Severe damage to the brain which may lead to difficulty carrying our normal daily tasks and to coma
		• Abnormal clotting of the blood which could lead to bleeding in the intestines or elsewhere
		• Inflammation and clotting of blood vessels which can lead to pain and swelling in the area of the clot
		• Infections including those caused by bacteria, virus, and fungus which could be locate in the skin, blood, throat, sinuses, lungs or abdomen (belly)
		• Severe rashes which can result in loss of skin and damage to mucous membranes
		• Erosion (ulceration) of the lining of the intestines which can result in pain and/or bleeding or a hole in the intestines which would cause leakage into the abdomen (belly) with pain and infection
		• Damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger
		• Severe kidney damage (which may be permanent)
		• Diabetes mellitus may develop later on - a condition where the sugar in the blood is not appropriately controlled and may require treatment with insulin by injection or drugs taken by mouth
		• Damage to the heart muscle which may make you tired, weak, feel

	• **Greater than normal numbers of white or red blood cells in the blood** • **Aches and Pains in the joints or muscles** • **Skin changes including pimples, change in color, increased tendency to sun burn and skin sores** • **Wounds may be slower to heal** • **Excessive hair growth such as on the face, eyebrows, arms and legs** • **Bleeding or tender gums, overgrowth of gum tissue** • **Changes in your vision or a decrease in vision** • **Ear pain or ringing in the ears** • **Gallstones**	**short of breath, and retain fluid and may require treatment** • **Excessive growth of white blood cells that may lead to lymphoma a cancer of the white blood cells** • **Increased chance of skin cancers**

Risks and side effects related to cyclosporine A include those which are:

Likely	Less Likely	Rare but serious

• High Blood Pressure
• Decreased ability of the body to fight infection
• Tremors
• A decrease in kidney function which may require lowering the dose
• Excessive hair growth such as on the face, eyebrows, arms and legs
	• Headache
	• Nausea and vomiting
	• Diarrhea
	• Lower levels of magnesium in the blood
	• Higher levels of potassium or creatinine in the blood which may mean that your kidneys are not working as well
	• Bleeding or tender gums, overgrowth of gum tissue
	• Fever
	• Reddening of the face with feelings of warmth
	• Pimples
	• Changes in your mood such that you feel depressed, confused or anxious
	• An increase in the levels of lipids (fats) in the blood
	• Rashes, itching and/or hives
	• Sleepiness or an inability to sleep
	• Cataracts
	• Dizziness
	• Damage to the ear causing balance problems and ringing in the ears
	• Gallstones
	• Enlarged breasts
	• Fewer red and white blood cells and platelets in the blood
	  o a low number of red blood cells can make you feel tired and weak
	  o a low number of white blood cells can make it easier to get infections
	  o a low number of platelets causes you to bruise and bleed more easily
	• Increased number of infections
	• Elevation in the blood of bilirubin and certain enzymes found in the liver which may mean the liver is not working as well
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever usually only with the IV form
		• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath. Usually only with the IV form.
		• Irregular heart beat
		• Chest pain, heart attack
		• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid and may require treatment
		• Convulsions
		• Damage to the brain that may lead to coma
		• Clotting in the small blood vessels of the kidney that can lead to kidney failure
		• Excessive growth of white blood cells that may lead to lymphoma a cancer of the white blood cells
		• Increased chance of skin cancers

Risks and side effects related to cyclophosphamide include those which are:

Likely	Less Likely	Rare but serious

• Loss of appetite
• Nausea
• Vomiting
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Hair loss
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
	• Abnormal hormone function which may lower the level of salt in the blood
	• Abdominal pain
	• Diarrhea
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Bleeding and inflammation of the urinary bladder
	• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
	• Temporary blurred vision
	• Nasal stuffiness with IV infusions
	• Skin rash
	• Darkening of areas of the skin and finger nails
	• Slow healing of wounds
	• Infections
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Abnormal heart rhythms
		• Damage and scarring of lung tissue which may make you short of breath
		• A new cancer or leukemia resulting from this treatment.
		• Damage or scarring of urinary bladder tissue
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Infertility which is the inability to have children

Risks and side effects related to Etoposide include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Hair Loss
• A feeling of weakness or tiredness
• fewer red and white blood cells and platelets in the blood
  o a low number of red blood cells can make you feel tired and weak
  o a low number of white blood cells can make it easier to get infections
  o a low number of platelets causes you to bruise and bleed more easily
	• Loss of appetite
	• Decreased blood pressure during the infusion which may require treatment
	• rashes
	• Diarrhea
	• Pain in the abdomen
	• Mouth sores
	• Tingling sensation or loss of sensation in fingers or toes
	• A feeling of extreme tiredness or weakness
	• The finger or toe nails may loosen from their nail beds
	• Inflammation of the vein through which the medication was given
	• Chest pain
		• Damage to the liver
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• A new cancer or leukemia resulting from this treatment
		• Severe rashes which can result in loss of skin and damage to mucous membranes
		• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid

Risks and side effects related to intravenous Busulfan include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Fever
• Headache
• Bloody nose
• Fewer red and white blood cells and platelets in the blood
  o a low number of red blood cells can make you feel tired and weak
  o a low number of white blood cells can make it easier to get infections
  o a low number of platelets causes you to bruise and bleed more easily
• Dizziness
• Difficulty sleeping
• Mood changes including depression and anxiety
• Rash with itching and/or hives
• Pain and inflammation in the vein through which the drug is given
• Back pain or pain in the abdomen
• Diarrhea or constipation
• Rectal pain or discomfort
• Loss of Appetite
• A fast heart beat which may cause pain in the chest
• Shortness of breath
• Fluid build-up in the tissues usually of the lower legs
• Inflammation and/or sores in the mouth, throat and/or esophagus
• Absence or decrease in the number of sperm and/or damage to the testis which may be temporary or permanent which may decrease the ability to have children in the future
• Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future
• Lower levels of certain salts in the blood such as calcium, magnesium, phosphate, and sodium
• High blood sugar which may require treatment
• Elevation in the blood of bilirubin found in the liver
• A feeling of discomfort or not feeling well and/or tiredness
	• Weight gain
	• Confusion
	• Temporary hair loss or thinning
	• Aches and pains in the muscles and joints
	• Increased levels of creatinine in the blood which could mean kidney damage
	• Darkening of the skin
	• Elevation in the blood of certain enzymes found in the liver
	• Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger.
	• Damage to the bladder which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also scarring of the bladder
	• Elevation in uric acid in the blood
	• Redness and burning at sites which have received radiation in the past
	• Cataracts later in life
	• Enlargement of the breast
		• Convulsions even though you will be treated with drugs to prevent convulsions
		• Vomiting blood
		• Bleeding into the lungs
		• A new cancer or leukemia resulting from this treatment
		• Abnormal heart rate
		• Damage to the adrenal glands that may affect the hormones that maintain blood pressure and prevent shock in stressful situations
		• Damage to the lungs that can lead to fluid in the lungs and/or scarring of the lung tissue, cough, and affect your ability to breath and the levels of oxygen in your blood.
		• Scarring of the heart muscle which could lead to heart failure
		• Damage to the bone which could lead to arthritis pain and weakness of the bone

Attachment #4
Certificate of Confidentiality Information

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

This model informed consent form has been reviewed by COG. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

COG ASCT0631
PBMTC SCT051
"A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation"
Donor Informed Consent Form

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by the Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 240 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

Your sibling has been treated for a cancer of the blood cells called leukemia. They have received chemotherapy treatment for their cancer and now have no visible signs of leukemia. Their doctor has recommended that they have a bone marrow transplant, which is a method of replacing blood-forming cells that are destroyed by cancer treatment.

You are being asked to participate in this study because you have agreed to donate bone marrow cells to your sibling for their transplant. Bone marrow transplant is recommended by many physicians for patients with leukemia that have a high chance of relapse with chemotherapy alone. Bone marrow transplant is not recommended for all types of leukemia. The bone marrow contains stem cells. If you choose to be part of this study, you may be given a drug called filgrastim, or Neupogen, or G-CSF. Throughout the rest of the consent form, we will call it G-CSF. The purpose of this study is to find out if G-CSF will increase the number of stem cells in the bone marrow. We also want to find out if patients who get bone marrow transplants from donors who had G-CSF do better.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating in this study. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part. You have a choice between participating in this clinical trial and standard donation of bone marrow or stem cells in the clinical setting that is not research related, for clinical use.

WHAT IS THE CURRENT STANDARD PROCEDURE FOR DONATING STEM CELLS?

The procedure to collect the donated stem cells is called the harvest. Prior to the harvest, a medical evaluation is done and blood is drawn to test for diseases such as hepatitis and AIDS. If you are a female who is able to become pregnant, a pregnancy test will be required from you. If your medical examination and the lab tests show any abnormalities, you will be informed.

If your medical evaluation and blood tests are normal, you will have the harvest in the operating room. Donated stem cells in children are usually collected from the bone marrow, but they can be collected from the blood as well *(peripheral blood stem cells).*

The largest amount of bone marrow that contains stem cells is found in the hip bone. The stem cells are collected from the hip bone by insertion of needles and aspiration (*removing by suction of a syringe*) of the marrow. The bone marrow cells are collected over a time period of one to two hours. This is almost always done in the operating room. The donor is given medicine so that they are asleep and don't feel the procedure. Hospitalization may be required on the day of the marrow harvest and you can expect to be discharged from the hospital one to two days later.

WHY IS THIS STUDY BEING DONE?

This is a phase III study of the drug G-CSF (filgrastim). A phase III study is done to compare the effects, good and/or bad of an experimental treatment against a standard treatment.

G-CSF (filgrastim) has been approved by the Food and Drug Administration *(FDA).* It is a white blood cell growth factor that is given to a donor, which can help increase the number of stem cells in their blood or bone marrow. This treatment has been previously used in a clinical trial. The main purpose of this study is to determine if G-CSF will increase the number of stem cells in your bone marrow, and if those increased numbers of stem cells might provide a benefit to your sibling in terms of improved survival.

The goal of this study is:

- **To evaluate the effects, good and/or bad, on the person having a bone marrow transplant when G-CSF is given to a donor before the bone marrow donation *(experimental treatment)* compared to a standard bone marrow donation *(standard treatment)*.**

In addition to the treatment goal, we would like to do a companion study *(RDSafe Study)* that involves follow-up by phone survey. The goal of this follow up portion of the study is:

- **To evaluate and compare the short and long-term risks for the donor, whether they have received G-CSF given before bone marrow donation *(experimental treatment)* or donated bone marrow without G-CSF *(standard treatment)*.**

The follow up information on this study may help us answer some research questions that might benefit future donors. You can choose to be in this clinical trial without taking part in the companion study.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of patients enrolled on this study is expected to be 425.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Random Assignment
Subjects (people participating in the study) will go on 1 of 2 different arms of the treatment plan. The arm you are assigned to is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer to make sure that there are about the same number of people on each treatment arm of the study. The randomization process is described in your sibling's COG Family Handbook for Children with Cancer.

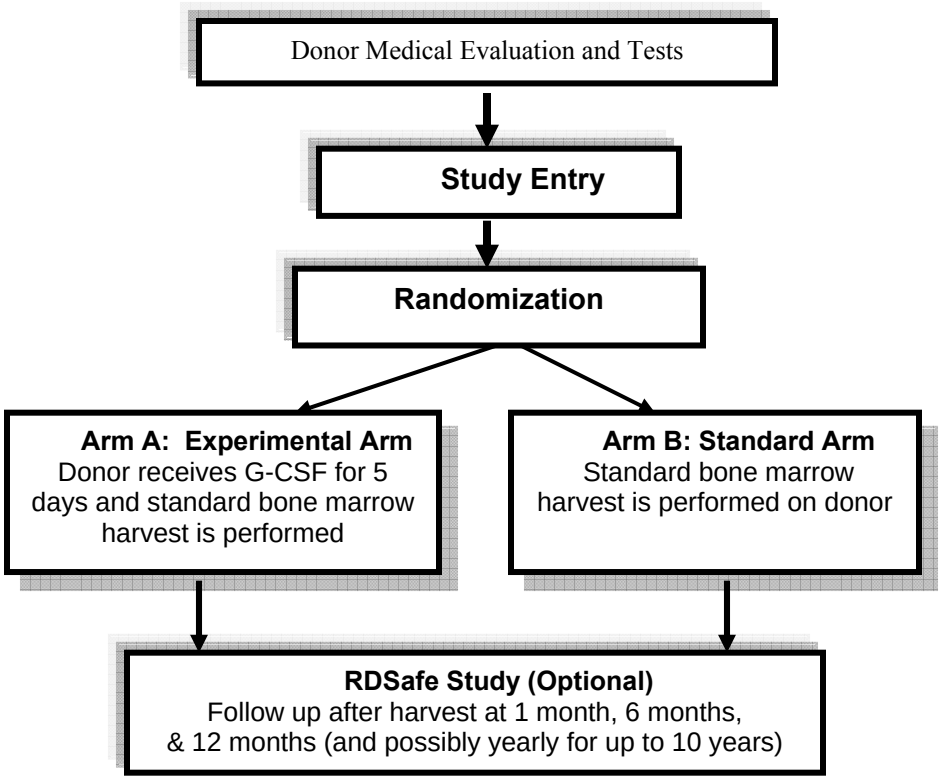
Treatment Plan
The two treatment arms of the study are called A and B as follows:

- Arm A: Experimental Treatment Arm *(G-CSF given to you before bone marrow donation)*
- Arm B: Standard Treatment Arm *(standard bone marrow donation)*

Randomization
Some participants will be randomized to receive the standard treatment arm. Others will get the experimental treatment arm. If you consent to take part in the study, randomization will be done after study entry.

A diagram and table of the treatment plan for both arms of the study can be seen below.

Diagram of treatment
A diagram of treatment can be seen below.



Treatment Plan Tables

The following tables show the difference in how treatment will be given to subjects on Arm A and Arm B of this study.

Treatment for subjects who get the experimental arm (Arm A)

Drug/Procedure	*How the drug/procedure will be given*	*Days*
Filgrastim (G-CSF)	*SQ Injection for 5 days*	*Daily before your sibling's transplant, for 5 days*
Standard bone marrow harvest	*Bone Marrow Collection for 1-2 hours*	*Day of sibling's transplant (Day 0)*

**SQ –Drug is given by injecting a needle into the tissue just under the skin (SQ shot)*

Treatment for subjects who get the standard arm (Arm B)

Drug/Procedure	*How drug/procedure will be given*	*Days*
Standard bone marrow harvest	*Bone Marrow Collection for 1-2 hours*	*Day of sibling's transplant (Day 0)*

If you are on Arm A, you will be given 5 mcg/kg/day of G-CSF daily for five days and your bone marrow will be harvested on the day of your sibling's transplant

If you are on Arm B, you will undergo a standard bone marrow harvest.

A follow up questionnaire will be administered after harvest on the same day.

Optional Research Studies

The researchers are also doing some additional studies that are optional. You can choose to take part in this clinical trial without taking part in these optional studies. The results will not be used to make any treatment decisions on this study and will not be given to you or your doctor. The results may help us answer some research questions that might benefit future donors. No matter what you decide, your care will not be affected. Check boxes for your decision about taking part in these optional studies are provided at the end of this consent form.

RDSafe Study (Optional Companion Study)

If you agree to participate in the RDSafe Study someone from the National Marrow Donor Program *(NMDP)* will call you after your harvest at 1 month, 6 months, and 12 months (and possibly yearly for up to 10 more years). The person will ask you questions related to your health and changes to your health. If you choose to take part in this study, we would like to share data, collected on you, with the NMDP.

Bone Marrow Cells Evaluation Studies

Researchers would like to evaluate and compare the cells of regular bone marrow against bone marrow treated with G-CSF. If you agree to participate in the Bone Marrow Cells Evaluation Study, about 2 teaspoons of bone marrow will be taken from the bone marrow collected at harvest. This will be tested for the immune *(body system that helps fight infections)* response of the cells and will also be stored for future testing.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study through the day their bone marrow will be collected (Day 0). After your bone marrow has been collected, you will be given a follow up questionnaire on the same day and will continue to receive standard clinical care for any bone marrow donation related complications.

Your doctor or the research doctors running the study may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment is available

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Study Risks Associated with G-CSF (*filgrastim*):

The most common side effects of G-CSF injection include pain, swelling and redness at the injection site. Other common side effects include bone pain and muscle cramps that may be severe and can last for several days after the last injection. Most pain should be relieved with acetaminophen (Tylenol) or ibuprofen (Advil). Aspirin or aspirin containing drugs must not be taken during G-CSF administration.

There is a small (estimated 1 in 10,000) risk of pain and bleeding from the spleen. Symptoms of this side effect are pain in the upper left side just below the rib cage. If you feel pain in this area you should contact your doctor immediately as this is a potentially serious side effect.

Risks and side effects related to filgrastim (G-CSF) include those which are:

Likely	Less Likely	Rare But Serious
• Aching or pain in the bones	• Local irritation at the site of the injection • Headache • Higher than normal levels of liver enzymes which may indicate liver irritation or damage and uric acid in the blood • A low number of platelets in the blood which may cause you to bruise and bleed more easily • Low fever • Enlargement of the spleen which may cause pain in the abdomen or left shoulder • Worsening of skin rashes • Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising • Higher than normal white blood count	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis. • Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening • Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected. • A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time.

There has not been a lot of study so far of the long-term effects of G-CSF (filgrastim) use in healthy people. But in the studies done so far, no serious long-term effects of G-CSF use have been seen. Healthy people are at risk for getting cancer, including leukemia, lymphoma, or other blood diseases during their lifetime. Researchers do not know if G-CSF increases or decreases a person's risk for getting cancer. In some rare cases, patients with white blood cells and bone marrow that are not normal have gotten leukemia after using G-CSF for years. Researchers do not know if using G-CSF had anything to do with these patients getting leukemia. Also, when high doses of this drug are given to normal cells in test tubes it can cause some changes in the genes of those cells. We think that it is very unlikely that the short use of G-CSF in Arm A of this study has any risk for causing cancer.

The data being collected during follow up with the RDSafe study will help find out if there are any positive or negative long-term effects from receiving a short treatment of G-CSF.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You will not receive any direct benefit from participating in this study. The potential benefit could include helping us find a better chance of prolonging your sibling's survival and getting rid of their cancer for a long time.

We expect that the information learned from this study will benefit other transplant patients and donors in the future.

WHAT OTHER OPTIONS ARE THERE?

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

- **Standard donation of bone marrow in the clinical setting.**
- **Use of G-CSF bone marrow is not standard therapy. However, your doctor could choose to use it in the clinical setting.**
- **Donating peripheral stem cells in the clinical setting.**
- **Not donating any stem cells.**

Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government which will help us protect the privacy of our research subjects. A copy of the certificate is in Attachment #2 of this consent.

It is very unlikely that the research testing might uncover important information about your current or future health. If this unlikely event occurs, the researchers may contact your doctor through COG's Data Center about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. It will remain confidential. Your doctor may discuss this unexpected finding with you. It is possible that your doctor may recommend that no additional action is necessary.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- **Children's Oncology Group and The Pediatric Blood and Marrow Transplant Consortium**
- **Representatives of the National Cancer Institute (NCI), and the Food and Drug Administration (FDA)**
- **Other US and international governmental regulatory agencies involved in keeping research safe for people**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The Institutional Review Board of this hospital**
- **The National Marrow Donor Program (NMDP)**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. These include the cost of the G-CSF if you get it. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

You will receive no payment or money for taking part in this study. If this study included providing tissue specimens to the researcher, you will not profit from any new products developed from research done on your specimens.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You may stop being in the study at any time. If you stop being in the study, you will not be penalized and you will not lose any benefits to which you are entitled. Physicians and hospital personnel will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your yearly follow-up period after harvest, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related problem or you are injured, contact Dr. XXXX or your doctor at XXXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at (XXXX

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX

WHERE CAN I GET MORE INFORMATION?

The *COG Family Handbook for Children with Cancer* has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources.

You may call the NCI's *Cancer Information Service* at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

Visit the *COG Web site* at http://www.curesearch.org

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

OPTIONAL RESEARCH QUESTIONS

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

1. I agree to participate in the companion study (RDSafe Study) by allowing the NMDP (sponsor of the RDSafe Study) to have access to my information so that they can call me to ask how I am doing, as part of the follow up portion of this clinical trial. I also agree to provide follow up information about my health status for the RDSafe study. I understand that the NMDP will be calling me for information on how I am doing, possibly for up to 10 years, and that I may withdraw from this study at any time by notifying Dr._____at XXX-XXXX.

   #1: Yes_____ No_____ _____/_____
   Initials Date

2. My bone marrow may be collected and sent to a COG laboratory to be kept for testing and storing in the Bone Marrow Cells Evaluation Studies.

   #2: Yes_____ No_____ _____ / _____
   Initials Date

3. Someone from the Children's Oncology Group or the NMDP may contact me in the future to ask me to take part in more research.

   #3: Yes_____ No_____ _____/_____
   Initials Date

SIGNATURE

I have been given a copy of all XX pages of this form. The form includes two (2) attachments.

I have been told what this research study is about. I have been given time to think about being in this research study and my questions have been answered. If I sign this form, it means I agree to be in this study. I will be given a copy of this form to keep after I sign it and so will my parents.

I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____
IRB# IRB Approved:

Attachment #1
Standard Risks of Bone Marrow Donation

1) **General anesthesia may produce acute heart, lung, or allergic reactions, which may prove to be fatal. The occurrence of these reactions is extremely rare (less than 1 in 10,000) and will be minimized by careful preoperative evaluation by your doctors.**

2) **Regional or spinal anesthesia may result in pain, numbness or weakness (caused by nerve damage) to the leg(s) or low blood pressure during surgery.**

3) **Marrow collection will be associated with pain and swelling at the sites of hip bones for several days.**

4) **Bleeding or infection at the aspirations are also possible but are minimized by careful surgical techniques in the operating room.**

5) **It may be necessary to transfuse red blood cells during or after marrow donation. This is more likely in cases where the donor is small and the recipient (your sibling) is large. Although these risks are extremely small, the transfusion of blood from someone other than you carries a risk of transfusion reaction and infection such as hepatitis or AIDS.**

Attachment #2
Certificate of Confidentiality Information

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SAMPLE ASSENT FOR RESEARCH

This model informed assent form has been reviewed by COG. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

COG ASCT0631
PBMTC SCT051
"A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation"

What is this study about and how does it affect me?

Your brother or sister has a disease that is called leukemia. This means unhealthy cells in their body are growing quickly and crowding their healthy cells, keeping them from doing their job.

They have been treated with cancer fighting drugs called chemotherapy. They will need to have a bone marrow transplant to help replace the blood cells destroyed during chemotherapy. You have agreed to help your brother or sister by donating your bone marrow cells for their transplant. Bone marrow has stem cells in it. When the stem cells are given to your brother or sister, they grow into new healthy blood cells. Research doctors want to know if giving you a drug before donating bone marrow will increase the number of stem cells in your bone marrow. This drug is called filgrastim, or G-CSF, or Neupogen. Throughout the rest of the form, we will call it G-CSF.

What will happen to me?

There is more than one treatment plan given on this study and the doctors want to know if one works better than the other. A goal of this study is to find out if one of the treatment plans is better. Normally, we don't give people G-CSF before they donate their bone marrow. The two treatment plans are:

- Treatment plan #1: G-CSF is given to you before you donate your bone marrow
- Treatment plan #2: No drugs are given to you before you donate your bone marrow

The treatment plan assigned to you will be chosen by a computer and not by your doctor, your parents or you. You have an equal chance of being assigned either one of the treatment plans.

If you choose to be in the study, a very small amount of blood (about 2 teaspoons) will be drawn from your vein in your arm in order to test for any disease. For girls who already have had their period, you will be tested to see if you are pregnant.

If you are on treatment plan #1 and your lab tests are normal, the drug G-CSF will be given to you before you donate your bone marrow. It will be injected under the skin once a day for five days in a row. If you are on treatment plan #2, you will not be given G-CSF before donating your bone marrow.

All siblings who donate bone marrow have this done in the operating room. You will be given medicine so you are asleep when the bone marrow is collected. The doctor will draw the bone marrow with a needle, going through the skin, (without cuts) near your hipbones. Within a short time, your bone marrow will re-grow back to normal. You may need to be hospitalized on this day when you donate the bone marrow, but you should be able to leave the hospital one to two days later.

What will happen after bone marrow donation?

After you have donated your bone marrow, the research doctors will ask you questions to see how you are feeling. The research doctors also want to continue to check on you by calling you to ask how you are feeling. If you agree to let the research doctors call you by phone to check on you, they will call you at one month, 6 months and every year for 5 to 10 years, after you leave the hospital.

Can being in this study hurt me?

If you are on treatment plan #1 and receive the drug G-CSF, some pain or achiness happens often, and you may need some pain medicine for this, which the doctor will give you. There may be a rash at the place where the drug is given. You may also have some cramping or feel weak. There are also some reactions to the medicine that are rare or very rare, such as bruising, allergic reactions, trouble breathing for a period of time, and shoulder pain. You should definitely tell your doctor if you have a lot of pain in the left shoulder, because a very small number of adults who have gotten G-CSF have had bleeding from an organ on the left side of your body called the spleen. This has not been seen in kids, but it could happen.

As a bone marrow donor, you will have some soreness and pain will be felt afterwards around your hip area for several days. You may also have some cramping or feel weak. Your doctor will give you some medicine to make you feel more comfortable and take away any pain.

When blood is drawn from your arm, a needle will be used. This will only hurt for about a minute. Your arm might be sore for one day, but it should not bother you too much.

Will I get anything for being in this study?

You or your parents will not get any money for being in this study. Giving you the G-CSF before we collect your bone marrow might make your bone marrow work better for your brother or sister, but we are not sure if this is true yet. This is why we are doing this study. Also, this study may help other people who need bone marrow transplants.

Do I have to be in this study?

If you don't want to be in this research study, you don't have to be. You can still help your brother or sister by donating your bone marrow cells at the hospital. Your doctor will explain to you what you can do if you decide not to be in this study.

Even though you agree now, you may feel differently later on. If you change your mind it will be okay. You may talk with your parents and/or your doctors at any time if you change your mind about being in the study.

Will I learn new things from this study?

The doctors will tell you if they find out new things that they didn't know about when they first explained this study to you. Years from now, when the study is all done, you may be able to find out from your doctor what was learned.

Will you tell anyone what I did in this study?

All the information collected about you for this study will be kept secret and your name will not be used on the study records. When the study is finished the doctors will write a report about what was learned. This report will not include your name or that you were in the study.

Your decision to be in the study or not

Dr. _____ told me what this research study is about. I have been given time to think about being in this research study and my questions have been answered. If I think of more questions later, I can call _____ at _____ or ask him/her next time.

If I put my name at the end of this form it means I agree to be in this study. I will be given a copy of this form to keep after I sign it and so will my parents.

Name (printed): _____

Signature: _____ Date: _____

ASCT0631 Data Entry and Submission Schedule

Data Submission Item	Send to	Study Entry	End of Each Reporting Period or End of Treatment	Follow Up (3, 8, 12, 24) following engraftment
Eligibility	REMOTE DATA ENTRY	X		
On-Study		X		
Conditioning HSCT			X	
Reporting Period			X	
Graph Characterization			X	
Acute GVHD			X	
Chronic GVHD			X	
Recipient and Donor Adverse Events			X[a]	
Donor Evaluation Form			X[b]	
Follow Up				X[c]
Relapse/Progression		At the time the event occurs.		
SMN				
Death				
Serious Adverse Event Reports	AdEERS Reporting System	If applicable, at each occurrence of an AdEERS		
Therapy Delivery Map	Do Not Send [d]			

[a] *Adverse events (toxicities) are to be reported for each course within each reporting period of treatment for both the recipient and the donor..*
[b] *Donor Evaluation Form is to be completed two weeks following bone marrow harvest for the donor only.*
[c] *When recipient is off protocol therapy follow-up is to be submitted at 3, 8, 12 months and then yearly thereafter until the recipient dies, is determined lost to follow-up, withdraws consent, enrolls onto another COG therapeutic study or the 5th anniversary of the study closure to accrual.*
[d] *Keep a copy of the Therapy Delivery Map in the Patient's Research Chart. This form will only be submitted if requested by the COG SDC.*

ASCT0631: Eligibility Form

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
ASCT0631 Stratum: Select the appropriate stratum according to patient's risk classification. See section 4.1.1 of the protocol for stratification criteria.	[] – Matched sibling donor, high risk [] – Matched sibling donor intermediate risk [] – Matched sibling donor, standard risk	1. This is a required filed	ASCT0631STRATUM
Treatment Start Date (MM/DD/YYYY) The date preparative regimen for the recipient must start no later than 28 calendar days after the date of study enrollment.	MM/DD/YYYY	1. This is a required field 2. Treatment start date must be <= 28days after study enrollment. 3. Date must be equal to or greater than today's date. 4. Reminder: the date preparative regimen is must start no later than 28 calendar days after the date of study enrollment	TREATMENT_START_DATE
RECIPIENT ONLY **INCLUSION CRITERIA (See section 3.2.1 of the protocol).** **<u>Important note</u>: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**			
Was the patient in the indicated age range at time of study enrollment? To be eligible, recipient must be <22 years of age at time of study entry.	[] – Yes [] – No	1. This is a required field. 2. Answer must be yes. 3. DOB check	PtAgeinRangeatStudyEnr
Did patient receive therapy that meets eligibility criteria?	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	RcvTxMecTP

Refer to Section 3.2.1.4 of the protocol. All eligible recipients should have completed re-induction therapy post-relapse, if applicable. Not all patients require relapse therapy, eg AML CR1.			
Does patient have MDS, JMML, or CML?	[] –Yes [] –No	1. This is a required field.	MDS_JMML_CML
Was patient in complete remission during the indicated time point? Refer to Section 3.2.1.2 of the protocol NOTE: This requirement does not apply to recipients with MDS or JMML. Recipients with CML should be in their 1st or 2nd chronic phase.	[] –Yes [] –No	1. If patient does not have either MDS, JMML or CML this must be answered 2. If patient has either MDS, JMML or CML this must not be answered 3. Answer must be yes.	CpltRmDuringITPrd
Does patient meet disease eligibility criteria? Refer to protocol section 3.2.1.5 of the protocol	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	DszEligCrit
RECIPIENT ONLY **EXCLUSION CRITERIA (See section 3.2.2 of the protocol)**			
Has a matched sibling donor been identified? Recipients with no matched sibling donor available are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	MtchSblDnrIdf
Does patient have Down syndrome? Recipients with Down syndrome are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	PtDownSyndromeIND2
Previously: **Did patient receive a stem cell transplant?**	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	PtReceiveStemCellXplan
Is patient pregnant or lactating? Female recipients pregnant or lactating are ineligible as the medications used in this protocol could be harmful to unborn children and infants.	[] –Yes [] –No [] –N/A patient is male	1. This is a required field. 2. If female, answer must be no.	PgtLctFl
Lansky Play Score: To be eligible, recipients less than or equal to 16	100 – Fully active, normal. 90 – Minor restrictions in	1. If patient is less than or equal to 16 years of age,	L_PERF_STAT_SCALE

years of age must have a Lansky play score greater than or equal to 60.	physically strenuous activity. 80 – Active, but tires more quickly. 70 – Both greater restriction of and less time spent in play activity. 60 – Up and around, but minimal active play; keeps busy with quieter activities. 50 – Gets dressed but lies around much of the day, no active play, able to participate in all quiet play and activities. 40 – Mostly in bed; participates in quiet activities. 30 – In bed; needs assistance even for quiet play. 20 – Often sleeping; play entirely limited to very passive activities. 10 – No play; does not get out of bed. 0 – Unresponsive.	this is a required field. 2. If patient is greater than 16 years of age, this must not be answered. 1. Answer must be greater than or equal to 60.	
Karnofsky Performance Score: To be eligible, recipients greater than 16 years of age must have a Karnofsky performance score greater than or equal to 60.	100 – Normal, no complaints, no evidence of disease. 90 – Able to carry on normal activity, minor signs or symptoms of disease. 80 – Normal activity with effort, some signs or symptoms of disease.	1. If patient is greater than 16 years of age, this is a required field. 2. If patient is less than or equal to 16 years of age, this must not be answered. 3. Answer must be greater than or equal to 60.	K_PERF_STAT_SCALE

	70 – Cares for self. Unable to carry on normal activity or to do active work. 60 – Requires occasional assistance, but is able to care for most of own needs. 50 – Requires considerable assistance and frequent medical care. 40 – Disabled, requires special care and assistance. 30 – Severely disabled, hospitalization is indicated although death is not imminent. 20 – Hospitalization necessary, very sick, active supportive treatment necessary, 10 – Moribund, fatal processes progressing rapidly. 0 – Dead.		
Does patient have an HIV status that violates the eligibility criteria? Recipients with HIV infection are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	HIVStVec
Does patient have an uncontrolled infection? Recipients with uncontrolled fungal, bacterial or viral infections are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	PT_INFEC_IND2
RECIPIENT ONLY **Organ Function Requirements (See section 3.2.3 of the protocol)**			
Does patient have adequate renal function?	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	PT_REN_FUN_REQ_IND2

Does patient have adequate liver function?	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	PT_LIV_FUN_REQ_IND2_1
Does patient have adequate cardiac function?	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	PT_CAR_FUN_REQ_IND2
Does patient have adequate pulmonary function?	[] –Yes [] –No	1. This is a required field. 2. Answer must be yes.	PT_PUL_FUN_REQ_IND2
DONOR ONLY **INCLUSION CRITERIA (See section 3.2.4 of the protocol)**			
Is patient in the indicated age range? Bone marrow donors must be >6 months of age at time of planned harvest.	[] – Yes [] – No	1. This is a required filed 2. Answer must be yes.	PtinIndAgeRangeIND2
Is the matched sibling donor of adequate size relative to the recipient? Refer to Section 3.2.4.2 of the protocol.	[] – Yes [] – No	1. This is a required filed 2. Answer must be yes	MtchSblDnrAdqSz
Has the donor undergone pre-harvest evaluation? Consistent with applicable FDA requirements and FACT standards.	[] – Yes [] – No	1. This is a required filed 2. Answer must be yes	DnrPrHvstEvalTPIND
DONOR ONLY **EXCLUSION CRITERIA (See section 3.2.5 of the protocol)**			
Does patient have an HIV status that violates the eligibility criteria? Donors with HIV infection are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	HIVStVec
Does patient have sickle cell trait? Donors that have sickle cell trait are ineligible.	[] – Yes [] – No	1. This is a required field. 2. Answer must be no.	SickleClTraitIND
Is patient high risk for bone marrow donation? Donors who are found to be high risk for bone marrow donation due to a pre-existing medical condition are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	HiRskBMDnrIND
Is patient pregnant or lactating? Pregnant or lactating females are ineligible as the medications used in this protocol could be harmful to unborn children and infants.	[] –Yes [] –No [] –N/A patient is male	1. This is a required field. 2. If female, answer must be no	PgtLctFl
Does patient have an uncontrolled infection? Donors with uncontrolled fungal, bacterial or viral	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	PT_INFEC_IND2

infections are ineligible.			
Does patient have an auto-immune disease? Donors who are found to have an auto-immune disease are ineligible.	[] –Yes [] –No	1. This is a required field. 2. Answer must be no.	AutoImmuneDsz
Regulatory Information			
Has written informed consent been obtained? from the recipient	[] – Yes [] – No	1. This is a required field. 2. Answer must be yes.	PT_CONSENT_SIG_IND2
Date Informed Consent Signed by the recipient Date entered is the date last authorized signature is obtained.		1. This is a required field. 2. Date must be equal to or less than today's date. 3. Date must be equal to or greater than DOB.	ICF_SIG_DT
Has written informed consent been obtained? from the donor	[] – Yes [] – No	1. This is a required field. 2. Answer must be yes.	PT_CONSENT_SIG_IND2
Date Informed Consent Signed by the donor: Date entered is the date last authorized signature is obtained.		1. This is a required field. 2. Date must be equal to or less than today's date. 3. Date must be equal to or greater than DOB.	ICF_SIG_DT_1
Was consent signed for correlative biology studies?	[]- Yes []- No	1. This is a required field.	ConsentCorrBioStudiesI
Has the patient given permission for optional sample banking for future cancer research studies?	[]- Yes []- No	1. This is a required field.	PtPermitSampleBankingf
Has the DONOR given permission for optional RDSafe long term follow up studies?	[]- Yes []- No	1. This is a required field.	RDSfLgTrmSdyDnrPrm
Comments			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	
PI	x	x	
Treating Physician			

ASCT0631 Eligibility

RC	X	X	
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 ON STUDY

Questions (Elements)	Valid Values	Rules and Validations	SDC Use Only
Method of Payment	[] - Other [] - Unknown [] - Private Insurance [] - Medicare and Private Insurance [] - Medicaid [] - Medicaid and Medicare [] – Medicare [] – Veterans sponsored [] –Self pay (no insurance) [] –No means of payment (no insurance) [] –Military sponsored (including CHAMPUS and TRICARE) [] –Military or Veterans sponsored NOS	1. This is a required field.	PT_PYMT_TP
Histologic diagnosis of malignancy for which this patient was enrolled on this study using **Simplified Disease Classification (SDC) v10 disease:**	[] –Please select from the list of codes in the dropdown menu.	1. This is a required field.	PtDxForEnrollThisStudy
TO BE COMPLETED FOR PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AT RELAPSE OR MYELOID MALIGNANCIES AT RELAPSE. **THIS SECTION MUST NOT BE COMPLETED FOR PATIENTS ENROLLED ON STUDY ASCT0431.**			
Is patient enrolled on ASCT0431?	[] –Yes [] –No	1. This is a required field	EnrASCT0431TCIND
Date of Relapse or Progression: (MM/DD/YYYY) Provide the date of 1st or 2nd relapse.	MM/DD/YYYY	1. If patient is not enrolled on ASCT0431, this must be answered. 2. If patient is enrolled on ASCT0431, this must not be answered.	RelapseorProgressionDA

		3. Must be less than or equal to today's date. 4. Must be greater than or equal to the date of birth.	
Site(s) of relapse: Check all that apply.	[] –Bone Marrow [] –CNS [] –Testicular [] –Other site	1. If patient is not enrolled on ASCT0431, this is required 2. If patient is enrolled on ASCT0431, this must not be answered.	LkRlp3St
If patient had bone marrow relapse, provide the **Bone marrow morphology: at the time of relapse**	[] –M 2: 5% to 25% blasts [] –M 3: Greater than 25% blasts	1. If patient had bone marrow relapse, this is a required field. 2. If patient did not have bone marrow relapse, this must not be answered.	BMMorphM13NApNAvBlast5
If CNS disease was present at relapse, provide the **CNS relapse type:** Refer to Section 3.3 of the protocol	[] –CNS 2 [] –CNS 3	1. If patient had CNS relapse, this is a required field. 2. If patient did not have CNS relapse, this must not be answered.	CNSRlpTp
Philadelphia chromosome positive?	[] –Yes [] –No [] –Indeterminate [] –Not evaluated	1. If patient is not enrolled on ASCT0431, this is required. 2. If patient is enrolled on ASCT0431, this must not be answered.	PhilChmPv
Immunophenotype Provide the immunophenotype at relapse.	[] –B-Precursor [] –T-Cell [] –Mixed Lineage (MLL) [] –Not Evaluated	1. If patient is not enrolled on ASCT0431, this is required. 2. If patient is enrolled on ASCT0431, this must not be answered.	ImmunophenotypeALLTYPE
Relapse therapy start date: (MM/DD/YYYY) Provide the date relapse therapy was initiated.	(MM/DD/YYYY)	1. If patient is not enrolled on ASCT0431, this is required 2. If patient is enrolled on ASCT0431, this must not be answered. 3. Date must be greater than or equal to date of relapse. 4. Date must be less than or	RlpTxSttTmtDt

		equal to today's date.	
Does patient have documented invasive fungal infection during the indicated period? The indicated period is during reinduction therapy.	[] –Yes [] –No	1. If patient is not enrolled on ASCT0431, this must be answered. 2. If patient is enrolled on ASCT0431, this must not be answered.	DocInvFunIfcIPrd
If patient had fungal infection during reinduction period, **Fungal infection type:**	[] –Candida [] –Aspergillus [] –Other	1. If patient had fungal infection, this is a required field. 2. If patient did not have fungal infection, this must not be answered.	FunIfcTp
If patient had fungal infection during reinduction period, **Was fungal infection treated to complete remission?**	[] –Yes [] –No	1. If patient had fungal infection, this is a required field. 2. If patient did not have fungal infection, this must not be answered.	FunIfcTrtCmptRm
Comments			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 Recipient & Donor HLA Histocompatibility

Questions (Elements)	Valid Values	Rules & Validations	SDC Use Only
RECIPIENT ONLY **HLA Histocompatibility-**			
Which HLA antigens were typed? List all antigens that were typed for both the donor and recipient. Check all that apply.	[] –A [] –B [] –HLA DRB1	1. This is a required field.	XgenTpHLASt
Donor Matching Method: Provide the method used to determine HLA A, B	[] –Serology [] –DNA technology	1. If HLA A, B is selected, this is a required field.	DnrMtchMtdTp
Recipient typing of **HLA A:** (first antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA A is selected, this is a required field. 2. If HLA A is not selected, this must not be answered.	A_HLATpTxt_1
Recipient typing of **HLA A:** (second antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA A is selected, this is a required field. 2. If HLA A is not selected, this must not be answered.	A_HLATpTxt_1
Recipient typing of **HLA B:** (first antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA B is selected, this is a required field. 2. If HLA B is not selected, this must not be answered.	B_HLATpTxt

Recipient typing of **HLA B:** (second antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA B is selected, this is a required field. 2. If HLA B is not selected, this must not be answered.	B_HLATpTxt
Recipient typing of **HLA DRB1:** (first antigen)	_ _ _ _	1. If HLA DRB1 is selected, this is a required field. 2. If HLA DRB1 is not selected, this must not be answered.	DRB1_HLATpTxt
Recipient typing of **HLA DRB1:** (second antigen)	_ _ _ _	1. If HLA DRB1 is selected, this is a required field. 2. If HLA DRB1 is not selected, this must not be answered.	DRB1_HLATpTxt
DONOR ONLY **HLA Histocompatibility-**			
Donor typing of **HLA A :** (first antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA A is selected, this is a required field. 2. If HLA A is not selected, this must not be answered.	A_HLATpTxt
Donor typing of **HLA A :** (second antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA A is selected, this is a required field. 2. If HLA A is not selected, this must not be answered.	A_HLATpTxt
Donor typing of **HLA B:** (first antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA B is selected, this is a required field. 2. If HLA B is not selected, this must not be answered.	B_HLATpTxt

Donor typing of **HLA B:** (second antigen) Example of format: Low resolution: 02XX High resolution: 0212	_ _ _ _	1. If HLA B is selected, this is a required field. 2. If HLA B is not selected, this must not be answered.	B_HLATpTxt_2
Donor typing of **HLA DRB1:** (first antigen)	_ _ _ _	1. If HLA DRB1 is selected, this is a required field. 2. If HLA DRB1 is not selected, this must not be answered.	DRB1_HLATpTxt
Donor typing of **HLA DRB1:** (second antigen)	_ _ _ _	1. If HLA DRB1 is selected, this is a required field. 2. If HLA DRB1 is not selected, this must not be answered.	DRB1_HLATpTxt_3
Comments			RSCH_COMMENTS_TXT

ASCT0631 CONDITIONING REGIMEN AND TRANSPLANT REPORTING PERIOD

This reporting period form covers the dates between the start of the conditioning regimen through end of the day of transplant. This form must be completed for all recipients. If recipient came off protocol therapy prior to starting or not completing the conditioning regimen, this form must be completed following the date recipient came off protocol.

Questions (Elements)	Valid Values	Rules and Validations	SDC Use Only
ASCT0631 Reporting Period:	Pre-populated	Pre-populated	ASCT0631Reporting Period
Reporting Period Start date: (MM/DD/YYYY) • Report the start date as the date conditioning regimen began. • If conditioning regimen was not delivered, report the start date as the enrollment date. • If recipient came off protocol therapy prior to starting conditioning regimen, the start date will be reported as the date of enrollment.	MM/DD/YYYY.	1. This is a required field. 2. Must be less than or equal to today's date. 3. Must be greater than or equal to the enrollment date. 4. If patient did not start conditioning regimen, the start date must equal the enrollment date.	TX_REP_PD_BEGDT

Reporting Period End date: (MM/DD/YYYY) • If recipient completed conditioning regimen and received transplant, report the end date as the date of transplant Day 0. • If recipient was off protocol therapy prior to starting or did not complete conditioning regimen and/or transplant, the end date is the date recipient came off protocol.	MM/DD/YYYY	1. This is a required field. 2. Must be less than or equal to today's date. 3. Must be greater than or equal to the enrollment date. 4. Must be greater than or equal to the reporting period start date.	TX_REP_PD_ENDDT
CONDITIONING REGIMEN ADMINISTRATION - CO-ENROLLED RECIPIENTS			
Has patient enrolled on a COG therapeutic study? Is recipient co- enrolled on either ASCT0431 or AAML0531 ?	[] –Yes [] –No	1. This is a required field	PtEnrollCOGTherapeutic
CONDITIONING REGIMEN ADMINISTRATION – RECIPIENTS NOT CO-ENROLLED			
Did patient start transplant conditioning regimen?	[] –Yes [] –No	1. If patient is not co-enrolled on COG treatment study, this is a required field. 2. If patient is co-enrolled on COG treatment study, this must not be answered	PtSttXptCndRgm
If recipient received conditioning regimen, **Did patient complete transplant conditioning**	[] –Yes [] –No	1. If patient received conditioning regimen, this is a required field.	PtCmptXptCndRgm

regimen?		2. If patient did not receive conditioning regimen, this must not be answered.	
Transplant conditioning regimen agents: The following are conditioning regimens on the study. Please provide which regimen recipient received. Preferred Regimen for Acute Lymphoblastic Leukemia patients: TBI/Thiotepa/Cyclophosphamide Variation 1: TBI/Cyclophosphamide/Etoposide Variation 2: Higher Dose TBI/Cyclophosphamide Regimen for Myeloid Malignancies: busulfan/ cyclophosphamide	[] – TBI/Thiotepa/Cyclophosphamide [] – TBI/Cyclophosphamide/Etoposide [] –Higher Dose TBI/Cyclophosphamide [] -busulfan/ cyclophosphamide	1. If patient received conditioning regimen, this is a required field. 2. If patient did not receive conditioning regimen, this must not be answered.	XptCndRgmAgt2Tp GDE Request
Have required data been sent to QARC (Quality Assurance Review Center)? Patients who receive TBI cranial or testicular irradiation must have QARC Post Treatment Review. The following data should be submitted to QARC:	[] –Yes [] –No	1. If patient received conditioning regimen, this is a required field. 2. If patient did not receive conditioning regimen, this must not be answered. 3. Email notification sent to QARC.	RqDatQARC_TP

Please see section 16.0 for radiation therapy guidelines and further detail.			
ALL OF THE REMAINING QUESTIONS ARE REQUIRED FOR ALL PATIENTS (CO-ENROLLED AND NOT CO-ENROLLED)			
TRANSPLANT DATA			
If recipient completed conditioning regimen, **Did patient receive a stem cell transplant?** If recipient had hematopoietic stem cell transplant, please complete graft characterization form.	[]–Yes []–No	1. If patient completed conditioning regimen, this is a required field. 2. If patient did not complete conditioning regimen, this must not be answered.	PtReceiveStemCellXplan
Stem Cell Transplant Date: (MM/DD/YYYY) If recipient received hematopoietic stem cell transplant, provide the transplant date.	MM/DD/YYYY	1. If patient had SCT, this is a required field. 2. Must be equal to or greater than the enrollment date and less than or equal to today's date. 3. Date must be greater than or equal to the RP start date and less than or equal to RP end date. 4. If patient did not have SCT, this must not be answered.	StemCellXplantDATE
RELAPSE/PROGRESSION			
Did the patient relapse during this reporting period? If recipient relapsed during this reporting period, recipient will be removed from protocol therapy. Please fill out the	[]–Yes []–No	1. This is a required field.	PtRelapseThisRptPeriod

relapse/progression form.			
ADVERSE EVENTS			
Did patient experience any adverse events during the indicated period? Did recipient experience any Grade IV-V adverse events during this Reporting Period? If yes, Adverse Events form must be completed.	[] –Yes [] –No	1. This is a required field.	ExprAeIPrd
SECOND MALIGNANCY			
Has a new primary cancer or MDS been diagnosed that has not been previously reported? If malignancy is acute myelogenous leukemia or myelodysplastic syndrome (MDS), submit the NCI secondary AML/MDS form, cytogenetics and pathology reports. If yes, please fill out the Second Malignant Neoplasm form.	[] – Yes [] – No	1. This is a required field.	NEW_CA_DX_IND3
OFF PROTOCOL THERAPY			
Was the patient off protocol therapy before completing all treatment in this reporting period? The protocol therapy is the transplant conditioning regimen and transplant.	[] –Yes [] –No	1. This is a required field. 2. Alert: If yes to relapse patient must be off protocol therapy and answer must be yes.	PtOffProtocolTxNotAllT
If recipient was off protocol therapy before completing all treatment,		1. If yes to off protocol therapy, this is a required	OffProtocolTherapyDATE

provide the **Date off protocol therapy:** (MM/DD/YYYY)	MM/DD/YYYY	field. 2. If no to off protocol therapy, this must not be answered. 3. Date must be greater than or equal to the RP start date and less than or equal to RP end date.	
If recipient is off protocol therapy, **Primary reason patient is off protocol therapy:**	[] –Physician determines it is in the patient's best interest [] –Refusal of protocol therapy by patient/parent/guardian [] –Relapse [] –Completion of planned therapy []-Death []- Lost to follow up []- Entry onto another COG therapeutic study []- Withdrawal of consent for any further data submission	1. If yes to off protocol therapy, this is a required field. 2. If no to off protocol therapy, this must not be answered. 3. If yes to relapse, relapse must also be selected as a reason. 4. If no to relapse, relapse must not be selected as a reason.	OffProtocolReasonInter
If recipient is off protocol therapy, select **Contributing reason(s) patient is off protocol therapy:** Check all that apply. Refer to Section 9.1 of the protocol	[] –Physician determines it is in the patient's best interest [] –Refusal of protocol therapy by patient/parent/guardian [] –Relapse [] –Completion of planned therapy []-Death []- Lost to follow up []- Entry onto another COG therapeutic study []- Withdrawal of consent for any further data submission []- None	1. The response(s) must not equal the answer to the question above. 2. Answer cannot be "None" and another reason. If "None", it must be the only answer selected.	CbtRopt

Comments	RSCH_COMMENTS_TXT

ASCT0631 REPORTING PERIOD

This reporting period form covers Day 0 – Day 200, following completion of stem cell transplant. This form must be completed for all recipients immediately following Days 60, 120 and 200. If a patient comes off protocol therapy at anytime during a reporting period, this form must be completed immediately following the date patient is off protocol therapy.

Questions (Elements)	Valid Values	Rules and Validations	SDC Use Only
ASCT0631 Reporting Period:	[] –Reporting Period 1 (Day 0-60) [] –Reporting Period 2 (Day 60-120) [] –Reporting Period 3 (Day 120-200)	1. This is a required field.	ASCT0631ReportingPeriod
Reporting Period Start date: (MM/DD/YYYY) Reporting Period 1: Report the start date as the date of transplant (Day 0). Reporting Periods 2 and 3: Report the start date as the end date of the previous reporting period.	MM/DD/YYYY	1. This is a required field. 2. Must be less than or equal to today's date. 3. Must be greater than or equal to the enrollment date.	TX_REP_PD_BEGDT
Reporting Period End date: https://members.childrensoncologygroup.org/_files/disc/CRA/sdc/EndofReportingPeriodDates.pdf	MM/DD/YYYY	1. This is a required field. 2. Must less than or equal to today's date. 3. Must be greater than or equal to the enrollment date. 4. Must be greater than or equal to the reporting period start date.	TX_REP_PD_ENDDT

		5. If primary or contributing reason off equals planned completion of therapy, then end date must be 10 number of days after the start date.	
Engraftment- to be completed if recipient is not enrolled on ASCT0431			
Did patient engraft neutrophils? ANC must be ≥ 500 for 3 consecutive measurements at least 1 day apart (Day of engraftment is the first day ANC is ≥ 500) Reporting Periods 2 and 3: If patient did not engraft neutrophils during the previous reporting period, this must be answered.	[] –Yes [] –No	1. This is a required field.	EgftNph
Neutrophil Engraftment Date: (MM/DD/YYYY)	MM/DD/YYYY	1. If yes to neutrophil engraftment, this is a required field. 2. If no to neutrophil engraftment or question was not answered, this must not be answered. 3. Date must be greater than or equal to RP start date and less than or equal to RP end date. 4. Date must be less than or equal to	NphEgftEvlDt

		today's date.	
Did patient engraft platelets? Platelet engraftment is defined as platelets > 20,000 for three consecutive days with no transfusions for 7 days prior. Reporting Periods 2 and 3: If patient did not engraft platelets during the previous reporting period, this must be answered.	[]–Yes []–No	1. This is a required field	PtGftPlt
Platelet Engraftment Date: (MM/DD/YYYY) Record the first date of platelets > 20,000 for three consecutive days with no transfusions for 7 days	MM/DD/YYYY	1. If yes to platelet engraftment, this is a required field. 2. If no to platelet engraftment or question was not answered, this must not be answered. 3. Date must be greater than or equal to RP start date and less than or equal to RP end date. 4. Date must be less than or equal to today's date.	PltEgftEvlDt
Engraftment Syndrome: Reporting Period 1 Only			
Did engraftment syndrome occur? An engraftment syndrome consists of a combination of symptoms including high fever, rash,	[]–Yes []–No	1. If RP 1, this is a required field. 2. If not RP 1, then this must not be answered.	GftSydOccur

respiratory symptoms, and diarrhea occurring just prior to or in association with neutrophil engraftment.			
Growth Factor Administration-Post Transplant: Recipients Only			
Did patient receive growth factor(s)? Did recipient receive growth factor/cytokine therapy?	[] –Yes [] –No	1. This is a required field.	PtRcvGf
If patient received growth factor(s), provide the **Growth factor type:** Check all that apply.	[] –Erythropoietin [] –Filgrastim (G-CSF) (granulocyte macrophage colony stimulating factor) [] –Kepivance [] –Sargramostim (GM-CSF) (granulocyte macrophage colony stimulating factor) [] –Other	1. If yes to growth factor, this is a required field. 2. If no to growth factor, this must not be answered.	Gf2Tp
Tacrolimus Administration- ALL patients only			
Did patient receive tacrolimus according to protocol?	[] –Yes [] –No	1. This is a required field.	PtRcvD100Atp_1
If yes to receiving tacrolimus, **Were there any dose modifications or additions/omissions to protocol treatment?**	[]- No []- Unknown []- Yes, planned: (i.e. the treatment was changed according to protocol guidelines) []- Yes, unplanned: (i.e. the treatment was not part of protocol guidelines)	1. If patient received tacrolimus, this is a required field. 2. If patient did not receive tacrolimus, this must not be answered.	DOSE_MOD_IND
Reason for dose modification: Check all that apply.	[] –Hyperlipidemia [] –Neurologic Toxicities [] –Renal Toxicities [] –Transplant Associated	1. If yes to dose modification, this is a required field. 2. If no to dose	DsTxModRsn

	Microangiopathy [] –Other, specify	modification, this must not be answered.	
If other reason for tacrolimus dose modification or unplanned**, Specify other:**	Text	1. If other reason for dose modification, this is a required field. 2. If other, specify is not selected, this must not be answered. 3. If dose modification was unplanned, this is a required field.	OTHER_SPECIFY
Cyclosporine Administration- Myeloid patients only			
Did patient receive cyclosporine according to protocol?	[] –Yes [] –No	1. This is a required field	RcvCyclspnAtpIND
If yes to receiving cyclosporine, **Were there any dose modifications or additions/omissions to protocol treatment?**	[]- No []- Unknown []- Yes, planned: (i.e. the treatment was changed according to protocol guidelines) []- Yes, unplanned: (i.e. the treatment was not part of protocol guidelines)	1. If patient received cyclosporine, this is a required field. 2. If patient did not receive cyclosporine, this must not be answered.	DOSE_MOD_IND
Reason for dose modification or discontinuation: Check all that apply.	[] –Hyperlipidemia [] –Neurologic Toxicities [] –Neutropenia [] – Renal Toxicities [] –Thrombocytopenia [] –Transplant Associated Microangiopathy [] –Other, specify	1. If yes to dose modification, this is a required field. 2. If no to dose modification, this must not be answered.	DsTxModRsn
If other reason for cyclosporine	Text	1. If other reason for	OtherSpecify1TEXT

dose modification or unplanned**, Specify other:**		dose modification, this is a required field. 2. If other, specify is not selected, this must not be answered. 3. If dose modification was unplanned, this is a required field.	
Methotrexate Administration			
Did patient receive methotrexate?	[] –Yes [] –No	1. This is a required field.	PtRcvD46_1
If yes to receiving methotrexate, **Were all doses of MTX given at full dose?**	[] –Yes [] –No	1. If yes to receiving methotrexate, this is a required field. 2. If no to receiving methotrexate, this must not be answered. 3. If answer is no, email notification will be sent to RC to call CRA to send TDM.	AllMTXDoseFullDoseYesN
Reason all doses of MTX not given at full dose: Check all that apply.	[] –Mucositis [] –Renal toxicity [] –Transaminitis [] –Hyperbilirubinemia [] –Other, specify	1. If no to receiving all doses of MTX, this is a required field. 2. If yes to receiving all doses of MTX, this must not be answered.	ReasonNotAllMTXDoseFul
If other reason**, Specify other**	Text	1. If other reason for dose modification, this is a required field. 2. If other, specify is not selected, this must not	OTHER_SPECIFY_1

		be answered.	
Relapse/Progression			
Did patient relapse or progress during the indicated period? If yes, please fill out the relapse/ progression form.	[]- Yes []- No	1. This is required field. 2. If the answer to this question is selected as yes, then the reason off protocol therapy must also be selected as relapse.	RlpPrgIPrd
Adverse Events RECIPIENTS ONLY			
Did patient experience any adverse events during the indicated period? Did patient experience any Grade III or higher adverse events during this Reporting Period? If yes, Adverse Events form must be completed.	[] –Yes [] –No	1. This is a required field.	ExprAeIPrd
Second Malignancy			
Has a new primary cancer or MDS been diagnosed that has not been previously reported? If yes, please fill out the Second Malignant Neoplasm form.	[] – Yes [] – No	1. This is a required field.	NEW_CA_DX_IND3
Acute GVHD and Chronic GVHD			
During this reporting period, **Did patient develop signs or symptoms of acute graft versus host disease (GVHD)?** If yes, please complete acute	[] –Yes [] –No [] –Indeterminate	1. This is a required field	DevSgnsSxAcuGVHD

GVHD form.			
During this reporting period, **Did patient develop chronic graft versus host disease (cGVHD)?** If yes, please complete chronic GVHD form.	[] –Yes [] –No [] –Unknown	1. This is a required field.	DevCGVHD_1
Off Protocol Therapy			
Was the patient off protocol therapy before completing all treatment in this reporting period?	[] –Yes [] –No	1. This is a required field.	PtOffProtocolTxNotAllT
If patient was off protocol therapy before completing all treatment, provide the **Date off protocol therapy:** (MM/DD/YYYY)	MM/DD/YYYY	1. If yes to off protocol therapy, this is a required field. 2. If no to off protocol therapy, this must not be answered. 3. Must be within the reporting period start date and end date.	OffProtocolTherapyDATE
If patient is off protocol therapy, **Primary reason patient is off protocol therapy:**	[] –Completion of planned therapy []- Patient confirmed lost to follow up [] –Physician determines it is in the patient's best interest [] –Refusal of protocol therapy by patient/parent/guardian []- Entry onto another COG therapeutic study [] –Relapse []-Death []- Withdrawal of consent for any further data submission	1. If yes to off protocol therapy, this is a required field. 2. If no to off protocol therapy, this must not be answered. 3. If yes to relapse, relapse must also be selected as a primary or contributing reason. If no to relapse, relapse must not be	PmyRopt

		selected as a reason.	
If patient is off protocol therapy, **Contributing reason(s) patient is off protocol therapy:** Check all that apply.	[] –Completion of planned therapy []- Patient confirmed lost to follow up [] –Physician determines it is in the patient's best interest [] –Refusal of protocol therapy by patient/parent/guardian []- Entry onto another COG therapeutic study [] –Relapse []-Death []- Withdrawal of consent for any further data submission	1. The response(s) must not equal the answer to the question above. 2. If yes to relapse and primary reason off protocol therapy is not relapse, then contributing reason must equal relapse. 3. If no to relapse, then contributing reason off protocol therapy cannot be relapse.	CbtRopt
Correlative Biology Studies			
Were blood specimens obtained for correlative biology study?	[] –Yes [] –No [] –Not applicable: Patient did not consent to correlative biology study at study enrollment	1. If patient consented to correlative biology studies, this is a required field. 2. If patient did not consent to correlative biology studies, this must not be answered.	BdSpcObtCrrBioSdyTP
Have specimens been sent? Have specimens been sent to the Biopathology Center?	[] –Yes [] –No	1. If yes to specimen collection, this is a required field. 2. If no to specimen collection, this must not be answered. 3. If specimen collected and has not been sent, RC will receive email notification to	SpecimenSentIND3

		follow up with center.	
Comments			RSCH_COMMENTS_TXT

ASCT0631: DONOR EVALUATION FORM

TO BE COMPLETED BY THE INSTITUTION TWO WEEKS POST BONE MARROW HARVEST FOR THE DONOR

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
Specimen collection date: MM/DD/YYYY		1. This is a required field 2. Date must be equal to or greater than enrollment date. 3. Date must be equal to or less than today's date.	SpcClcSmpDt
24 HR POST DONATION HEMATOLOGY			
WBC x 10^9/L (x10^3/mm^3)	_ _._	1. This is a required field 2. Valid Range(0-100)	HMT_WBC_LAB_UNS_VAL
Hemoglobin: units: g/dL	_ _._	1. This is required filed 2. Valid Range(0-18)	HMT_HGB_LAB_SPEC_VAL
Hematocrit (HCT) (%):	_ _._	1. This is a required filed 2. Valid Range(0-60)	Hematocrit1
Platelets: x 10^9/L (x10^3/mm^3)		1. This is a required field 2. Valid Range(0-1000)	PltClctI0U12
Segs Neutrophils (%)		1. This is a required field 2. Valid Range(0-100)	HMT_SEG_LAB_SPEC_VAL
Bands Neutrophils (%)		1. This is a required field 2. Valid Range (0-100)	HMT_BAN_LAB_SPEC_VAL
Metamyelocytes (%):		1. This is a required field 2. Valid Range (0-100)	MtmlcytCf3U11
Myelocytes (%):		1. This is a required field 2. Valid Range (0-100)	MelcytCf3U11
Peripheral Promyelocytes (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_PROMYELOCYTES
Peripheral Eosinophils (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_EOSINOPHILS_C
Peripheral Basophils (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_BASOPHILS_CEL

Peripheral Blasts (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_BLASTS_CELL_P
Peripheral Lymphocytes (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_LYMPHOCYTES_C
Peripheral Monocytes (%)		1. This is a required field 2. Valid Range (0-100)	LAB_HEME_MONOCYTES_CEL
Specify Other: Eg LUC, unclassified cells (%)		1. This is a required field	OtherSpecify1TEXT
HOSPITALIZATION			
Was patient hospitalized during this reporting interval?	[] - Yes [] - No	1. This is a required field	HOSPITALIZATIONIND
If yes**,** **Reason for hospitalization:**	[]- Complication of procedure []- Observation	1. If yes to hospitalization, then this is a required field. 2. If no to hospitalization, then this must not be answered.	HospitalizeReason1TYPE
Days Hospitalized: Number of days the donor remained in the hospital.		1. If yes to hospitalization, then this is a required field. 2. If no to hospitalization, then this must not be answered.	DaysHospitalizedINTERV
PLEASE SUBMIT AN ADVERSE EVENT FORM EACH TIME THE DONOR EXPERIENCES AN ADVERSE EVENT			
Was patient evaluated for the indicated adverse event (AE)? Please refer to section 7.4 of the protocol for details on donor related adverse events.	[]-Yes []-No	1. This is a required field	PtEvlIAeTP
Did patient experience splenic rupture?	[]-Yes []-No	1. This is a required field.	ExprSplnRprIND

Comments:			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 Graft Characterization

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
Recipients **Weight:** in kg	|_|_|_|.|_|	1. This is a required field. 2. Provide for one decimal place 3. 0-999.9	PT_WT_MSRMT
Donors **Weight:** in kg	|_|_|_|.|_|	1. This is a required field 2. Provide for one decimal place 3. 0-999.9	PT_WT_MSRMT
Growth Factor Administration: Donor Only			
Did donor receive G-CSF? Did donor receive Filgrastim (G-CSF, Neupogen) therapy?	[] –Yes [] –No	1. This is a required field.	DnrRcvGCSFTPIND
Growth factor administration start date: (MM/DD/YYYY) Provide the date G-CSF was first administered to the donor.	MM/DD/YYYY	1. If yes to growth factor, this is a required field. 2. If no to growth factor, this must not be answered. 3. Must be in date format. 4. Date must be greater than or equal to enrollment date and less than or equal to today's date.	GfAdmrSttDt
Growth factor administration end date: (MM/DD/YYYY) Provide the date G-CSF administration ended to the donor.	MM/DD/YYYY	1. If yes to growth factor, this is a required field. 2. If no to growth factor, this must not be answered. 3. Must be in date format. 4. Date must be greater than or equal to enrollment date and less than or equal to today's date. 5. Date must be greater than or	GfAdmrEndDt

		equal to the growth factor administration start date.	
G-CSF Dose Administered: In mcg/kg		1. If patient received G-CSF, then this is a required field 2. If patient did not receive G-CSF, this must not be answered. 3. Valid Range (0-20)	DsAdmrGCSFFLGSTDsN3ug
Did patient undergo bone marrow harvest? Please note we are referring to the donor.	[]-Yes []- No	1. If patient received G-CSF, this is a required field. 2. If patient did not receive G-CSF, this must not be answered.	UndergoBmHvstIND
Bone Marrow harvest date: MM/DD/YYYY		1. If patient underwent BM harvest, this is a required field. 2. If patient did not undergo BM harvest, this must not be answered. 3. Must be in date format 4. Date must be greater than or equal to enrollment date and less than or equal to today's date date. 5. Date must be greater than or equal to the growth factor administration end date.	BmHvstPdrDt
Volume of Harvest: cc		1. If patient underwent BM harvest, this is a required field. 2. If patient did not undergo BM harvest, this must not be answered. 3. Valid Range (0-2000)	BmVolHvstMsI0U73
Infused Cell Counts for Bone Marrow			
Was CD34 cell count performed? Was CD34 count of hematopoietic stem cell product performed?	[] –Yes [] –No	1. This is a required field.	CD34ClCtPrfm_1

If CD34 count was performed, provide the infused **CD 34 cell count:** |_| |_| . |_| x 10^6 cells/kg recipient weight		1. If CD 34 count was performed, this is a required field. 2. If CD 34 count was not performed, this must not be answered. 3. If answered value range must be between 0-99.9	CD34ClCt_1
Was total nucleated cell count (TNC) performed? Was total nucleated cell count for hematopoietic stem cell product performed?	[] –Yes [] –No	1. This is a required field	TtlNucClCtPrfm
If total nucleated cell count was performed, provide the infused **Total nucleated cell count:** |_| |_| . |_| x 10^8 cells/kg recipient weight		1. If total nucleated cell count was performed, this is a required field. 2. If total nucleated cell count was not performed, this must not be answered. 3. If answered value range must be between 0-99.9	TtlNucClCt
Was CD3/ 4+ (or CD4+) cell count performed? Was **CD3/ 4+ (or CD4+)** count of hematopoietic stem cell product performed?	[] –Yes [] –No	1. This is a required field	CD3CD4ClCtPrfmIND
If **CD3/ 4+ (or CD4+)** count was performed, provide the infused **CD3/ 4+ cell count:** |_| |_| . |_| x 10^8 cells/kg recipient weight		1. If **CD3/ 4+**cell count was performed, this is a required field. 2. If **CD3/ 4+**cell count was not performed, this must not be answered. 3. If answered value range must be between 0-99.9	CD3_4IfxClCtU49

Was CD3/ 8+ (or CD8+) cell count performed? Was CD3/8+ **(or CD8+)**count of hematopoietic stem cell product performed?	[] –Yes [] –No	1. This is a required field	Cd3CD8ClCtPrfmIND
If CD3 /8+ **(or CD8+)** count was performed, provide the infused **CD3 /8+ (or CD8+) cell count:** |_| |_| . |_| x 10^8 cells/kg recipient weight		1. If **CD3 /8+**cell count was performed, this is a required field. 2. If **CD3 /8+**cell count was not performed, this must not be answered. 3. If answered value range must be between 0-99.9	IfsCD3CD8ClCtU49
Was total mononuclear cell count (TMC) performed? Was total mononuclear cell count for hematopoietic stem cell product performed?	[] –Yes [] –No	1. This is a required field	TtlMnucClCtPrfmIND
If total mononuclear cell count was performed, provide the infused **Total mononuclear cell count:** |_| |_| . |_| x 10^8 cells/kg recipient weight		1. If total mononuclear cell count was performed, this is a required field. 2. If total mononuclear cell count was not performed, this must not be answered. 3. If answered value range must be between 0-99.9	TtlMnucClCtU49
Comments:			RSCH_COMMENTS_TXT

ASCT0631 ACUTE GRAFT VERSUS HOST DISEASE

If patient developed acute GVHD during a reporting period, this form must be completed only if patient is not enrolled on ASCT0431.

Questions (Elements)	Valid Values	Rules and Validations	SDC Use Only
Serial #: Automatically assigned by the system.	[] -1 [] -2 [] -3 [] -4 [] -5	1. This is a required field.	SerialNumber
ASCT0631 Reporting Period:	[] –Reporting Period 1 (Day 0-60) [] –Reporting Period 2 (Day 60-120) [] –Reporting Period 3 (Day 120-200) []–Reporting Period 4: Follow-up 1: 3 months	1. This is a required field.	ASCT0631Reporting Period
Acute graft versus host disease (GVHD) diagnosis date: (MM/DD/YYYY)	MM/DD/YYYY	1. This is a required field. 2. Must be greater than or equal to the enrollment date. 3. Must be less than or equal to today's date.	AcuGVHDDxDt
Were biopsies done to confirm acute graft versus host disease (GVHD)?	[] –Yes [] –No [] –Unknown	1. This is a required field.	BxToCfmAcuGVHD
Biopsy site(s): If biopsies were done to confirm aGVHD, what sites were biopsied? Check all that apply.	[] –Gastrointestinal Tract [] –Liver [] –Skin [] –Other, specify	1. If yes to aGVHD biopsy, this is a required field. 2. If no or unknown to aGVHD biopsy, this must not be answered.	BxSct1St
If other site was biopsied, provide the site.	Text	1. If other site was biopsied, this is a	

Specify other		required field. 2. If other, specify is not selected, this must not be answered.	
If biopsies were done to confirm aGVHD, provide the: **Date of biopsy:** (MM/DD/YYYY)	MM/DD/YYYY	1. If yes to aGVHD biopsy, this is a required field. 2. If no or unknown to aGVHD biopsy, this must not be answered. 3. Must be equal to or greater than enrollment date. 4. Must be equal to or less than today's date.	BX_DT
Provide the MAXIMUM **Stage of acute GVHD of the Skin:** During this reporting period, provide the MAXIMUM stage of aGVHD of the skin as defined by Appendix II of the protocol.	[] -0: No GVHD rash [] -1: Maculopapular rash on <25% of BSA [] -2: Maculopapular rash on 25-50% of BSA [] -3: Maculopapular rash on >50% of BSA [] -4: Generalized erythroderma with bullous formation and desquamation > 5%BSA	1. This is a required field 2. Check only one answer	AcuGvhdSkn2St_1
Provide the MAXIMUM **Stage of acute GVHD of the Liver:** During this reporting period, provide the MAXIMUM stage of aGVHD of the liver as defined by Appendix II of the protocol.	[] -0: Bilirubin < 2 mg/dL [] -1: Bilirubin 2-3 mg/dL [] -2: Bilirubin 3.1-6 mg/dL [] -3: Bilirubin 6.1-15 mg/dL [] -4: Bilirubin >15 mg/dL	1. This is a required field.	AcuteGVHDLiverSTAGE_1

Provide the MAXIMUM **Stage of acute GVHD of the Intestinal tract:** Provide the MAXIMUM stage of aGVHD of the intestinal tract as defined by Appendix II of the protocol.	[] -0: Adult stool output < 500ml/day (<10ml/kg/day in children) [] -1: Adult stool output 500-999 ml/day (10-19.9 ml/kg/day in children) or persistent nausea, vomiting, or anorexia, with a positive EGD biopsy. [] -2: Adult stool output 1000-1500 ml/day (20-30 ml/kg/day in children [] -3:Adult stool output >1500 ml/day (>30 ml/kg/day in children) [] -4: Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)	1. This is a required field.	AcuGvhdGi2St_1
Provide the MAXIMUM **Overall Grade of acute graft versus host disease (aGVHD):** Provide the MAXIMUM overall grade of aGVHD as defined by Appendix II of the protocol.	[] – 0: No stage 1-4 of any organ [] – 1: Stage 1-2 rash and no liver or gut involvement [] – 2: Stage 3 rash, or Stage 1 liver involvement, or Stage 1 GI [] – 3: Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI [] – 4: Stage 4 skin, liver or GI involvement	1. This is a required field.	OvGdAcuGVHD1Tp
GVHD Treatment			
Did patient receive treatment for acute GVHD? Did patient receive treatment for acute GVHD, in addition to prophylactic tacrolimus, sirolimus and/or methotrexate?	[] –Yes [] –No [] –Unknown	1. This is a required field.	PtReceiveTxforAcuteGVH
GVHD treatment:	[] –mycophenolate mofetil	1. If yes to treatment for	GVHDTx1TYPE

Check all treatment given for acute GVHD. Not including tacrolimus, sirolimus or methotrexate given as per protocol for GVHD prophylaxis	[] –Alemtuzumab [] –Antithymocyte Globulin (ATG) [] –Antilymphocyte Globulin (ALG) [] –corticosteroids [] –cyclosporine [] –Dacluzimab [] -Extra-corporeal photopheresis (ECP) [] –Infliximab [] –Pentostatin [] –Rituximab [] –Other GVHD therapy, specify	acute GVHD, this is a required field. 2. If no or unknown is selected for treatment for acute GVHD, then this must not be answered.	
If other treatment for acute GVHD was given, **Specify other:**	Text	1. If other aGVHD treatment was given, this is a required field. 2. If other, specify is not selected above, this must not be answered.	OTHER_SPECIFY_2
Comments:	Text		RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

CHRONIC GRAFT VERSUS HOST DISEASE

If patient developed chronic GVHD during a reporting period or follow up period, this form must be completed only if patient is not enrolled on ASCT0431.

Questions (Elements)	Valid Values	Rules and Validations	SDC Use Only
ASCT0631 Reporting Period:	[]–Reporting Period 1 (Day 0-60) []–Reporting Period 2 (Day 60-120) []–Reporting Period 3 (Day 120-200) []–Reporting Period 4: Follow-Up 1: 3 months []–Reporting Period 5: Follow-Up 2: 8 months []–Reporting Period 6: Follow-Up 3: 1 year []–Reporting Period 7: Follow-Up 4: 2 years	1. This is a required field.	ASCT0631ReportingPeriod
Date of Onset of Chronic GVHD (MM/DD/YYYY)	MM/DD/YYYY	1. This is a required field. 2. Must be less than or equal to today's date. 3. Date must be greater than or equal to the date of enrollment.	OnsetChcGVHDDt
Maximum grade of chronic GVHD: Note: limited chronic GVHD is not equivalent to mild extensive chronic GVHD. For details regarding organ involvement, please see Appendix III of the protocol.	[] –Limited: Localized skin involvement and/or liver dysfunction or involvement of only one target organ [] –Extensive: (a) Generalized skin involvement ≥ 50% of body surface area or (b) Localized skin involvement and/or liver dysfunction plus at least one of the following: • Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis • Eye involvement (Schirmer's test with < 5 mm wetting) • Involvement of minor salivary glands or oral mucosa on lip biopsy • Involvement of any other target organs or (c) Involvement of at least two target organs	1. This is a required field.	MaxChcGVHDGd2Tp

Comments			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631: Recipient and Donor Adverse Event Form

If an adverse event can not be coded by the CTC AE v. 3, it is not a toxicity that needs to be reported. A pre-existing condition is defined as any condition exhibited by the patient that can be coded and graded using the CTC AE version 3.0 prior to the date of treatment start. All deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution, must be reported via AdEERS. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via AdEERS.

DONOR REPORTING REQUIRMENTS:
Report all grades of adverse events the donor experiences on this form.

FOR DONOR PAIN EVENTS ONLY, SUBMIT A SEPARATE ADVERSE EVENT FORM TO REPORT A CHANGE IN GRADE.
If the donor experiences a change in the grade of their pain between 4 days prior to, and 48 hours following bone marrow harvest, please report this as a separate adverse event.

Example: If donor experiences grade 3 pain on day 2 prior to bone marrow harvest and donor's pain increases to grade 4 24 hours following bone marrow harvest, please be sure to report this as a separate adverse event.

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
Serial #: Automatically assigned by the system.		1. This is a required field.	SerialNumber
Which study participant experienced an adverse event?	[] – Recipient [] – Donor	1. This is a required field	PtptExprAeTp
For recipients only, **ASCT0631 Reporting Period:**	[] –Conditioning Regimen and Transplant [] –Reporting Period 1 (Day 0-60) [] –Reporting Period 2 (Day 60-120) [] –Reporting Period 3 (Day 120-200) [] –Reporting Period 4: Follow-Up 1: 3 months	1. If recipient experienced an adverse event, this is a required field. 2. If recipient did not experience an adverse event, this must not be answered.	ASCT0631Reporting Period

CTCAEv3.0 Adverse Event(- Select) TYPE Please select the applicable CTCAE v.3 Adverse Event Help Document	Please select from the drop down menu	1. This is a required field.	CTCAEv30AESelTYPE
If other (e.g. pain, other) is selected above, please specify here. **Specify adverse event:**	Text	1. If other specify is selected, this is a required field. 2. If other specify is not selected, this must not be answered.	SpfAeTxt
CTC Adverse Event Grade:	[]- 1 Mild []- 2 Moderate []- 3 Severe []- 4: Life threatening or Disabling []- 5: Death	1. This is a required. 2. If donor then grade can be 1, or 2 or 3 or 4 or 5 can be selected for the donor. 3. If recipient then grade can be either 3 or 4 or 5.	CTC_AE_GD
CTC Adverse Event Attribution:	[] - Definite [] - Possible [] - Probable [] - Unlikely [] - Unrelated	1. This is a required field.	CTC_AE_ATTR_SCALE
Adverse Event Onset Date (MM/DD/YYYY):	MM/DD/YYYY	1. This is a required field 2. Date must be greater than or equal to enrollment date 3. Date must be less than or equal to today's date.	CTC_AE_ONSET_DT
Has an AdEERs report been filed? Recipient Requirements: Code only for Grade 4 and 5 adverse events or for any adverse event for which an AdEERs is filed	[] – No [] – Yes	1. This is a required field.	AdEERSRptFld

for recipient. Donor Requirements: Please refer to section 12.5 Donor-Related Adverse Event Reporting Requirements of the protocol for details.			
If AdEERs report was filed provide the **AdEERs ticket number:** AdEERs reports are to be submitted one per course. If a report was filed for a given course, and subsequent information is found that was not on the initial report, please amend the report. Please do not fill out a new AdEERs report.		1. If an AdEERs is filed, this is a required field. 2. If an AdEERs was not filed, this must not be answered.	AdEERsTktNbr
Comments:			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC			
Statistician			
PC			
Reference Lab			
Study Chair			
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 Follow Up

Questions (Elements)	Valid Values	Rules & Validations	SDC Use Only
Serial Number: Automatically assigned by the system		1. This is a required field.	SerialNumber
ASCT0631 Reporting Period:	[]–Reporting Period 4: Follow-Up 1: 3 months []–Reporting Period 5: Follow-Up 2: 8 months []–Reporting Period 6: Follow-Up 3: 1 year []–Reporting Period 7: Follow-Up 4: 2 years []–Reporting Period 8: Follow-Up 5: 3 years []–Reporting Period 9: Follow-Up 6: 4 years []–Reporting Period 10: Follow-Up 7: 5 years	1. This is a required field.	ASCT0631Reporting Period
Follow-up start date: (MM/DD/YYYY) This date should match the Reporting Period End Date of the previous reporting period or follow-up period.	MM/DD/YYYY	1. This is a required field 2. Date must not be greater than enrollment date. 3. Must be in date format. 4. Date must less than or equal to today's date. 5. Date must less than or equal to follow up end date.	FuSttObvEvlDt
Follow-up end date: (MM/DD/YYYY) Date patient's status last known.	MM/DD/YYYY	1. This is a required field. 2. Must be in date format. 3. Date must less than or equal to today's date. 4. Date must greater than or equal to follow up start date.	FuEndObvEvlDt
Vital Status: If patient died, the end date of this follow-up period is the patient's death date. Submit the death form.	[] – Alive [] – Dead	1. This is a required field.	PT_VST

Was the patient's disease status evaluated during this reporting interval? The medical record should contain evidence of an evaluation during this period.	[] - Yes [] - No [] - Unknown	1. This is a required field.	DszStEvlTrp
If patient's disease status was evaluated during this follow up period, record the **Date of evaluation: (MM/DD/YYYY)**	MM/DD/YYYY	1. If yes to patient disease evaluation, this is a required field. 2. If no or unknown to patient disease evaluation, this must not be answered. 3. Must be in date format. 4. Date must be within follow up start and end dates.	EvaluationDate
If disease status was evaluated, **Did patient relapse or progress during the indicated period?** If patient relapsed during this follow-up period, please fill out the relapse/progression form.	[] –Yes [] –No	1. If disease status was evaluated, this is a required field. 2. If disease status was not evaluated, this must not be answered.	RlpPrgIPrd
During the 1st and 2nd year of follow-up, **Did patient develop chronic graft versus host disease (cGVHD)?** If yes, please complete chronic GVHD form.	[] –Yes [] –No [] –Not Available	1. If reporting period 4, 5, 6 or 7 then, this is a required field. 2. If reporting period is not 4, 5, 6 or 7 then, this must not be answered.	DevCGVHD

Did the patient withdraw consent for follow-up at the end of the reporting period? Note: Withdrawal of consent is to be coded only when the patient no longer wants to participate in the study and asks data no longer be submitted. If the patient withdraws consent, then the date of the end of the reporting period is the date consent was withdrawn.	[] – No [] – Yes	1. This is a required field.	PT_FOL_CON_WIT_IND2
Was the patient confirmed lost to follow-up at the end of this reporting period? If the patient is declared lost to follow-up, the end date of this reporting period should be the date of last patient contact.	[] – No [] – Yes	1. This is a required field.	PtConfLTFUThisRpt Perio
Was the patient enrolled on another COG therapeutic study at the end of the reporting period?	[] – Yes [] – No [] –Unknown	1. This is a required field.	PtEnrollonDiffCOGTx Stu
Has a new primary cancer or MDS been diagnosed that has not been previously reported? If yes, please fill out the Second Malignant Neoplasm form.	[] – Yes [] – No [] –Unknown	1. This is a required field.	NEW_CA_DX_IND3
Comments			RSCH_COMMENTS _TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC			
Statistician			
PC			
Reference Lab			
Study Chair			
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 Relapse/Progression

Questions (Elements)	Valid Values	Rules and Validations	FOR SDC USE ONLY
ASCT0631 Reporting Period:	[]–Conditioning Regimen and Transplant []–Reporting Period 1 (Day 0-60) []–Reporting Period 2 (Day 60-120) []–Reporting Period 3 (Day 120-200) []–Reporting Period 4: Follow-Up 1: 3 months []–Reporting Period 5: Follow-Up 2: 8 months []–Reporting Period 6: Follow-Up 3: 1 year []–Reporting Period 7: Follow-Up 4: 2 years []–Reporting Period 8: Follow-Up 5: 3 years []–Reporting Period 9: Follow-Up 6: 4 years []–Reporting Period 10: Follow-Up 7: 5 years	1. Required field	ASCT0631ReportingPeriod .
Date of Relapse or Progression: Date (MM/DD/YYYY) of relapse or progression on this study.	MM/DD/YYYY	1. Required field. 2. Must be in date format 3. Must be greater than or equal to enrollment date 4. Must be less than or equal to today's date	RelapseorProgressionDA
Site(s) of relapse Check all that apply	[] – Bone Marrow [] – CNS [] – Testicular [] – Other site, specify	1. Required field.	LeukemiaRelapse1SITE
If other site of relapse, please **Specify other:**	Text	1. If other site, specify is selected, this is a required field 2. If not equal to other site, specify, this must not be answered.	OtherSpecify1TEXT
Was relapse/progression confirmed by institutional pathology review?	[] – Yes [] - No	1. Required Field.	SpcDocRpCfmPthTP
If yes to the question above, **ICD-O V3 site code (topography):** Check all that apply.		1. If relapse/progression was confirmed pathologically, this is a required field. 2. If relapse/progression was not confirmed pathologically, this must not be answered.	Tpo3
Comments			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631: SMN

Please remember to enter this information in the registry as well. If applicable, please submit this form during protocol therapy and/or while in follow-up.

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
Serial #: Automatically assigned by the system.		1. Required field	SerialNumber
ASCT0631 Reporting Period:	[]–Reporting Period 1 (Day 0-60) []–Reporting Period 2 (Day 60-120) []–Reporting Period 3 (Day 120-200) []–Reporting Period 4: Follow-Up 1: 3 months []–Reporting Period 5: Follow-Up 2: 8 months []–Reporting Period 6: Follow-Up 3: 1 year []–Reporting Period 7: Follow-Up 4: 2 years []–Reporting Period 8: Follow-Up 5: 3 years []–Reporting Period 9: Follow-Up 6: 4 years []–Reporting Period 10: Follow-Up 7: 5 years	1. Required field	ASCT0631Reporting Period
New Cancer Diagnosis Date MM/DD/YYYY format. If SMN is acute myelogenous leukemia or myelodysplastic syndrome (MDS), submit the NCI secondary AML/MDS form, cytogenetics and pathology reports.		1. Required field. 2. Must be less than or equal to today's date and greater than or equal to the enrollment date.	NEW_CA_DX_DT
New Cancer Diagnosis ICD-O Code ICD-O Morphology code.		1. Required field.	NwCanIcdoM
New Cancer Site ICD-O Code ICD-O Topography code.		1. Required field.	NwCanStIcdoT
Comments:			RSCH_COMMENTS_TXT

ASCT0631 DEATH

This form is to be submitted if a death occurred during a reporting period or a follow-up period.

Question (Element)	Valid Value	Rules and Validations	For SDC USE ONLY
ASCT0631 Reporting Period:	[]- Conditioning Regimen and Transplant [] –Reporting Period 1 (Day 0-60) [] –Reporting Period 2 (Day 60-120) [] –Reporting Period 3 (Day 120-200) []–Reporting Period 4: Follow-up 1; 3 months []–Reporting Period 5: Follow-Up 2: 8 months []–Reporting Period 6: Follow-Up 3: 1 year []–Reporting Period 7: Follow-Up 4: 2 years []–Reporting Period 8: Follow-Up 5: 3 years []–Reporting Period 9: Follow-Up 6: 4 years []–Reporting Period 10: Follow-Up 7: 5 years	1. This is a required field	ASCT0631Reporting Period
Which patient died?	[] – Recipient [] – Donor	1. This is a required field.	PtptDiedTp
Date of Death: (MM/DD/YYYY)	MM/DD/YYYY	1. This is a required field. 2. Must be less than or equal to today's date. 3. Date must be greater than or equal to the date of enrollment.	DeathDATE
Primary Cause of Death: If primary cause of death was due to GVHD Prophylaxis, “protocol treatment” must be	[] – Due to secondary or other malignancy [] – Due to protocol treatment [] –Idiopathic Pneumonia Syndrome (IPS) [] –Transplant Associated Microangiopathy (TAM) [] –Other transplant related toxicities, specify [] – Disease Relapse/Progression [] – Graft Versus Host Disease (GVHD)	1. This is a required field.	PmyCzDthDueToTp

selected.	[] – Hepatopathy (VOD) [] – Unknown [] – Other, specify		
If “other, specify” or “other transplant related toxicities, specify” is selected above, describe the cause of death not listed among the choices. **Describe cause of death**	Text	1. If “other, specify" or “other transplant related toxicities, specify” is selected above, this is a required field. 2. If “other, specify” or “other transplant related toxicities, specify” is not selected, this must not be answered.	PT_DEATH_SPEC
Contributing cause(s) of death: Check all that apply.	[] – Due to secondary or other malignancy [] – Due to protocol treatment [] –Idiopathic Pneumonia Syndrome (IPS) [] –Transplant Associated Microangiopathy (TAM) [] –Other transplant related toxicities, specify [] – Disease Relapse/Progression [] – Graft Versus Host Disease (GVHD) [] – Hepatopathy (VOD) [] – Unknown [] –None [] – Other specify	1. This is a required field. 2. If “None” is selected, another reason cannot also be selected. 3. If answered, contributing cause of death cannot be the same as primary cause of death.	CbtCzDthDueToTp
If “other, specify” or “other transplant related toxicities, specify” is selected above, describe the cause of death not listed among the choices. **Describe cause of death**	Text	1. If “other, specify" or “other transplant related toxicities, specify” is selected above, this is a required field. 2. If “other, specify” or “other transplant related toxicities,	PT_DEATH_SPEC_2

		specify" is not selected, this must not be answered.	
Autopsy? Performed? If yes, please submit report when available and if required by the protocol.	[] – Yes [] – No [] –Unknown	1. This is a required field.	A_PERF_IND3
How were the side effects of protocol therapy related to the patient's death?	[] – Not related [] – Minor contribution to death [] – Major contribution to death [] – Exclusive cause of death	1. This is a required field. 2. If primary cause is answered as "due to protocol treatment", then this question should not be answered as "not related".	DEATH_PROT_ATTR_TP
Comments:			RSCH_COMMENTS_TXT

Role	Read (View)	Write (Add)	Edit
CRA	x	x	x
PI	x	x	x
Treating Physician			
RC	X	X	X
Statistician	X		
PC			
Reference Lab			
Study Chair	X		
Nursing			
Study Cardiologist			
Study Pathologist			
Study Cytogeneticist			

ASCT0631 Study Eligibility Review

This form must be completed for all patients enrolled on Phase I and II studies and select Phase III studies.

Questions (Elements)	Valid Values	Rules and Validations	FOR SDC USE ONLY
Is the patient eligible?* If eligibility status cannot be confirmed, please select "No".	[] - Yes [] – No	1. Required field 2. If no, send e-mail to notify (RC, Stat, etc.).	EligPtTc
If no, **Reason patient did not meet eligibility criteria:** Check all that apply	[] – Disease type / histology [] – Organ function requirements [] – Patient characteristics (e.g., age, performance status, etc.) [] – Prior therapy [] – Stage, extent of disease [] – Timing of enrollment [] – Timing of start of protocol therapy [] – Other , specify	1. If yes above, must be blank 2. If no above, must be answered	RsnNtMecTpTP
Other, specify:		1. If "other, specify" above, must be answered 2. If not "other, specify" above, must be blank	OTHER_SPECIFY2035188
If no, **Source of information:**	[] – Audit [] – Central review (surgery, pathology, etc.) [] – Institutional report [] – Other, specify	1. If yes above, must be blank 2. If no above, must be answered	InfoSourceTp
Other, specify:		1. If "other, specify" above, must be answered 2. If not "other, specify" above, must be blank	OTHER_SPECIFY2035188_1
Comments:			RSCH_COMMENTS_TXT

Study chair (co- and vice-chair included) and study statistician have add/edit/read access. RC has read access.

Single-iteration form