BMT CTN 1205

Easy-to-Read Informed Consent (ETRIC) for Hematopoietic Cell Transplantation Clinical Trials

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BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

Easy-to-Read Informed Consent (ETRIC) for Hematopoietic Cell Transplantation Clinical Trials

BMT CTN PROTOCOL 1205
Version 5.0

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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 1205

Easy-to-Read Informed Consent (ETRIC) for Hematopoietic Cell Transplantation Clinical Trials

Study Chairs: Navneet S Majhail, M.D., M.S.
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Study Design: This study will be conducted as a supplement to the BMT CTN 1101 and 1301 clinical trials. Note that the BMT CTN 0901 trial and BMT CTN 1203 trial were removed as parent trials due to their closure on April 18, 2014 and May 13, 2016, respectively. The study has two parts:

(1) **Randomized Study:** Randomized, multicenter, prospective comparative study of ETRIC or standard consent form to improve patient comprehension of BMT CTN parent clinical trials. Patients who are being considered for one of the clinical trials will be approached, and on providing verbal consent to 1205, will be randomized to and will undergo the consent process for the parent trial using either ETRIC or standard consent form. Assessments will be conducted for patient comprehension of the clinical trial and satisfaction and anxiety related to the consent process.

(2) **Evaluation Study:** To understand barriers to implementation of ETRIC, site visits to 9 transplant centers participating in the BMT CTN parent studies will be conducted with semi-structured interviews of IRB administrators, site protocol investigators, and study coordinators. Sites will include centers that are participating and are not participating in the ETRIC study.

Primary Objective: Primary objective of the randomized study is to compare objective comprehension scores on the Quality of Informed Consent (part A) instrument between patients randomized to the ETRIC versus the standard consent arms.

Secondary Objectives: Secondary objectives of the randomized study are to compare the following measures between the two arms: (1) subjective comprehension scores on the Quality of Informed Consent (part B) instrument and the modified Deaconess Informed Consent Comprehension Test instrument, (2) state anxiety scores on State Trait Anxiety Inventory instrument, (3) satisfaction scores, (4) time taken for information location, and (5) patient consent rates on parent clinical trials.

Eligibility: Inclusion and exclusion criteria for the ETRIC study will be the same as the eligibility criteria for the BMT CTN parent studies. Additional inclusion criterion specific for the ETRIC study will include:

1. Adult patients (≥ 18 years)
2. Speaking and reading proficiency in English
3. Willing and able to provide informed consent for the ETRIC study
4. Stated willingness to comply with study procedures and reporting requirements

Study Interventions: Each ETRIC form for the parent protocols will have a two-column format with specific attention towards enhancing readability and processability including layout, organization of content, typography, and using plain language.

The standard consent form for the parent protocols will have a single column format and will lack the formatting and readability enhancements of the ETRIC form.

The content of both forms will be similar and both will contain all federally required elements for informed consent. Individual clinical trial sites will be allowed to make modifications to the ETRIC and the standard consent forms to meet requirements of their local IRBs. The protocol team will ensure that any such modifications to the ETRIC form conform to the easy-to-read format.

Accrual Objective: 198 patients will be randomized 1:1 between the two study arms for the randomized study.

Accrual Period: 3 years for the randomized study.

Study Duration: For the randomized study, assessments will occur within 7 business days of the consent discussion for the parent studies. No subsequent patient followup is planned for this study.

Statistical Issues: For the randomized study, patients will be randomized 1:1 between the ETRIC and standard consent arms. A total of 198 patients will be accrued in this study (99 in each arm), which will allow detection of a 0.5 standard deviation difference with 80% power in the mean Quality of Informed Consent part A comprehension scores between the two study arms.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

Informed consent is essential to the ethical conduct of research. Research shows that participants who better comprehend the studies in which they participate have better protocol adherence and less attrition.[1,2] However, many clinical trial participants have misconceptions about the trials in which they are participating, including overestimation of benefits, underestimation of the unproven nature of the study intervention, and failure to recognize the primary purpose of the trial.[3-7] In a study of 207 adults who were queried shortly after cancer clinical trial enrollment, Joffe et al. found that 74% did not recognize non-standard treatment, 70% were not aware of the unproven nature of the treatment, 63% did not recognize the potential for incremental risk from participation, 29% did not recognize the uncertainty of benefits to self, and 25% did not understand that trials are done mainly to benefit *future* patients.[5]

While consent is an ongoing process that includes more than just the written consent form, the form continues to be a key component of the process. Consent forms, especially for cancer clinical trials, have become longer and more complex which can compromise patient comprehension.[8-10] This is described as a conflict between completeness and comprehensibility. As consent forms become longer and more complete, they also become less comprehensible.[11] Indeed, patient inability to understand complex treatment protocols is partly blamed for the very low accrual rates on cancer clinical trials.[12,13] Patient comprehension of the consent form depends on many factors. Health literacy level may be a major determinant of patients' ability to understand most informed consent forms and to participate in the decision-making process.[14,15] Federal requirements state that information must be understandable to participants, yet studies indicate that most informed consent forms are complicated to the point that the average person in the United States is likely to find them difficult to read.[10] Failure to provide information in a way that is understandable precludes adherence to the principle of respect for persons, described in the Belmont Report as demanding that "subjects enter into the research voluntarily and with adequate information."[16]

1.1. Informed Consent in HCT Clinical Trials

The informed consent process for clinical trials in hematopoietic cell transplantation (HCT) entails unique challenges. HCT is a highly specialized and sophisticated medical treatment. It is usually offered to patients with very high risk hematologic cancers (e.g., leukemia, lymphoma, and myeloma) and non-malignant disorders (e.g., aplastic anemia, inherited metabolic, and immune deficiency diseases), where the alternative is a high probability of mortality due to the underlying disease. These diseases themselves are not common and patients must cope with trying to understanding the esoteric and frightening disorder with which they are afflicted as well as understanding treatments (both on and off trials) that are outside the average person's zone of medical familiarity. HCT increases the chances of survival, but at the same time can be associated with complications that by themselves cause significant morbidity and mortality. In fact, depending on the underlying disease and transplant type, treatment related mortality rates in the first 3 months after HCT range from 5-50%.[17] The complexity of the transplantation

processes, procedures, and toxicities is difficult to explain at the "layperson level", even without the added nuances of research and study specific details (e.g., randomization, multiple study arms). Patients often face the dilemma of being confronted by a life-threatening illness and having to rapidly assimilate a large amount of unfamiliar and highly complex medical information that is conveyed in the ambiguous language of risk and probability. Stress caused by disease severity, the urgency to move ahead with treatment, and persistent cognitive effects of illness and treatment may interfere with their ability to fully understand the information provided to them. Furthermore, a patient may be eligible for several different types of transplant treatments, each with a different toxicity profile, adding an additional level of complexity to their decision making process. Also, research advances have led to rapid changes in transplant technology and practice, and patients may find it challenging to weigh the risks and benefits of experimental innovative therapy in comparison to standard but relatively new transplant treatments. Finally, it is sometimes difficult to distinguish risk inherent to the HCT procedure itself, whether applied on or off trial, from the potential incremental risk associated with a particular trial. Patients may refuse participation in a trial because they may fear these risks, even though the risks will be present if they receive HCT as standard of care.

Despite these known challenges, very little research has been done to address and increase patient comprehension and satisfaction with the informed consent process in HCT clinical trials.[18,19] To study the complex ethical issues arising in this setting, Stevens and Pletsch interviewed 12 mothers whose children with leukemia had participated in HCT clinical trials to evaluate their experience with the informed consent process.[19] The mothers identified four themes in explaining their experiences when faced with questions of enrolling their children in clinical research. First, the presence of a life-threatening disorder impacts the context in which consent is considered – mothers struggled with research consent when their children were desperately ill and could not adequately analyze the purpose, procedures, risks, and benefits of the proposed research or perceive alternatives available to them. The second theme was the effect of mothers' own emotional trauma on their ability to absorb and understand information provided during the consent process. The third theme was the pressure of needing to make a quick decision because of the urgency to begin treatment. The last theme was the burden of responsibility *after* consenting to research involving their children. Although this study did not address issues specifically related to the consent form, the authors suggested simplifying the consent process as one intervention to increase parents' comprehension of HCT clinical trials.

It seems reasonable that improved presentation of risks and benefits in a more understandable fashion would improve that consent process for HCT trials. We propose a study of a novel, easy-to-read informed consent (ETRIC) form to increase patient comprehension and satisfaction and decrease anxiety related to the consent process for participation in HCT clinical trials conducted through the BMT CTN. Better understanding of the clinical trial and the risks and benefits associated with participation will certainly allow better adherence to the ethical principle of respect for persons and may translate to higher consent and participation rates on BMT CTN clinical trials. Furthermore, conduct of this study within the BMT CTN, the largest cooperative network for HCT research in the country, will facilitate dissemination of the intervention if it is proven effective and therefore ensure that the intervention has a major impact on the conduct of HCT clinical trials.

1.2. Development of ETRIC Form for the BMT CTN

Recognizing the need for shorter and less complicated informed consent documents, the NCI, along with the Office of Human Research Protections and the US Food and Drug Administration, presented "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" in 1998.[20] The recommendations and suggested templates shortened and simplified the informed consent forms, made them easier to understand, and incorporated federally required elements of informed consent. However, they did not provide recommendations on best practices for legible document design. To improve comprehension, experts suggest that both readability (reading level) and processability (incorporation of explicit information, layout, mental images, and context) of informed consent documents must be improved.[21,22] Furthermore, research shows that even 15 years since their publication, the guidelines are not followed universally and consent forms for a large proportion of cancer clinical trials continue to be lengthy, complex, and written at a higher than recommended grade level; both investigator- and IRB-level barriers contribute to this.[8-10,23-25]

The BMT CTN has an established process to ensure that clinical trial informed consent forms meet the federal guidelines and include all required elements.[20] The National Marrow Donor Program's Patient Services department, which has expertise in health literacy, patient education, and patient advocacy, develops a template consent form for each trial in consultation with the protocol team and Data Coordinating Center staff. This template is distributed to participating centers for submission, with the protocol, to their IRBs. If a center must revise this form to meet local requirements (which is universally the case), the revised consent must be previewed by the Data Coordinating Center to ensure that all required elements are retained before submission to the local IRB. If the IRB requests additional changes, the final consent form must be again reviewed by the Data and Coordinating Center before it can be used.

An ad hoc task force was convened by the BMT CTN to address concerns that trial consent forms continued to be long and deficient in clarity and readability, even though they met all federal guidelines. The aim was to evaluate the prevalent format of BMT CTN consent forms and to provide recommendations for an easier-to-read informed consent template that followed evidence-based recommendations for readability and processability but still included all federally required elements for informed consent. Areas of expertise among task force members included IRB participation, research ethics, clinical trial design and conduct, health services research, medically underserved populations, health literacy and education, and patient advocacy. The task force performed a comprehensive literature search on adult literacy, patient education and readability, and informed consent and pediatric assent development. Clinical trial consent and assent forms for previous BMT CTN clinical trials were reviewed for completeness, readability, length, and format. Feedback was obtained from BMT CTN investigators and trial sites and their IRBs. The task force created a template for the ETRIC form (published recommendations are summarized in Table 1-2).[26]

Table 1-2. Summary of BMT CTN task force recommendations for ETRIC form

Layout
- Use a two-column format
- Limit characters/line
- Balance white space with text and graphics
- Keep headers as close to text as possible
- Leave left margins justified and right margins ragged
- Make headings 1-2 font size larger than the body text

Organization
- Sequence of information should mirror the reader's mental process and concerns
- Include important information near the beginning
- Use simple headers to break up text

Typography
- Prefer serif fonts for text
- Prefer sans-serif fonts for section headers
- Use 11-13 point size; vary text size among fonts

Plain Language
- Reading level should be eighth-grade or lower
- Keep paragraphs short; convey one idea per paragraph
- Keep sentences short, simple and direct
- Break up long sentences into bulleted lists
- Use verbs in active voice
- Use words that are familiar to the reader
- Keep words and terminology consistent throughout the document
- Use simple graphics that work with the text, are culturally relevant and reproduce well

Avoid
- Large blocks of print
- Underlining or italicizing blocks of text
- Stylized initial letters or all capitals
- Professional jargon
- Acronyms, symbols and abbreviations

One innovative feature of the ETRIC form is the layout of the consent document. The ability to locate information within a text is an essential consideration in comprehension and requires a series of distinct cognitive operations that are dependent on text features and layout.[15] A two-column text layout was recommended as it is more familiar to readers (e.g., similar to newspaper articles) and can facilitate information location within a text as readers can more effectively identify target words.[21,27-32] Based on studies of text legibility, layout, and design, recommendations were provided on the organization of text and typography and the use of plain language specifically targeting specialized terminology related to HCT.[27]

Institutional barriers to the implementation of the ETRIC form exist. Some investigators and IRBs are not willing to deviate from their standard formats for consent documents. In some instances, investigators have been reluctant to even submit the new format to their IRBs for fear of delaying the IRB approval process. In others, the IRB has refused to accept the new format. A strength of ETRIC is that it is a method that provides flexibility for varying requests from different IRBs, instead of a static format.

1.3. ETRIC vs. Other Interventions to Increase Comprehension of Cancer Trials

Flory and Emanuel conducted a systematic review of interventions to improve research participants' understanding in informed consent for biomedical research.[33] Only a few studies have investigated enhanced consent form interventions (e.g., shortening length, revising content, improving formatting, adding graphics) and their results were mixed, with some trials showing gain in understanding and others not. Very few studies included multicenter cancer clinical trials and no studies included HCT recipients.[27,34]

A study by the Eastern Cooperative Oncology Group randomized 44 clinical trial sites participating in lung and breast cancer trials (N=226 patients) to a standard consent form versus

an easy-to-read consent form with a modified layout where readability was adjusted to a 7th-8th grade level from a 12th-14th grade level.[27] Even though a 2-column format was not utilized in their study, their easy-to-read consent document was associated with reduced patient consent anxiety and increased satisfaction with the consent form, but not with improved patient comprehension. Their study did not include many individuals with low literacy levels, which was not unexpected as patients recruited onto clinical research studies tend to have higher levels of education than the general population. However, their results showed that the use of simpler materials does not offend well-educated participants and reduces anxiety for the population in general.

A second non-randomized study assessed comprehension after informed consent using either a standard Southwestern Oncology Group form (16th grade level) or a simplified booklet form (7th grade level) in 183 healthy participants and cancer patients.[34] A significantly larger proportion of participants preferred the simplified form to the standard consent form (62% vs. 38%; $P<0.01$) and found the simplified form easier to read (97% vs. 75%; $P<0.01$). However, the degree to which the participants understood the information in the two forms was similar (58% vs. 56%).

The available literature suggests that much more work is needed in improving the forms used for consenting patients for participation in cancer clinical trials. The current studies do not include the broad spectrum of patients being approached for such participation; there are *no* data in the multicenter HCT trial setting. The challenge will be to not only improve patient satisfaction, which the above two studies demonstrated to be possible, but also to improve understanding. We believe that the ETRIC form, with its novel readability and processability enhancements, has the potential to meet this important unmet need.

1.4. Summary of Background, Significance and Innovation

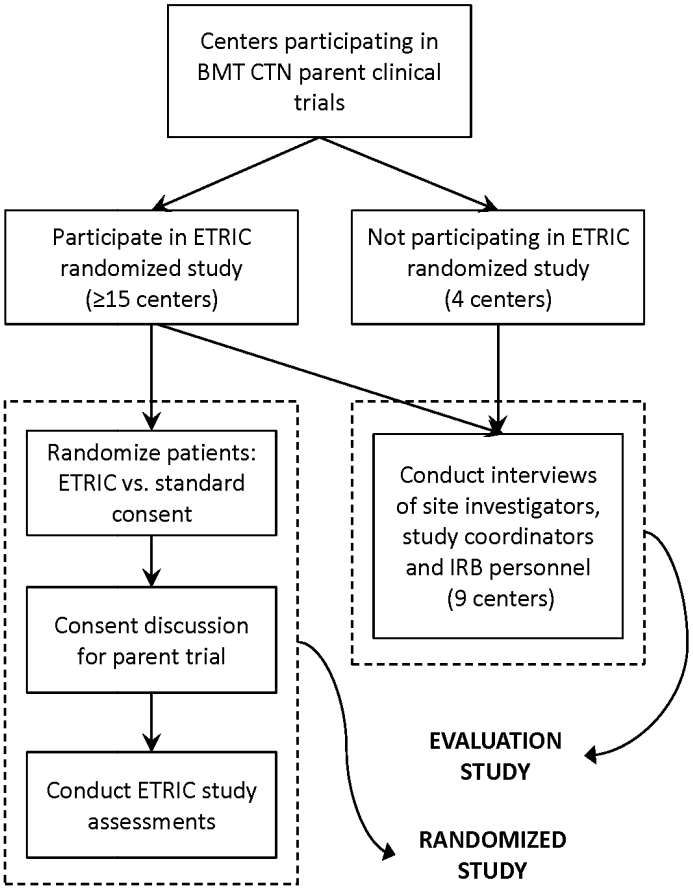
There is an urgent need to develop interventions that can increase patient comprehension of HCT clinical trials. This study hypothesizes that use of a novel evidence-based ETRIC form template with enhanced readability and processability components will be associated with higher levels of patient comprehension of BMT CTN treatment protocols than use of the existing standard institution-specific consent forms. Furthermore, the ETRIC form will be associated with lower anxiety and greater satisfaction with the consent process. Also, institutional barriers exist to the implementation of the ETRIC form and it is important to understand what these are so that they can be addressed effectively if this form is proved to be superior to standard forms. Using the platform of ongoing large, multicenter BMT CTN clinical trials, we propose a study of the effectiveness and acceptability of the ETRIC form that has the potential to change national consent practices in HCT clinical trials and to inform efforts to improve informed consent across the landscape of trials for cancer and other serious diseases. Also provided are important data to inform educational efforts at the institutional level to increase acceptance of new approaches to informed consent documents.

CHAPTER 2

2. STUDY DESIGN

The study has two parts: (1) **Randomized Study** to evaluate the effectiveness of ETRIC, and (2) **Evaluation Study** to understand barriers to implementation of ETRIC (Figure 2-1).

Figure 2-1. Study Schema



2.1. Randomized Study

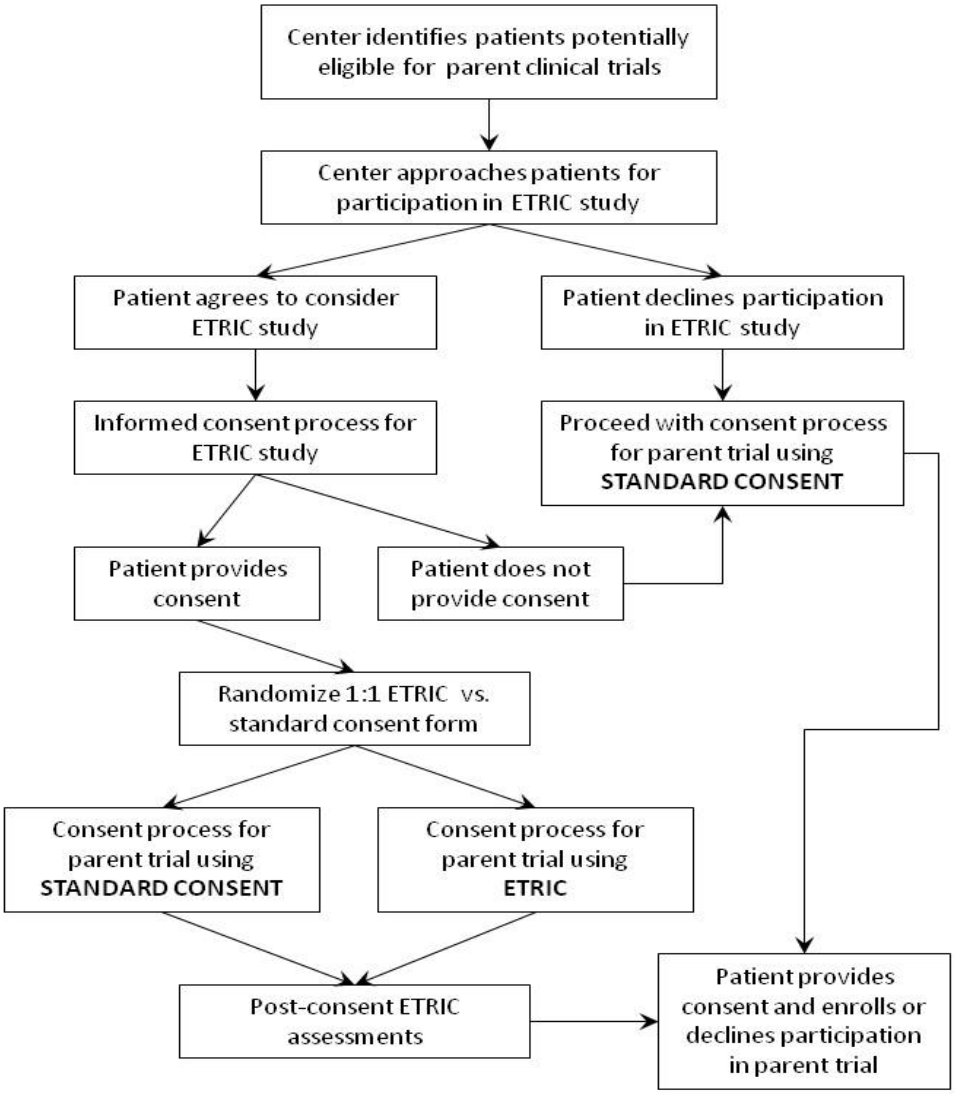
2.1.1. Study Overview

Randomized, multicenter, prospective comparative study of ETRIC or standard consent form to improve patient comprehension of HCT clinical trials.

A two-arm, randomized study will be conducted in patients about to undergo consent discussion for participation in a large, multicenter BMT CTN clinical trial. Once they agree to participate in this ETRIC study, they will go through the consent process for the parent trial using either a

standard or the ETRIC form. Note that the BMT CTN 0901 trial was removed as a parent trial due to its closure on April 18, 2014. The content of both forms will be similar but the ETRIC form will incorporate a two-column format with specific attention towards enhanced readability and processability. Following the consent discussion for the parent trial, patients will complete assessments of health literacy, comprehension of the parent trial, and satisfaction and anxiety related to the consent process. These assessments will be completed within 7 business days of the consent discussion. The schema for the randomized study is shown in Figure 2-2.

Figure 2-2. Schema for Randomized Study



2.1.2. Summary of the BMT CTN 1101 and 1301 Protocols

2.1.2.1. BMT CTN 1101 Protocol (Double Cord vs. Haplo)

BMT CTN 1101 study is a phase III, multicenter, randomized clinical trial investigating allogeneic HCT using one of two stem cell donor sources, unrelated double umbilical cord blood versus HLA-haploidentical related bone marrow, in patients with acute leukemia and lymphoma. The primary objective is to compare progression-free survival at 2 years between the two study arms. Overall survival, relapse, non-relapse mortality, complications, and quality of life are secondary endpoints. .

2.1.2.2. BMT CTN 1301 (CNI-Free)

BMT CTN 1301 study is a three arm randomized Phase III, multicenter trial comparing two calcineurin inhibitor (CNI)-free strategies for GVHD prophylaxis to standard calcineurin inhibitor tacrolimus and methotrexate (Tac/Mtx) in patients with acute leukemia or myelodysplasia undergoing myeloablative conditioning hematopoietic stem cell transplantation. The primary objective of the randomized trial is to compare chronic GVHD/relapse-free survival [CRFS] as a time to event endpoint after hematopoietic stem cell transplant (HSCT) between each of the CNI-free interventions and a Tac/Mtx control. Secondary objectives are: comparison of rates of grade II-IV and III-IV acute GVHD, chronic GVHD, chronic GVHD-free survival, immunosuppression-free survival at one year, neutrophil and platelet engraftment, disease relapse, transplant-related mortality, rates of Grade ≥ 3 toxicity; incidence of CMV and EBV reactivation, incidence of infections, immune reconstitution, quality of life and overall survival.

2.1.3. Rationale for Study Design

These BMT CTN multicenter clinical trials were selected based on their total accrual goal and current enrollment rates to use as a platform to conduct this randomized study. These trials were chosen to reflect common indications and/or complications of HCT and the diversity and complexity of transplant technologies and supportive care treatments. Random allocation to the two study arms will reduce selection bias and will ensure that socio-demographic factors (including education status and health literacy levels) and disease characteristics of patients are comparable. There is a potential that patients, if aware that they are on the ETRIC arm, may overestimate their comprehension and satisfaction scores and underestimate their anxiety levels.

2.1.4. Hypothesis and Study Objectives

The primary hypothesis is that the patients consenting using the ETRIC form will have higher levels of comprehension of BMT CTN transplant protocols and risks associated with participation in the trial compared to patients consented using standard consent forms. The secondary hypotheses are that patients using the ETRIC forms will have lower anxiety and greater satisfaction with the consent process.

2.1.4.1. Primary Objective

The primary objective of the study is to determine whether the ETRIC form increases patient comprehension of informed consent compared to the standard consent form for the BMT CTN

parent studies. This will be achieved by comparing patient comprehension scores on the Quality of Informed Consent (QuIC) Part A instrument between patients randomized to the two arms.

2.1.4.2. Secondary Objectives

The secondary objectives are to compare additional measures of comprehension and measures of patient anxiety, satisfaction, and information location between the two arms. Specifically, these will include subjective comprehension scores on the QuIC (Part B) instrument, comprehension scores on the modified Deaconess Informed Consent Comprehension Test (DICCT), state anxiety scores on the State Trait Anxiety Inventory (STAI), satisfaction scores, and time taken for information location. The study will also explore patient consent rates on parent clinical trials for the two arms.

2.1.5. Patient Eligibility Criteria

Inclusion and exclusion criteria for the ETRIC randomized study will be the same as the eligibility criteria for the BMT CTN parent studies. Additional inclusion criterion specific for the ETRIC study will include:

1. Adult patients (≥ 18 years).
2. Speaking and reading proficiency in English (as most of this study's instruments have not been translated and validated in languages other than English).
3. Willing and able to provide informed consent.
4. Stated willingness to comply with study procedures and reporting requirements.

2.1.6. Study Interventions

Patients will be randomized to either the ETRIC arm or the standard consent arm. The ETRIC consent form was developed by NMDP's Patient Services department, which has expertise in health literacy and in development of consent documents for clinical trials, in consultation with clinical trial protocol team. The ETRIC form has a two-column format with specific attention towards enhancing readability and processability including layout, organization of content, typography, and using plain language (Section 1.2). The standard consent form has a single column format and lacks the formatting and readability enhancements of the ETRIC form. For patients randomized to the standard consent arm, participating centers will be allowed to use the standard consent form they are presently using for consenting patients for the parent studies. The content of both forms are similar and both contain all federally required elements for informed consent. Individual clinical trial sites will be allowed to make modifications to the ETRIC and the standard consent forms to meet requirements of their local IRBs. The BMT CTN 1205 protocol team will ensure that any such modifications to the ETRIC form conform to the easy-to-read format.

2.1.7. Hematopoietic Cell Transplantation

The BMT CTN 1205 study is a non-therapeutic ancillary study. Patients will receive HCT and/or its associated treatments and supportive care as outlined in the BMT CTN parent protocols. In the event that a patient does not consent for participation in the BMT CTN parent trial, he/she will receive standard HCT and/or its associated treatments as recommended by his/her treating physician.

2.1.8. Study Risks and Benefits

Risks of study participation are expected to be minimal. Similarly, the study interventions are not expected to impact clinical outcomes. It is unknown whether study participants will experience any benefits.

2.1.9. Study Withdrawal

Subjects may be withdrawn from study participation if the treating physician believes it is in the patient's best interest.

2.2. Evaluation Study

2.2.1. Study Overview

For the evaluation study, site visits will be scheduled to 9 transplant centers to understand barriers to the implementation of the ETRIC form. This will include visits to 5centers that are participating in the randomized consent form study as well as another 4 trial sites that are not participating in the consent study but are enrolling patients on the BMT CTN parent clinical trials. This approach will provide us with a wide spectrum of procedures related to the consent process that are followed by trial sites and their IRBs.

At each site, we will conduct semi-structured interviews of IRB administrators, site protocol investigators, and study coordinators. Semi-structured interviews will last 30-45 minutes and will examine: (1) willingness to utilize and acceptability of ETRIC two-column format, (2) perceived barriers to implementation, (3) previous experience with alternative format informed consent forms or novel methods of obtaining consent, (4) perception of value of ETRIC, and (5) helpfulness of resources provided to facilitate implementation of ETRIC (e.g., quick reference resources for design and format elements, template with default settings for format and design, additional resources for design support, educational resources for IRB and protocol team members, BMT CTN recommendations).

Qualitative analyses will be conducted to identify themes representing facilitators and barriers to the local implementation of the ETRIC form. Other methods to conduct interviews (e.g., telephone interviews) were considered. However, face-to-face interviews have certain advantages. First, high unit and item response rates, valid data and detailed information can be captured by face-to-face interviews because longer interviews can be conducted and support can be provided by interviewers as they observe non-verbal expressions of respondents.[35,36] Also, we would like the interview participant to give feedback on specific elements of the ETRIC form

which would be easier with the face-to-face interview than a telephone interview given the length of the consent forms and range of familiarity with the ETRIC form.

2.2.2. Center Selection Criteria

All centers participating in the BMT CTN parent clinical trials will be eligible to participate in the evaluation study. The BMT CTN 1205 (ETRIC) study protocol team will invite centers to participate in this study based on center interest and accrual rates on the parent BMT CTN clinical trials.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Study Endpoints for Randomized Study

The instruments that will be used for study assessments are described in Section 4.4.

3.1.1. Primary Endpoint

The primary endpoint objective of this study is to compare objective comprehension scores on the QuIC Part A instrument between patients randomized to the ETRIC and the standard consent arms.

3.1.2. Secondary Endpoints

The secondary endpoints will compare the following measures between the two arms: (1) subjective comprehension scores on the QuIC (part B) instrument and the modified DICCT instrument, (2) state anxiety scores on STAI instrument, (3) satisfaction scores, (4) time taken for information location, and (5) patient consent rates on parent clinical trials.

3.2. Study Endpoints for Evaluation Study

For the evaluation study, using qualitative research methods (semi-structured interviews), the study will determine: (1) willingness to utilize and acceptability of ETRIC two-column format, (2) perceived barriers to implementation, (3) previous experience with alternative format informed consent forms or novel methods of obtaining consent, (4) perception of value of ETRIC, and (5) helpfulness of resources provided to facilitate implementation of ETRIC (e.g., quick reference resources for design and format elements, template with default settings for format and design, additional resources for design support, educational resources for IRB and protocol team members, BMT CTN recommendations).

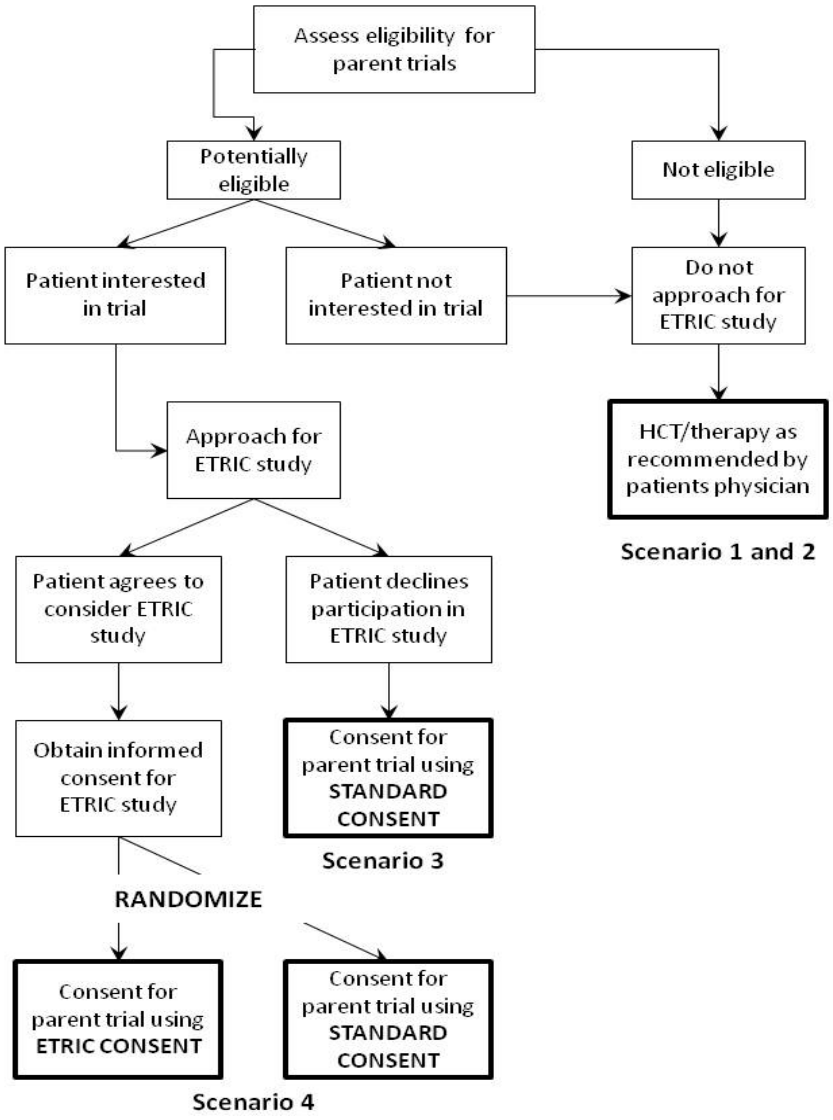
CHAPTER 4

4. PATIENT REGISTRATION AND ENROLLMENT FOR RANDOMIZED STUDY

4.1. Approaching Patients, Eligibility Screening and Obtaining Consent

Subjects may be approached for enrollment on the ETRIC protocol once they have been identified as potential participants for the BMT CTN 1101 or 1301 studies. Note that the BMT CTN 0901 trial and BMT CTN 1203 trial were removed as parent trials due to their closure on April 18, 2014 and May 13, 2016, respectively, and no further patients will be enrolled from these studies. The following scenarios regarding eligibility/participation in the ETRIC study can occur (Figure 4-1):

Figure 4-1. Possible Scenarios for Patient Registration



1) Scenario 1: On patient assessment, he/she is not found to be eligible for the parent trial. In this case, the patient would not be approached for participation in the BMT CTN 1205 (ETRIC) randomized study. He/she will proceed with HCT or other treatments as recommended by his/her physician.
2) Scenario 2: On patient assessment, he/she is found to be potentially eligible for the parent trial. However, on approaching the patient for the study, he/she indicates no interest in participation or going through the consent process. He/she will proceed with HCT or other treatments as recommended by his/her physician.
3) Scenario 3: On patient assessment, he/she is found to be potentially eligible for the parent trial and is interested in proceeding with the consent process for the study. Once patient expresses interest in the parent study, he/she will be approached for participating in the

BMT CTN 1205 (ETRIC) study. In this case, patient declines participation in the BMT CTN 1205 (ETRIC) study, and he/she will proceed with the consent process for the parent trial using their standard consent form.

4) Scenario 4: On patient assessment, he/she is found to be potentially eligible for the parent trial and is interested in proceeding with the consent process for the study. Once patient expresses interest in the parent study, he/she will be approached for participating in the BMT CTN 1205 (ETRIC) study. In this case, patient agrees to participate in the BMT CTN 1205 (ETRIC) study. He/she will be randomized and will undergo consent discussions for the parent study using either the ETRIC or the standard consent forms.

In case a patient consents to and is enrolled on the BMT CTN 1205 (ETRIC) study, and then subsequently is found to not meet the eligibility criteria for the parent study (prior to the consent discussion for the study), he/she will be removed from the BMT CTN 1205 (ETRIC) study (this situation would be similar to Scenario 1 above). No ETRIC assessments will be conducted for such patients.

Patients who agree to participate in the BMT CTN 1205 (ETRIC) study, and then go through the consent process for but decline participation in or are later found ineligible for the parent study, will continue on the BMT CTN 1205 (ETRIC) study. They will be asked to complete all the assessments for the BMT CTN 1205 (ETRIC) study even though they do not proceed onto the parent study.

Transplant physicians or other center staff will evaluate patient eligibility for enrollment for the BMT CTN 1205 (ETRIC) study. Eligibility criteria will be verified and ineligible patients will proceed off study and no further study procedures will be conducted. Eligible patients willing to potentially participate in the BMT CTN 1205 (ETRIC) study will have a thorough discussion about the protocol with an investigator, a sub-investigator, clinical research nurse, or research coordinator. If necessary, this discussion may take place by telephone. During the discussion, the purpose of the study and study procedures will be presented as objectively as possible, and the potential benefits and risks of participation will be explained. Patients will be registered through EMMES AdvantageEDC^{SM} (Electronic Data Capture, an Internet-based data entry system).

4.2. Study Registration and Randomization

Once the subject is deemed eligible, has given informed consent, and the transplant center has confirmed patient eligibility, randomization occurs. A subject may be randomized on to one of two arms: ETRIC vs. standard consent.

4.3. Consent

Given the number of consents and randomization conversations subjects will encounter, the randomized portion of the ETRIC study will seek a waiver of the requirement to document consent from the IRBs of participating sites according to the requirements of the Common Rule (Section 46.117(c)(2)) (also see Appendix A). This does not mean that informed consent will not occur but rather that informed consent process will be verbal and subjects will neither read nor sign an informed consent form. Specific items will still need to be addressed in the consent

conversation as required by the federal regulations, as shown in the consent script (Appendix D). Subjects will be given a written information sheet about the BMT CTN 1205 (ETRIC) study that addresses all required elements of informed consent (Appendix E). Additionally, a sample letter to the participating site's IRB requesting a waiver from the requirement to document consent is attached as Appendix C. The Principal Investigator or his/her designee at each transplant center will contact the candidates to enroll them onto the study. The study coordinator at each center will provide the patient with information about the purpose of the study and obtain verbal consent, either in person or over the phone. The date of verbal consent will be recorded and saved in the patient's study file.

4.4. Patient Assessment

4.4.1. Study Assessments

Table 4-4-1 describes the patient reported assessments that will occur as part of the BMT CTN 1205 (ETRIC) study. All assessments will occur at one time – within 7 business days of consent discussion for the parent trial. These assessments will be conducted in addition to other assessments being performed for the parent trials and any other ancillary studies in which the patient might be participating. (Note, there are no patient reported assessments for the 1203 trial.)

Table 4-4-1: Summary of Study Assessments

Instrument	Description	Administration
Health Literacy		
- Rapid Estimate of Adult Literacy in Medicine (REALM)[37]	Medical-word recognition and pronunciation test comprising 11 medical terms, arranged in order of complexity by the number of syllables and pronunciation difficulty; scores assigns health literacy skills into 4 categories of grade-equivalent reading level	Study coordinator, 2 minutes
- Newest Vital Sign (NVS)[38]	Measures health literacy level using 1 scenario of an ice cream container nutrition label; 1 score (6 items) includes assessment of two main constructs, numeracy and reading comprehension	Study coordinator, 3 minutes
Comprehension		
- Quality of Informed Consent (QuIC)[4]	Measures subjects actual (objective - part A, 16 items) and perceived (subjective - part B, 14 items) understanding of cancer clinical trials to address 13 independent domains of informed consent; responses measured in a 3 item (part A) or 5 item (part B) Likert scale	Self administered, 7 minutes
- Modified Deaconess Informed Consent Comprehension Test (DICCT)[39-41]	Semi-structured interviews assess subjects understanding of 8 core elements of disclosure for the study they have agreed to participate in. Scores of 2,1 or 0 are assigned to responses that indicate complete, partial or no understanding of each element.	Study coordinator, 5 minutes
Anxiety		
- State Trait Anxiety Inventory (STAI)[42]	Measures anxiety and distinguishes it from depressive syndromes; 40 items to assess state/trait anxiety; responses rated on a 4 point Likert scale	Self administered, 5 minutes
Satisfaction		
- Study specific and QuIC Supplement[43]	Short study specific questionnaire and selected questions from the QuIC supplement questionnaire will query participants about their overall satisfaction with the consent process, helpfulness of information provided, and comprehension of key study-specific elements of treatment	Self administered, 5 minutes
Information location		
- Study specific	Participants will be asked to identify 5 items of information within the consent document; time taken to locate items will be measured	Study coordinator, 5 minutes

4.4.2. Choice of Study Instruments

In choosing study instruments, two considerations were taken into account. First, instruments were sought that have been well-validated to assess the endpoints of interest, where available. Second, the study was tailored to be sensitive to the critical nature of these patients' illnesses and the stressful climate in which their decisions are being made. Consequently, the selected instruments will minimize the burden of participation by keeping the patient time commitment required to a minimum.

Although available tools are unable to completely capture the complexity of the construct of health literacy, the Rapid Estimate of Adult Literacy in Medicine (REALM) instrument is a validated and reliable instrument that has been extensively used in assessing health literacy, especially in the context of informed consent studies among cancer patients.[14,15,27] The Newest Vital Sign (NVS) instrument consists of a single scenario, an ice cream container nutrition label,

and 6 questions measuring word comprehension and application and numeracy.[38] The REALM and NVS were chosen over other literacy assessments such as the Test of Functional Health Literacy in Adults (TOFHLA) standard and short forms because collectively they require significantly less time to administer, measure both comprehension and numeracy and are more sensitive to marginal health literacy.

The Quality of Informed Consent (QuIC) instrument will be used to measure comprehension.[4,44] QuIC incorporates the basic elements of informed consent specified in federal regulations, assesses therapeutic misconceptions, and measures actual (part A) and perceived (part B) understanding of cancer clinical trials. It has good test-retest reliability (interclass correlation coefficient 0.66-0.77).[4] Part A consists of 16 statements to which subjects can respond "agree", "disagree", or "unsure." Part B includes 14 questions with responses measured on a 5-point scale that ranges from "I didn't understand this at all" to "I understood this very well." Each section is scored on a normalized scale from 0 to 100. The QuIC was chosen over other instruments that measure subject comprehension of consent forms (e.g., Brief Informed Consent Evaluation Protocol [BICEP],[45] Deaconess Informed Consent Comprehension Test [DICCT][41]) as the QuIC has been developed specifically for cancer clinical trials, has been well validated in the literature, and measures both objective knowledge and self-reported subjective understanding of a subject undergoing the informed consent process in a clinical trial.[4,8,44,46-49] As a secondary endpoint, the study will use a modification of the DICCT to evaluate subject comprehension of 8 core elements of disclosure for the study in which they are considering participation.[39-41] The test uses semi-structured interviews to obtain open-ended responses to questions related to study purpose, protocol, risks, direct benefits, indirect benefits, freedom to withdraw, alternative treatments, and voluntariness. Responses are scored as 2, 1, or 0 to indicate complete, partial, or no understanding and a composite score is determined.

Anxiety related to the consent process will be measured using the State Trait Anxiety Inventory (STAI), a commonly used and validated tool with good internal consistency, test-retest reliability.[42] There are no validated instruments for measuring satisfaction with the informed consent process. A short questionnaire that can be self-administered by patients will be developed to measure satisfaction and understanding of key study-specific elements. In addition, selected questions will be used from the QuIC supplement to assess satisfaction.[43] There are no validated instruments for measuring consent information location (text search ability). To measure information location and to differentiate it from comprehension, the time it takes for subjects to locate 5 important items of information in the consent form will be determined.

4.4.3. Timing of Study Assessments

For the BMT CTN 1205 (ETRIC) study, enrolled patients will complete assessments within 7 business days of consent discussion for the parent trial. These will include assessments for health literacy and assessments for study endpoints (comprehension, anxiety, satisfaction, information location). These assessments will be conducted irrespective of whether the patient participates (and signs consent) or declines participation (and does not sign consent) for the parent study.

There are two sets of assessments:

- *Coordinator administered assessments:* These include – (1) REALM (health literacy), (2) NVS (health literacy), (3) Modified DICCT (comprehension), and (4) assessment for information location. Preferably, these assessments should occur right after the consent discussion for the parent clinical trial. However, if that is not feasible, they could be completed in a separate visit within 7 business days.
- *Patient self-administered assessments:* These will include – (1) QuIC (comprehension), (2) STAI (anxiety), and (3) assessment for satisfaction with the consent process. Preferably, these assessments should occur right after the consent discussion for the parent study. However, if that is not feasible, patients can be allowed to take them home and complete and return them by mail to the transplant center within 7 business days.

All study assessments will be administered using paper-based forms. Table 4-4-3 shows the timing of the study assessments for this study and their relation to patient reported assessments for the parentstudies.

Table 4-4-3: Patient Reported Assessments in the BMT CTN 1205 and Parent Studies

Study/Instrument	Administered by	# of items	Within 7 business days of post-consent*	Pre-HCT[1]	100 Days	180 Days	12 mos	24 mos	Time required
1205									
Health Literacy									
- REALM	Coordinator	11	X						2 minutes
- NVS	Coordinator	6	X						3 minutes
Comprehension									
- QuIC (A and B)	Self	30	X						7 minutes
- Modified DICCT	Coordinator	11	X						5 minutes
Anxiety									
- STAI	Self	40	X						5 minutes
Satisfaction									
- Satisfaction Survey	Self	7	X						5 minutes
Information location									
- Study specific	Coordinator	5	X						5 minutes
1101									
- FACT-BMT	Self	37		X			X	X	6 minutes
- MOS SF-36	Self	36		X			X	X	6 minutes
- Global HRQoL	Self	4		X			X	X	< 1 minute
- Occupational Functioning	Self	6		X			X	X	< 1 minute
- EQ-5D	Self	5		X			X	X	1 minute
1301									
- FACT-BMT	Self	37		X	X	X	X	X	6 minutes
- MOS SF-36	Self	36		X	X	X	X	X	6 minutes
- MDASI	Self	19		X	X	X	X	X	< 5 minutes

[1] Depending on a center's processes, there is a possibility that the post-consent assessments for the 1205 study and the pre-transplant assessments for the 1101 or 1301 study will occur at the same time.

Note: There are no patient-reported assessments for the BMT CTN 1203.

4.5. Study Monitoring

Monitoring for this study will follow the mechanisms already established for the parent trials, whichever trial the patient is being considered for. Given the minimal risks associated with the BMT CTN 1205 (ETRIC) study interventions and the subsequent short followup period, no additional monitoring will be conducted for the BMT CTN 1205 (ETRIC) study. Patients will be monitored clinically with laboratory assessments, physical exams, restaging studies, and other testing deemed to be standard practice and appropriate by the treating physician and the transplant center.

4.5.1. Case Report Forms

The procedures required for forms completion and timeliness of submission can be found in the AdvantageEDC^{SM} User's Guide. Assessments that are not completed in AdvantageEDC^{SM} within 30 days of participant enrollment onto 1205 are considered delinquent. Transplant centers can view submitted past due and expected forms via AdvantageEDC^{SM}. A missing form will continue to be requested either until the form is reported or until an exception is granted.

4.5.2. Reporting Patient Deaths

Patient deaths related to the BMT CTN 1205 (ETRIC) study are not anticipated. Reporting of patient death to the BMT CTN Data and Coordinating Center (DCC) will be conducted according to established procedures for the parent trials.

4.5.3. Reporting Serious Adverse Events

Reporting of patient serious adverse events (SAE) will be consistent with standard BMT CTN procedures but be limited to events which are possibly, probably, or definitely associated with participation in this study since this protocol does not involve any pharmacologic treatment or invasive procedures. Unexpected, grades 3-5 adverse events (AEs) will be reported through an expedited AE reporting system via the web-based electronic data capture system, AdvantageEDC. Unexpected, grades 4-5 AEs must be reported within 24 hours of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Other SAEs will be tracked periodically as defined in the Form Submission Schedule, staged according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The Data and Safety Monitoring Board will receive summary reports of all adverse experiences on at least an annual basis.

4.5.4. CIBMTR Data Reporting

Centers participating in BMT CTN trials must register and provide transplant outcome data on all consecutive hematopoietic stem cell transplants done at their institution during their time of BMT CTN participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedure and forms developed by CIBMTR for the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allogenic transplant recipients.)

Patients enrolled in this trial will remain on pre selected form submission track (Transplant Essential Data track also known as "TED" track or Comprehensive Report From track also known as "CRF" track) that was originally assigned by the CIBMTR algorithm. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design for Randomized Study

The randomized study will test two interventions – the ETRIC consent form vs. the standard consent form for patients participating in the BMT CTN 1101 and 1301 studies. The BMT CTN 0901 trial and BMT CTN 1203 trial were removed as parent protocols for the BMT CTN 1205 study due to their closure to accrual on April 18, 2014 and May 13, 2016, respectively. Those who enrolled in the BMT CTN 1205 prior to the BMT CTN 0901 and BMT CTN 1203 closures will be included in the analysis.

5.1.1. Accrual

It is estimated that 3 years of accrual will be necessary to enroll the targeted sample size of 198 patients (99 in each arm). Accrual will be reported by race, ethnicity, and sex. Study assessments will be conducted after the consent process. No patient follow-up will be conducted for this study.

5.1.2. Randomization

Patients will be randomized at a ratio of 1:1 between the two consent arms. Randomization will be stratified by center and by parent BMT CTN treatment protocol. Study ID numbers will be randomized within strata. Study personnel will be blinded to randomization assignment until a study participant agrees to participate and is assigned a study ID number.

5.1.3. Study Endpoints

The primary endpoint of this study is to compare objective comprehension scores on the QuIC (part A) instrument between patients randomized to the ETRIC versus the standard consent arms. Secondary endpoints will compare the following measures between the two arms: (1) subjective comprehension scores on the QuIC (part B) instrument and the modified DICCT instrument, (2) state anxiety scores on STAI instrument, (3) satisfaction scores, (4) time taken for information location, and (5) patient consent rates on parent clinical trials.

5.2. Sample Size and Power Calculations

Based on previous studies in the literature,[4,43,44] this study is designed to detect a 4-point difference in the mean QuIC part A comprehension scores between the two study arms. This difference represents a 0.5 standard deviation difference and has been considered to represent a clinically meaningful difference in comprehension scores in previous studies. The sample size for a two-sample t-test will require 64 participants per group to detect a 4-unit difference between group means (α=5%, power=80%, standard deviation=8). Asymptotic relative efficiency of the Mann-Whitney test to the 2-sample t-test is 0.864 under any symmetric

distribution, which means that 15% more subjects will need to be recruited, leading to 74 per group or 148 in total. Another 25% is added to account for possible dropouts (e.g., patients consent for this study, but are subsequently not able to participate in the consent process for the BMT CTN parent clinical trial [e.g., due to disease progression or determined ineligible to participate]). The study will need to enroll 198 subjects (approximately 99 in each arm). The stratified randomization will eliminate possible association between trial and center strata and consent group assignment, which potentially increases power properties.

5.3. Interim Analysis Plan

5.3.1. Interim Analysis for Efficacy

No interim analysis for efficacy will be performed for several reasons. This study is a non-therapeutic study with minimal risks to the study participants. Stopping enrollment to one of the intervention arms at an interim analysis would impact the ability to evaluate secondary endpoints for the study.

5.3.2. Interim Analysis for Futility

No interim analysis for futility will be performed. Both intervention arms are considered minimal risk to participants.

5.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients. Characteristics to be examined include: patient characteristics (age, sex, race/ethnicity, performance status, disease and disease risk, educational status, household income, as well as health literacy level); donor characteristics (donor type, HLA-match); and transplant characteristics (transplant type, conditioning). Characteristics will be recorded for all patients who enroll on the BMT CTN 1205 (ETRIC) study, irrespective of whether they subsequently consent for the parent BMT CTN protocol. Between groups comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test. The study will also apply Mantel-Haenszel methods to account for stratification by center and protocol. We are not expecting that the strata effect will be strong enough to change our findings. However, if a Kruskal-Wallis and Mantel-Haenszel produce different conclusions the underlying assumptions will be investigated for each of the tests and proceed with a method more appropriate for a given situation.

5.5. Analysis Plan

The primary analysis will be performed using the intention-to-treat principle so that all randomized patients will be included in the analysis. The t-test or the Mann-Whitney test will be used if the t-test assumptions are violated. Secondary endpoints of subjective comprehension, anxiety, satisfaction, and information location will be analyzed with the Mann-Whitney test. The binary outcome of consent rates will be compared using the Fisher exact test. The above unadjusted analyses will be complemented by analyses that adjust for potentially confounding

variables in regression analyses. Generalized estimating equations (GEE)[50] will be used to control for effect of confounding variables (e.g., patient demographics, health literacy level, strata) and a potential consenter effect (as more than one clinician could be involved in the consent process at a clinical trial site). GEE with identity link will be used for comprehension, anxiety and satisfaction analyses. Information location will be analyzed with LOG link and LOGIT link with accrual outcome. Variance will be estimated with the sandwich estimator if the number of consenters is > 30; otherwise the "leave-one-consenter-out" jackknife variance estimation will be used.[51] Exact logistic regression will be used with accrual if the problem of small counts appears. Otherwise Wald tests will be used for significance testing. All two-way interactions between the group indicator (ETRIC vs. standard) and confounding variables will be tested and added to the model if significant. It is expected that all confounders will be analyzed as fixed effects except for the consenter which will be the repeated factor in the GEE. The form of continuous predictors will be either linear, quadratic, or categorized depending on the number of clusters observed in the dataset. Every category in categorical variables will have at least 10 subjects otherwise we will consider merging with neighboring categories. The presence of missing data in excess of 10% will be addressed by developing an imputation model for missing components given the observed part. Then, the multiple imputations approach will be used to estimate regression parameters and their standard errors.[52]

5.6. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures.

5.7. Study Design for Evaluation Study

The evaluation study will use qualitative research methods to understand barriers and facilitators to the use of ETRIC consent form at BMT CTN clinical trial sites participating in the parentstudies.

5.7.1. Center Accrual

Assessments will be conducted at 9 transplant centers. This will include 5 centers that participate in and another 4 centers that are not participating in the ETRIC randomized study. During a one-day visit at each site, semi-structured interviews will be conducted of: (1) IRB administrators, members, and other relevant personnel involved in the consent approval process, (2) site protocol investigators, and (3) study coordinators/research personnel who interact with patients during the consent process.

5.7.2. Analysis Plan

Assessments at each site will be conducted by two study team members with expertise in qualitative research methods and knowledge of transplantation and IRB processes as well as health literacy and readability concerns outlined in the literature. Interviews will be recorded and notes will be taken during the interviews to record nonverbal behavior of participants and to provide a back-up in case the recording fails. Evaluation study participants will not receive any incentives for participation.

For the semi-structured interviews, systematic, sequential, transcript-based analysis will be utilized concurrently with data collection to identify saturation of themes across the data.[53] Two experienced reviewers familiar with the area of study and preliminary research will analyze the data to assess the reliability and validity of the coded data through inter- and intra-coder agreement measures.[54] Inter-coder reliability refers to consistency among different coders while intra-coder reliability refers to consistency within a single coder. The qualitative analysis process includes four steps as outlined below.

Step 1: The transcribed data will be organized by question in order to examine responses across all participants, looking for consistencies and differences. This step includes reassigning responses to an alternate question (asked earlier or later in the interview) rather than the original question posed if it better answers the alternate question.

Step 2: The next major stage of qualitative data analysis will involve creating a codebook and coding the textual data line by line (i.e., segmenting the data into meaningful analytical units). This study will use inductive codes developed by the analysts through direct examination of the data. During coding, a master list (i.e., codebook) will be created consisting of six basic components: the code, a brief definition, a full definition, guidelines for when to use the code, guidelines for when not to use the code, and examples.[55] The code is used to index text for retrieval and to assign values to text such as the frequency, amount, or presence/absence of information.[56-58] Because initial coding instructions often yield poor agreement, two coders will independently code the text segments two times. The purpose of this first coding comparison is to pretest and remedy problems with the code book. Once problems are identified and fixed, the same two coders will use the amended code book to recode the same segments.

Step 3: Validity and reliability of results will be assessed through: (1) a detailed review which assesses consistency of code application within segments and (2) inter-coder and intra-coder statistical analysis. In the first technique, the study will compare the sets of codes that each coder assigned to each of the text passages. A response is considered to be coded the same only if both coders use the identical set of codes. Presence of one or more disagreements will be counted as a coding discrepancy. Using this method, comparison of the code book pretest will demonstrate the level of reliability of text analysis.[54] In the latter technique, a simple measure of agreement for how a code is assigned (the proportion of times that the two raters agree) will be used. To correct for the possibility that coders might agree by chance, calculations will use the kappa statistic.[59] A kappa < 0.90 will indicate a problem with agreement in the way a code is being used.[54] As a way to ensure consistency in subsequent analysis steps, one study team member will resolve any remaining inter-coder discrepancies in the text passages and assign codes for the rest of the data.

Step 4: In the last step of qualitative analysis, coded textual data are explored inductively using content analysis to generate categories and explanations. This will identify hierarchical relationships among codes, creating families of codes that can be aggregated, reviewed, and analyzed at an increasingly general level.[55] This process is referred to as content analysis for saturation of themes. The themes will be reported with quoted text included as support and context.

Computer assisted qualitative data analysis software (CAQDAS), NVivo, will be used to add rigor to the research through electronic search of the transcripts and to provide transparency on how the analysis process is carried out, increasing the ability to replicate the analysis methods.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

Waiver of the requirement to document informed consent: Given the number of consents and randomization conversations subjects will encounter, the randomized portion of this study will seek a waiver of the requirement to document consent from the IRBs of participating sites. We believe that our study meets the criteria for waiver of the requirement to obtain written informed consent (CFR §46.117 (c) (1): An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: … (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.).

This does not mean that informed consent will not occur but rather that informed consent process will be verbal and subjects will neither read nor sign an informed consent form. Subjects will be provided with a written statement regarding the research that includes all the required elements of informed consents. Specific items will still need to be addressed in the consent conversation as required by the federal regulations, as shown in the attached consent script (Appendix D). Additionally, a sample letter to the participating site's IRB requesting a waiver from the requirement to document consent is attached as Appendix C.

Subject consent: Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates and provide the patient with information about the purpose of the study, obtain verbal consent, and enroll/randomize the patient on the BMT CTN 1205 trial. The Network will provide template consent forms (ETRIC and standard consent) to each center. Centers will be allowed to modify the standard consent form according to their local IRB requirements, if needed. IRB specific changes to the ETRIC consent will be allowed, as long as the easy-to-read format is maintained. Each center must provide evidence of IRB approval for the BMT CTN 1205 (ETRIC) study as well as the BMT CTN parent studies.

Additionally, there may be some concern that participants who are randomized to the ETRIC consent arm will consent to the parent BMT CTN trial using an experimental, untested consent. The content of the standard consent and the ETRIC consent will be the same, both containing all of the required elements for informed consent per federal regulations. The only difference in the ETRIC consent arm is enhanced formatting and a two-column layout. Furthermore, to ensure that participants have given truly informed consent, we will incorporate open ended (as opposed to yes/no) questions at the end of the consent process to ensure comprehension. These questions will address the voluntary nature of participation in research and the ability to withdraw from the study at any time without consequence, the purpose and nature of the study, the risks of the study, and alternative options. These questions will be asked of participants in both study arms.

Table A-1 highlights various required components of informed consent that will be met by the ETRIC script (Appendix D) that will be provided to site investigators as guidance for obtaining consent and by the study information sheet (Appendix E). Hence, even though waiver of

requirement to document informed consent will be requested, the consent process for the BMT CTN 1205 (ETRIC) study will comply with all regulatory requirements for informed consent.

Table A-1: Regulatory requirements met by ETRIC study consent materials

Requirement	Notes
(a) Required regulatory elements for consent:	
(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Requirement met
(2) A description of any reasonably foreseeable risks or discomforts to the subject	Requirement met
(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Requirement met
(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Requirement met
(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Requirement met
(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Not addressed as this is a minimal risk study
(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Requirement met
(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Requirement met
(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:	
(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable	Not applicable
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Not applicable
(3) Any additional costs to the subject that may result from participation in the research	Requirement met
(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Requirement met
(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	Requirement met
(6) The approximate number of subjects involved in the study	Requirement met

Confidentiality: Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

Participation of women, children, minorities and other populations: Women and ethnic minorities will be included in this study. Children will not be included, as the study assessments for BMT CTN 1205 measure adult level comprehension.

Accrual will be monitored within each center with the expectation that the enrolled patient population is representative of the transplanted patient population at each center. Representation will be examined by comparing gender, race, ethnicity, and age distributions. Accrual of minority patients will be expected to be in proportion to the number of minority patients transplanted at each center. The DCC and NHLBI will discuss enrollment anomalies with the centers.

APPENDIX B

REFERENCES

APPENDIX B

REFERENCES

1. Singer DA, Donnelly MB, Messerschmidt GL. Informed consent for bone marrow transplantation: identification of relevant information by referring physicians. *Bone Marrow Transplant*. 1990;6(6):431-437.
2. von Wagner C, Semmler C, Good A, Wardle J. Health literacy and self-efficacy for participating in colorectal cancer screening: The role of information processing. *Patient Educ Couns*. 2009;75(3):352-357.
3. Aaronson NK, Visser-Pol E, Leenhouts GH, et al. Telephone-based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. *J Clin Oncol*. 1996;14(3):984-996.
4. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent: a new measure of understanding among research subjects. *J Natl Cancer Inst*. 2001;93(2):139-147.
5. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet*. 2001;358(9295):1772-1777.
6. Kuehn BM. Patients' unrealistic hopes for cancer trial benefits may hinder consent. *JAMA*. 2011;305(12):1186-1187.
7. Lidz CW, Appelbaum PS, Grisso T, Renaud M. Therapeutic misconception and the appreciation of risks in clinical trials. *Soc Sci Med*. 2004;58(9):1689-1697.
8. Beardsley E, Jefford M, Mileshkin L. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? *J Clin Oncol*. 2007;25(9):e13-14.
9. Berger O, Gronberg BH, Sand K, Kaasa S, Loge JH. The length of consent documents in oncological trials is doubled in twenty years. *Ann Oncol*. 2009;20(2):379-385.
10. Sharp SM. Consent documents for oncology trials: does anybody read these things? *Am J Clin Oncol*. 2004;27(6):570-575.
11. May T, Craig JM, Spellecy R. Viewpoint: IRBs, hospital ethics committees, and the need for "translational informed consent". *Acad Med*. 2007;82(7):670-674.
12. Lara PN, Jr., Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol*. 2001;19(6):1728-1733.
13. Mills EJ, Seely D, Rachlis B, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol*. 2006;7(2):141-148.
14. Raich PC, Plomer KD, Coyne CA. Literacy, comprehension, and informed consent in clinical research. *Cancer Invest*. 2001;19(4):437-445.
15. Davis TC, Williams MV, Marin E, Parker RM, Glass J. Health literacy and cancer communication. *CA Cancer J Clin*. 2002;52(3):134-149.
16. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2006;12(4):375-396.
17. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2011. Available at: http://www.cibmtr.org.

18. Massimo L. Ethical problems in bone marrow transplantation in children. *Bone Marrow Transplant*. 1996;18 Suppl 2:8-12.
19. Stevens PE, Pletsch PK. Ethical issues of informed consent: mothers' experiences enrolling their children in bone marrow transplantation research. *Cancer Nurs*. 2002;25(2):81-87.
20. Benyunes MC, Sullivan KM, Deeg HJ, et al. Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. *Int J Radiat Oncol Biol Phys*. 1995;32(3):661-670.
21. Tait AR, Voepel-Lewis T, Malviya S, Philipson SJ. Improving the readability and processability of a pediatric informed consent document: effects on parents' understanding. *Arch Pediatr Adolesc Med*. 2005;159(4):347-352.
22. Ancker J. Developing the informed consent form: a review of the readability literature and an experiment. *American Medical Writers Association Journal*. 2004;19(3):97-100.
23. Jefford M, Moore R. Improvement of informed consent and the quality of consent documents. *Lancet Oncol*. 2008;9(5):485-493.
24. Greene SM, Geiger AM. A review finds that multicenter studies face substantial challenges but strategies exist to achieve Institutional Review Board approval. *J Clin Epidemiol*. 2006;59(8):784-790.
25. Burman W, Breese P, Weis S, Bock N, Bernardo J, Vernon A. The effects of local review on informed consent documents from a multicenter clinical trials consortium. *Control Clin Trials*. 2003;24(3):245-255.
26. Denzen EM, Santibanez ME, Moore H, et al. Easy-to-read informed consent forms for hematopoietic cell transplantation clinical trials. *Biol Blood Marrow Transplant*. 2012;18(2):183-189.
27. Coyne CA, Xu R, Raich P, et al. Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation: a study of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2003;21(5):836-842.
28. Institute for Healthcare Advancement. Health Literacy: Bridging Research and Practice. La Habra, CA: Institute for Healthcare Advancement; 2009. Available at: http://www.iha4health.org/ (accessed 05/01/12).
29. Doak C, Doak L, Root J. Teaching patients with low literacy skills. Philadelphia, PA: JB Lippencott Company. 2007.
30. dos Santos Lonsdale M, Dyson M, Raynolds L. Reading in examination-type situations: The effects of text layout on performance. *J Research Reading*. 2006;29(4):433-453.
31. Foster J. A study of the legibility of one- and two-column layouts for BPS publications. *Bull Br Psychol Soc*. 1970;23:113-114.
32. Guthrie J, Kirsch I. Distinctions between reading comprehension and locating information in text. *J Edu Psychol*. 1987;79(3):220-227.
33. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA*. 2004;292(13):1593-1601.
34. Davis TC, Holcombe RF, Berkel HJ, Pramanik S, Divers SG. Informed consent for clinical trials: a comparative study of standard versus simplified forms. *J Natl Cancer Inst*. 1998;90(9):668-674.
35. Chittleborough CR, Taylor AW, Baum FE, Hiller JE. Non-response to a life course socioeconomic position indicator in surveillance: comparison of telephone and face-to-face modes. *BMC Med Res Methodol*. 2008;8:54.

36. Jackle A, Roberts C, Lynn P. Telephone versus face-to-face interviewing: mode effects on data quality and likely causes. Inst. for Social and Economic Research; 2006. Available at: https://www.iser.essex.ac.uk/files/iser_working_papers/2006-41.pdf.
37. Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med*. 1993;25(6):391-395.
38. Weiss BD, Mays MZ, Martz W, et al. Quick assessment of literacy in primary care: the newest vital sign. *Ann Fam Med*. 2005;3(6):514-522.
39. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part II): assent of children participating in clinical anesthesia and surgery research. *Anesthesiology*. 2003;98(3):609-614. Prepublished on 2003/02/28 as DOI.
40. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part I): parental consent for children participating in clinical anesthesia and surgery research. *Anesthesiology*. 2003;98(3):603-608. Prepublished on 2003/02/28 as DOI.
41. Miller CK, O'Donnell DC, Searight HR, Barbarash RA. The Deaconess Informed Consent Comprehension Test: an assessment tool for clinical research subjects. *Pharmacotherapy*. 1996;16(5):872-878.
42. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press. 1983.
43. Truong TH, Weeks JC, Cook EF, Joffe S. Outcomes of informed consent among parents of children in cancer clinical trials. *Pediatr Blood Cancer*. 2011;57(6):998-1004.
44. Hoffner B, Bauer-Wu S, Hitchcock-Bryan S, Powell M, Wolanski A, Joffe S. "Entering a Clinical Trial: Is it Right for You?": a randomized study of The Clinical Trials Video and its impact on the informed consent process. *Cancer*. 2012;118(7):1877-1883.
45. Sugarman J, Lavori PW, Boeger M, et al. Evaluating the quality of informed consent. *Clin Trials*. 2005;2(1):34-41.
46. Bergenmar M, Johansson H, Wilking N. Levels of knowledge and perceived understanding among participants in cancer clinical trials - factors related to the informed consent procedure. *Clin Trials*. 2011;8(1):77-84.
47. Ford ME, Kallen M, Richardson P, et al. Effect of social support on informed consent in older adults with Parkinson disease and their caregivers. *J Med Ethics*. 2008;34(1):41-47.
48. Bergenmar M, Molin C, Wilking N, Brandberg Y. Knowledge and understanding among cancer patients consenting to participate in clinical trials. *Eur J Cancer*. 2008;44(17):2627-2633.
49. Juraskova I, Butow P, Lopez A, et al. Improving informed consent: pilot of a decision aid for women invited to participate in a breast cancer prevention trial (IBIS-II DCIS). *Health Expect*. 2008;11(3):252-262.
50. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73(1):13-22.
51. Paik MC. Repeated measurement analysis for nonnormal data in small samples. *Communications in Statistics*. 1988;B17:1155-1171.
52. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd Edition, New York, NY: Wiley. 2002.
53. Krueger RA, Casey MA. Focus Groups: A Practical Guide for Applied Research. 3rd ed. Sage Publications, Inc., Thousand Oaks, CA. 2000.

54. Carey JW, Morgan M, Oxtoby MJ. Carey JW, Morgan M, Oxtoby MJ. Intercoder agreement in analysis of responses to open-ended interview questions: Examples from tuberculosis research. *Field Methods*. 1996;8(3):1-5.
55. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook development for team-based qualitative analysis. *Cultural Anthropology Methods*. 1998;10(2):31-36.
56. Bernard HR, Ryan GW, Bernard HR. Text Analysis: Qualitative and Quantitative Methods. In: Handbook of research methods in cultural anthropology qualitative research. Alta Mira Press, Walnut Creek, CA. 1998.
57. Seidel J, Kelle U. Different Functions of Coding in the Analysis of Textual Data. In: Kelle U, ed. Computer-aided qualitative data analysis: Theory, methods and practice. Thousand Oaks, CA: Sage Publications Ltd. 1995.
58. Bernard RH. Research methods in anthropology - qualitative and quantitative approaches. Alta Mira Press, Walnut Creek, CA. 1994.
59. Gorden RL. Basic Interviewing Skills. Waveland Press Inc., Long Grove, IL. 1998.

APPENDIX C

LETTER TEMPLATE INTRODUCING STUDY TO PARTICIPATING SITE IRBS

Date:

Dear IRB Chair,

As part of the Easy-to-Read Informed Consent (ETRIC) study, we are asking for a waiver of the requirement for the documentation of informed consent for the randomized portion of the ETRIC study (Chapter 4 in the protocol). Please note, we are not requesting a waiver for the parent BMT study (BMT CTN protocols 1101 and 1301), as those studies will still document written informed consent, nor are we requesting a waiver for the interviews with IRB administrators, principal investigators, and study coordinators in the evaluation study.

We are seeking a waiver of the requirement to document informed consent to reduce the number of written consent forms that participants must read and sign, a concern that was raised to us by blood and marrow transplant researchers. We believe that the randomized portion ETRIC study meets the second criterion for a waiver of documentation of consent at 45 CFR 46.117 (c), which states, "…the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."

For the randomized portion of the ETRIC study, the procedures are reading the consent form, providing opinions regarding the consent form (e.g., Quality of Informed Consent, information location) and questionnaires that measure health literacy, comprehension, and anxiety. The questionnaires are similar to those that patients routinely undergo in a clinical setting with specific written consent for the questionnaire. Additionally, similar studies focused on informed consent assessing attitudes, preferences, and comprehension have been deemed exempt by IRBs,[1, 2] though we are seeking only a waiver to document informed consent.

Additionally, please note that while the ETRIC is novel, to ensure that participants have given truly informed consent, we will incorporate open ended (as opposed to yes/no) questions at the end of the consent process to ensure comprehension. This will be done for both the standard consent arm and the ETRIC arm to ensure that participants understand the parent study to which they are consenting.

While we are requesting a waiver of the requirement to document informed consent, we will still obtain fully informed consent verbally, including all of the eight required elements of informed consent at 45 CFR 46.116. We believe we will still meet the requirements of respect for persons, as consent will be verbally obtained.

Sincerely,

(Participating site Principal Investigator)

References

1. Dresden GM, Levitt MA. Modifying a standard industry clinical trial consent form improves patient information retention as part of the informed consent process. *Acad Emerg Med.* 2008; 8(3): 246-252.

2. Davis TC, Berkel HJ, Holcombe RF, Pramanik S, Divers SG. Informed consent for clinical trials: A comparative study of standard versus simplified forms. *J Natl Cancer Inst.* 1998; 90(9): 668-674.

APPENDIX D

SCRIPT FOR INTRODUCING ETRIC STUDY TO PARTICIPANTS

APPENDIX D

SCRIPT FOR INTRODUCING ETRIC STUDY TO PARTICIPANTS

Thank you for your interest in this consent form study. This research study seeks to learn whether a new alternate consent form is easier to comprehend or understand, creates greater satisfaction for participants, improves the ability to find information in the consent form, and creates less anxiety than traditional research consent forms, as well as learn the opinions of people like you about this new style of consent form as well as traditional research consent forms. If you do not want to participate in this consent study, you can still participate in the (insert appropriate parent BMT CTN trial here) with the traditional consent form.

If you decide to participate, you will be randomized (like flipping a coin) to receive either the alternative consent form or the standard consent form. Both forms contain the same information, but are organized and formatted differently. Your participation for the study will take about 30 minutes to read the consent form and complete some surveys that will measure your understanding of the information in the consent form, health literacy, and anxiety. These assessments might be done in one visit, or might be spaced out, depending on your schedule.

The risks of the study are that your confidentiality could be compromised if the study records are accessed by unauthorized people. To prevent that, we will identify you with a code and we will mask your name. The code key that links your code with your name is kept in a separate, secure location. While we do not expect you to personally benefit from this study today, we hope to learn how to improve the informed consent process for research for people like you in the future.

If you have any questions about the research, you can contact (insert site PI), or if you have any questions about your rights as a research participant, you can contact (insert site research subject advocate here). I will give you this paper so you have the contact information for both of these people in case you have questions later.

Do you have any questions for me about the consent study?

- If yes, ask your clinic personnel.
- If no, proceed to next step.

Great. Please remember that your participation in the consent study is voluntary. It is your choice to participate or not, and whether you participate or not will have no effect on your medical care or your participation in other studies. Also, you can stop participation in the consent study at any time without any penalties to you. Would you like to participate in the consent study?

- If yes, notify your clinic personnel.
- If no, proceed with standard consent for parent BMT CTN trial.

APPENDIX E

INFORMATION SHEET FOR ETRIC STUDY

BMT CTN 1205 Study

Alternate Consent Form for Hematopoietic Cell Transplantation Clinical Trials

Information Sheet

1. Introduction

Choosing to join a clinical trial or research study is an important personal decision. This information sheet has basic information about a study that is testing an alternate consent form to find out if it's easier to understand than a standard consent form.

This study does not treat your cancer or disease.

This Information Sheet will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.

2. Study Sponsors

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

3. Study Purpose

We invite you to join this research study because you have been asked to join 1 of these BMT CTN studies:

- 1101 - A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus

HLA-Haploidentical Related Bone Marrow (Haplo) for Patients with Hematologic Malignancies

- 1301 - A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus-Host Disease

Our main goal is to learn if an alternate consent form is easier to understand than a standard consent form. The other goals are to learn if the new consent helps you feel:

- Less nervous about deciding to be part of a study (informed consent process), and
- More satisfied with the informed consent process.

4. Right to Ask Questions and Withdraw

You have the right to ask questions about the study at any time. If you have questions about the study or you want to leave the study, please contact:

[insert contact info for site PI]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way. It will also not affect your relationship with the BMT CTN.

5. Study Information

If you agree to join the study, we will randomize you to 1 of 2 groups. We will not assign you to a group. You will be put in one or other group by chance, just like flipping a coin (randomize). We will randomize you to get the alternate consent form or the standard consent form.

After you finish talking about consent for the study, we will ask you to take 7 tests. These tests will take about 30 minutes to finish and will occur preferably in 1 day of consent but no more than 7 business days after the consent discussion for the transplant study.

You will take some of the tests on your own, but a researcher will help you with the other tests.

Keep in mind that if you also join the transplant research study, you will be taking more tests. Your study doctor and study staff will be available to discuss how long the transplant study tests will take to finish.

Our goal is to have 198 people join the study.

6. Risks and Discomforts

There are no medical or physical risks to being part of this study.

7. Possible Benefits

Taking part in this study will not make your health better. The information from this study will help us know if the alternate consent form is easier to understand than a standard consent form. This information could improve the experience of being in a research study for future patients.

8. Privacy, Confidentiality and Use of Information

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. [insert name of Transplant Center] and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits related to this research. We may give out your personal information if required by law.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to:

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Study investigators

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains information about registered studies. This data bank can be accessed by you and the general public at: www.ClinicalTrials.gov. Federal law requires study information for certain studies to be submitted to the data bank.

9. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. If we ask you to leave the study, the reasons will be discussed with you.

We ask that you talk with the research doctor before you leave the study. Even if you leave the study, the information collected from your participation will be included in the study results, unless you specifically ask that it not be included.

10. Physical Injury as a Result of Participation

It's not likely that you will be injured from this study. However, it is important to tell your study doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured from taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

11. Payment

You will not be paid for taking part in this study.

12. Costs and Reimbursements

It will not cost you anything to participate in this study. You will not be reimbursed for participating in this study.

13. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff at the telephone numbers listed here:

[Insert name and contact detail]

14. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about the project, or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

For questions about your rights while taking part in this study, call the _____[name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

APPENDIX F

ETRIC TEMPLATES FOR PARENT STUDIES

APPENDIX F

ETRIC TEMPLATES FOR PARENT STUDIES

Samples of the ETRIC templates for the parent studies are included as part of this appendix. For each participating site, the content of the ETRIC form will be similar to the standard consent forms that have already been approved by the site IRBs for the parent studies. To accomplish this, the version of the standard consent form that has been approved by each site's IRB will be reformatted into the ETRIC format. The main difference between the two consents will be formatting and layout enhancements to present information about the study in an easy-to-read format in the ETRIC form. Note that the BMT CTN 0901 trial and BMT CTN 1203 trial were removed as parent trials due to their closure on April 18, 2014 and May 13, 2016, respectively. The BMT CTN 0901 ETRIC and BMT CTN 1203 ETRIC are in Appendix G.

Sample ETRIC Informed Consent Template for the BMT CTN 1101 Study

BMT CTN 1101, v5.0

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Your Name: _____

Study Title: A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Protocol: BMT CTN #1101

Co-Investigator: Ephraim Fuchs, M.D.
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Phone: 206-667-1968 Email: podonnel@fhcrc.org

Co-Investigator: Claudio Brunstein, M.D.
University of Minnesota Medical Center
420 Delaware Street SE, MMC 286, Minneapolis, MN 55455
Phone: 612-624-5620 Email: bruns072@umn.edu

Transplant Center Investigator: _____

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this research because we want to learn more about reduced intensity transplants that use a mismatched donor. These results will help us understand if one kind of mismatched donor is better or if there is no difference at all.

This study will take at least 4 years and will include about 400 participants. Your study participation will last for **3 years** after your transplant.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN will direct the research study. The BMT CTN and the NIH will make decisions about how to manage the study.

A stem cell transplant is the only treatment at this time that may cure your disease. An **allogeneic** transplant uses blood-making cells from a family member or an unrelated donor to remove and replace your abnormal blood cells. Your doctor may recommend that you have a transplant that uses lower amounts of chemotherapy and radiation. This type of transplant is also called a

reduced intensity, **non-myeloablative**, or "**mini**" transplant. Because of your age or health problems and because you do not have a matched donor, you may have a higher chance of health problems from a standard stem cell transplant that uses high doses of chemotherapy and/or radiation.

Recent studies by the BMT CTN suggest the results are very similar for reduced intensity transplants when they use either mismatched cord blood or use mismatched bone marrow from a family member.

There is no guarantee or promise that this procedure will be successful.

3. Study Purpose

We are inviting you to take part in this study because you have a cancer of the blood or lymph glands and a stem cell transplant is a treatment option.

Tissue typing shows that you do not have a completely matched donor available in your family. You also do not have a matched donor outside of your family who can donate when you need them to. However, you do have two other donor choices available for a transplant: (1) partially matched units of unrelated cord blood, and (2) a family donor who is a partial match.

We are doing this research to learn more about reduced intensity transplants that use a mismatched donor. We will use either cord blood from an unrelated donor or bone marrow from a family member, and then compare the transplant results.

These results will help us understand if one kind of mismatched donor is better or if there is no difference at all.

4. Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about the study or you want to leave the study, please contact:

[insert contact info for site PI]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for several years after you finish your treatment.

Before You Start Your Treatment

We will ask you to take quality of life surveys. The surveys will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

You may skip any questions you wish.

We will also ask you to provide optional Blood Samples for Future Research (see **Section 18: Optional Blood Samples for Future Research**).

Randomization

We will use a computer to randomly assign you to 1 of 2 study groups. One group will receive partially matched cord blood from an unrelated donor, and one group will receive bone marrow from a partially matched family member. You will have an equal chance of being placed in either group.

During Your Treatment

- **Conditioning Regimen Before Transplant (chemotherapy and radiation)**

You will be treated with a type of chemotherapy called **fludarabine**, which is given daily for 5 days. If you receive cord blood, you will also be given a type of chemotherapy called **cyclophosphamide** for 1 day. If you receive bone marrow, you will be given cyclophosphamide for 2 days.

After the chemotherapy is completed, you will receive a small dose of radiation to your whole body (**Total Body Irradiation**) in a single dose. The chemotherapy and radiation may cause side effects. Some of these side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

If you receive cord blood, and have not had cytotoxic chemotherapy within the last 3 months or an autologous transplant within the last 2 years, you will receive a slightly higher dose of radiation (300 cGy instead of 200 cGy). This slightly higher dose of radiation has shown hematopoietic recovery is comparable to that seen with low dose radiation for patients who have had chemotherapy in the last 3 months or an autologous transplant in the last 2 years.

Reinfusion of Stem Cells (Transplant)

On your transplant day, if you receive cord blood, it will be given to you through your catheter like a blood transfusion. If you receive bone marrow, your family donor will have his or her marrow collected in the operating room. The donated marrow may be taken to a laboratory where red cells will be removed. The donor cells will be given to you through your catheter and will travel to

your bone marrow where they will start to make healthy, new blood cells.

If you receive cord blood you will start to take the immune suppressing drugs **cyclosporine** and **mycophenolate mofetil (MMF)** for 3 days before transplant. These drugs may help prevent a complication called **graft-versus-host disease** (**GVHD;** see **Section 6: Risks and Discomforts**).

If you receive bone marrow, you will be given another dose of cyclophosphamide on days 3 and 4 after your transplant. You will start to take the immune suppressing drugs **tacrolimus** and MMF to help prevent GVHD on day 5 after your transplant.

In both study groups (partially matched cord blood from an unrelated donor or bone marrow from a partially matched family member), you will continue to take MMF for about 5 weeks and cyclosporine or tacrolimus for up to 6 months.

If you receive cord blood, you will be given **filgrastim (G-CSF)** through your catheter or by injection under your skin beginning on day 1 after your transplant. If you receive bone marrow, you will be given filgrastim (G-CSF) beginning on day 5 after your transplant. Filgrastim speeds up the recovery of white blood cells. In both study groups, you will receive filgrastim daily until your white blood cells have recovered.

The immune suppressing drugs and filgrastim may cause side effects. These side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

If needed, you will receive blood transfusions to maintain normal blood cell levels and antibiotics to treat or prevent infection. You may also receive extra nutrients and pain drugs during or after your transplant. They will be given to you through your catheter.

- **Health Evaluations**

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

Health evaluations after treatment:

1) Physical exam to assess toxicities, and infections weekly until Day 56 and then at Days 180, 365, and 730.
2) Physical exam to assess GVHD weekly until Day 90 and then at Days 180, 365, and 730.
3) Routine blood tests (cell counts and liver and kidney function) weekly until Day 56 and then at Days 180, 365, and 730.
4) Blood or bone marrow tests to find the amount of donor cells in your body on Days 28 and 56. This is also called *chimerism*.
5) Restaging tests to see how much cancer you have after treatment on Day 730.
6) A quality of life survey (see Before You Start Your Treatment**)** at Days 365 and 730.
7) Optional blood samples for future research (see **Section 18: Optional Blood Samples for Future Research**).

- **Long-term follow-up**

Data regarding your clinical situation after 2 years may be obtained from the CIBMTR, which captures information on all US transplants.

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to very serious.

The risks and discomforts in participating in this study will be similar to what you may have with blood or marrow cell transplant if you do not participate in this trial. Other complications from transplants, such as graft-versus-host disease (GVHD) and infections happen equally in patients who have either type of regimen.

Your health care team will give you medicines to help lower side effects such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or may never go away.

Risks Related to Medications or Total Body Irradiation Used in Conditioning Regimens

All chemotherapy and radiation treatments used as conditioning regimens in this study are commonly used in allogeneic hematopoietic cell transplantation.

TABLE 1 – Risks and Side Effects

Likely	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Cyclophosphamide (Cytoxan®)

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with increased risk of infection ▪ Temporary hair loss ▪ Nausea ▪ Vomiting ▪ Loss of appetite ▪ Sores in mouth or on lips ▪ Diarrhea ▪ Stopping of menstrual periods in women ▪ Decreased sperm production in men ▪ Decreased platelet count (mild) with increased risk of bleeding ▪ Blood in urine	▪ Anemia ▪ Temporary tiredness ▪ Damage to the fetus if you become pregnant while taking drug	▪ Scarring of lung tissue, with cough and shortness of breath ▪ Severe heart muscle injury and death at very high doses ▪ New (secondary) cancers

Fludarabine (Fludara®)

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with risk of infection ▪ Decreased platelet count with increased risk of bleeding ▪ Anemia ▪ Tiredness ▪ Nausea ▪ Vomiting	▪ Diarrhea ▪ Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet ▪ Changes in vision	▪ Pneumonia ▪ Agitation or nervousness ▪ Confusion ▪ Cough ▪ Difficulty breathing ▪ Weakness ▪ Severe brain injury and death

Filgrastim (G-CSF; Neupogen®)

Likely	Less Likely	Rare, but Serious
▪ Ache or pain inside the bones ▪ Increased levels of liver enzymes and uric acid in the blood ▪ Low number of platelets in the blood ▪ Headache ▪ Tiredness	▪ Local irritation (skin) at the injection site ▪ Nausea	▪ Allergic reaction ▪ Low fever ▪ Enlargement or rupture of the spleen ▪ Worsening of pre-existing skin rashes

Mycophenolate mofetil (MMF; CellCept®)

Likely	Less Likely	Rare, but Serious
▪ Miscarriage ▪ Birth defects ▪ Diarrhea ▪ Damage to unborn baby ▪ Limited effectiveness of birth control ▪ Stomach pain ▪ Upset stomach ▪ Vomiting ▪ Headache ▪ Tremors ▪ Low white blood cell count with increased risk of infection ▪ Increased blood cholesterols ▪ Swelling of the hands, feet, ankles, or lower legs	▪ Anemia ▪ Rash ▪ Difficulty falling asleep or staying asleep ▪ Dizziness ▪ Uncontrollable hand shakes	▪ Difficulty breathing ▪ Unusual bruising ▪ Fast heartbeat ▪ Excessive tiredness ▪ Weakness ▪ Blood in stool ▪ Bloody vomit ▪ Change in vision ▪ Secondary cancers, such as lymphoproliferative disease or lymphoma ▪ Progressive Multifocal Leukoencephalopathy

Total Body Irradiation

Likely	Less Likely	Rare, but Serious
▪ Fatigue ▪ Hair loss ▪ Infertility ▪ Loss of appetite ▪ Mouth sores ▪ Nausea	▪ Vomiting ▪ Cataracts ▪ Inflammation of the parotid glands ▪ Skin pigmentation (reversible) ▪ Stunted growth ▪ Low white blood cell count with increased risk of infection ▪ Low platelet count with increased risk of bleeding ▪ Anemia	▪ Diarrhea ▪ Lung fibrosis ▪ Second cancers

Tacrolimus (Prograf®; FK-506)/Cyclosporine

Likely	Less Likely	Rare, but Serious
▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors ▪ Increases in cholesterol and triglyceride	▪ Nausea ▪ Vomiting ▪ Liver problems ▪ Changes in how clearly one can think ▪ Insomnia ▪ Unwanted hair growth ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Dizziness ▪ Red blood cell destruction

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

Risks and Toxicities Related to Transplant

The following problems may occur as a result of cord blood or marrow transplant. These risks may occur whether a transplant was done as part of the study or not:

1. Slow recovery of blood counts. The red blood cells, white blood cells, and platelets can be slow to recover after blood or marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. To speed the recovery of the white cells as much as possible you will receive filgrastim.

2. Graft failure. The cord blood or bone marrow stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10-15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. If your counts do not recover, you may need to receive a second transplant. Graft failure can be fatal.

3. Graft-versus-Host Disease (GVHD). GVHD results from the bone marrow or cord blood cells in the graft recognizing your body as foreign and attacking it. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it. Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

4. Other complications. Other complications may include:

a. **Damage to the vital organs in your body.** The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys and bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections or the chemotherapy and radiation.

b. **Serious infections.** Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will be prescribed certain drugs to reduce the chance of those infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

c. **Relapse of disease or a new blood cancer.** Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases, a new blood cancer may develop from the donor cells. Cyclophosphamide can cause

damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average.

The risk of developing a new blood cancer after allogeneic blood or marrow transplant is probably less than 2%. However, if you receive bone marrow, your donor's marrow is exposed to the chemotherapy drug, cyclophosphamide, after the transplant. There is a risk that a blood cancer may develop in your donor's blood cells. This risk is unknown, but it may be as high as 5%. If cancer develops in your donor's blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

d. Risk to the unborn. The treatments in this study have <u>not</u> been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must refrain from all acts of vaginal sex (abstinence) or use two forms of effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD. Effective birth control is defined as the following:

1. Consistent use of birth control pills
2. Injectable birth control methods (Depo-Provera, Norplant)
3. Tubal sterilization or male partner who has undergone a vasectomy
4. Placement of an IUD (intrauterine device)
5. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

<u>Reproductive Risks</u>

The drugs used in this research study may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of the study.

If you are a woman and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use two effective methods of birth control or abstinence during your transplant and continue until you are finished with your GVHD prevention treatment.

If you are a man, your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

Please check with your doctor to understand more about these risks.

<u>Unforeseen Risks</u>

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about reduced intensity transplants that

might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

Additional Information about MMF

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills less effective and increase your chances of becoming pregnant while you are taking it.
- If you could become pregnant, you must use 2 effective forms of birth control or abstinence for 4 weeks before starting MMF, during treatment, and for 6 weeks after stopping MMF.
- In this study, you will be assigned to receive MMF for about 5 weeks, so you should not become pregnant during that time. If you think you might be pregnant or could be become pregnant during the upcoming 5 weeks, you should not join the study.

Other Treatments or Drugs

Some drugs react with each other. It is important to tell the study doctor or staff about any other drugs or treatments you are taking. This includes over-the-counter drugs, vitamins and herbal treatments.

It is also important that you tell the study staff about changes to any of your drugs during the study.

For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant
- An allogeneic blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care.

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about reduced intensity transplant as a treatment for people with a blood cancer and who have a mismatched donor. This information could help people with a blood cancer who may need a transplant in the future.

9. New Information Available During the Study

During this study, the study doctors may learn new information about the study drug or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer take part in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation and will offer you all available care to meet your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- Study investigators

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

For questions about access to your medical records, please contact /name/ at /number.

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs (see **Section 6: Risks and Discomforts**) too soon after transplant, your body could reject the donor stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

- If you decide to leave this study after the start of treatment, or your doctor asks you to leave the study for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study results, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important to tell your study doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured from taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to receive payment by signing this Consent Form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

14. Costs and Reimbursements

Most of the visits for this study are standard medical care for your allogeneic transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for the costs of standard treatment in this study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

You or your insurance will not be charged for tests that are only done for research on this study.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

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.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert name and contact detail]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about the project, or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

For questions about your rights while taking part in this study, call the _____[name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

17. Cost-effectiveness Research

Study purpose: The study doctors want to learn more about the costs of the two types of transplant that are being tested in the larger transplant study: 1) partially matched units of unrelated cord blood and 2) family donors who are a partial match. This research will help doctors know which type of transplant is more cost effective.

Lead study doctor: Scott Ramsey of the Fred Hutchinson Cancer Research Center in Seattle is the lead study doctor for the cost-effectiveness research. Dr. Ramsey is a medical doctor and well-known health economist.

Your health insurance and out-of-pocket medical costs: If you agree to join this study, we will ask for the following information about your health insurance:

1) Type
2) Provider
3) Policy number
4) Group number
5) Policy holder's name and date of birth.

We will also want to know about your out-of-pocket transplant costs (costs not covered by your insurance). The out-of-pocket costs you and your family have to cover are important in understanding the overall cost of transplant, so we want to collect information this information as well. For example, we want to know how much you spend on:

1) Medical costs (for example, co-pays, prescriptions)
2) Travel and lodging
3) Cost of time away from work for both you and your caregivers (family and friends).

Your health insurance and out-of-pocket information is called the 'study data' in this consent form.

How we will use your health insurance information: After you have finished the transplant study, we will use your insurance information to learn about the reimbursements your health insurer made and calculate the cost of your transplant. Illness and transplant-related costs happen before the transplant and go on for many years after, so we want to collect reimbursement information for the 12 months before your transplant, and for the 2 years following.

Privacy, confidentiality and use of information: Only the study doctors at the Fred Hutchinson Cancer Research Center will have access to your health insurance and out-of-pocket cost information (study data). To maintain your confidentiality, we will not link your name to the study data. Also, all of the study doctors signed a confidentiality agreement and promised to keep electronic data protected under passwords and physical data (paper or other media such as CDs) in secure facilities (for example, on-campus locked offices and locked filing cabinets).

Collecting the study data: We will collect your health insurance and out-of-pocket information using an online questionnaire and diary. You will get a user ID number and password to log on to the system. The system was designed to be very user friendly, but we will help you with the online questionnaire and diary over the phone if needed. We will also send email reminders. The option to complete a mail-out survey will also be available.

As stated above, we will collect reimbursement information starting 12 months before your transplant until 2 years after.

We will collect out-of-pocket costs every month for the first 6 months after transplant and every 3 months after that until the end of the study (2-years). We think each online entry will take between 5 and 25 minutes, but this depends on how much information there is to enter.

Help from your caregiver(s): We ask that you give us the name(s) and contact information of your main caregiver(s). This may be your spouse, partner, parent, adult child or sibling, and friends. You may not feel like using the online diary when you're recovering from your transplant, so we ask that your caregiver(s) help enter this information.

We also want to know the time your caregiver(s) spend caring for you after your transplant and the time they spend away from work or school.

Be sure to talk to your caregiver(s) about this study and get their permission before giving us their name and contact information. If you give us the name of your caregiver(s), we will explain the study to them and what they would need to do. They will also get their own consent form to participate in this study.

Risks to participating: The risks to participating in the cost-effectiveness study are small. We will make every effort to keep your health insurance and out-of-pocket cost information private. We will only use this data to get reimbursement information. A possible risk is the loss of confidentiality about your medical information, but the chance of this happening is very small.

Payment and costs: You will not get paid for participating in this study. You will not be charged for taking part in this study.

If you provide out-of-pocket costs, we will give you a summary of these costs at the end of the study. This may be helpful information for tax reporting.

Right to ask questions and/or withdraw: You do not have to be part of the cost-effectiveness research study. Your involvement is totally voluntary and deciding not to be part of this study will not affect the medical care or services you are receiving. You can also leave the study at any time.

For more information: Contact Lederle Tenney, Fred Hutchinson Cancer Research Center at (855) 267-9045 or email: ltenney@fhcrc.org.

18. Blood Samples for Research (Optional)

This section of the informed consent form is about future research studies that will use blood samples from people who are taking part in the main study. You may choose to give blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give blood samples for future research studies.

There are no major risks associated with drawing blood. Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In rare cases, a blood draw can cause fainting. Only trained people will draw your blood.

If you agree to provide blood samples, here is what will happen:

a.) We will collect five extra blood samples at the same time you have routine blood tests done. The amount of blood collected from you is about 4 tablespoons (50 ml) each time. If you weigh less than 50 kg, the amount of blood collected will be based on your weight (1 ml per kg).

b.) We will collect samples at five different dates in the study: Prior to transplant, Day 28, Day 56, Day 180, and Day 365.

c.) The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to your name or other identifying information by future researchers testing your samples.

d.) Samples stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical information will be made available outside of this network.

e.) Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

f.) DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype

and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission.
- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.
- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.
- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

You can change your mind at any time about allowing us to use your samples and health information for research.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Health Insurance Portability and Accountability Act 1 (HIPAA[1]) Authorization to use and disclose research purpose

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

D. Parties Who May Receive or Use My Individual Health Information:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

Principal Investigator and the researcher's staff

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data Coordinating Center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

(FDA) and the Office of Human Research Protections (OHRP)

U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

PROTOCOL NUMBER: BMT CTN #1101

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- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.
- I understand that the treatment intensity will be randomly assigned to me.
- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed Consent Form.

_____ _____
Participant Name Date

_____ _____
Signature Date

Statement of Consent for Cost Effectiveness Research

The purpose of the cost effectiveness research, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to participate in the cost effectiveness research. If I decide to not participate, it will not affect my medical care in any way.

- ❑ I agree to be part of the cost-effectiveness research.
- ❑ I do not agree to be part of the cost-effectiveness research.

Signature _____ Date _____

Statement of Consent for Research Samples

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and clinical information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my blood samples to be stored for research.
- ❑ I do not agree to allow my blood samples to be stored for research.

Signature _____ Date _____

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Name of Counseling Physician _____ Date _____

Signature of Counseling Physician _____ Date _____

Sample ETRIC Informed Consent Template for the BMT CTN 1301 Study

BMT CTN 1301, v3.0

A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

Your Name: _____

Study Title: A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

Protocol: BMT CTN # 1301

Principal Investigator: *[Insert local PI name]*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this study because we want to compare 3 types of treatment to see which one is best at preventing **chronic Graft-versus-Host Disease (GVHD)**. You are being asked to join this study because:

- You have a disease that can be treated by an **allogeneic stem cell transplant** (using bone marrow or peripheral blood stem cells (PBSCs) from a donor) and
- Your doctor plans to use a **standard intensity conditioning regimen** for your transplant.

See **Section 2: Study Background** for a definition of the bolded terms.

Your study participation will last for **2 years after your transplant**. This study will take at least 2 years total and will include 345 participants. There will be 115 participants in each of the treatment groups.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at *[insert name of facility or institution]*.
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

The Miltenyi Biotec company is supporting this study with supplies and money. This company makes a tool that helps prepare the donated stem cells before giving them to patients.

An **allogeneic stem cell transplant** (allogeneic transplant) is a standard treatment for blood cancers like acute leukemia and myelodysplastic disorder. An allogeneic transplant replaces your abnormal (or diseased) blood cells with blood cells from a donor. It requires a close tissue match between you and the donor. Your donor could be a family member, like a sister or brother, or it could be an unrelated person.

An allogeneic transplant first uses chemotherapy and possibly radiation to destroy the abnormal blood cells or stop them from growing. Then, we replace the destroyed cells with the new cells from your donor.

The chemotherapy and radiation you get to destroy the abnormal cells and prepare your body for transplant is called the **conditioning regimen**.

A common problem after allogeneic transplant is a condition called Graft Versus Host Disease (GVHD). "Graft" is the donor blood cells that you will get during your transplant. "Host" is the person (in this case, you) who gets the donated cells.

GVHD is a side effect where the donor cells (or graft) attack and damage some of your tissue. There are 2 kinds of GVHD: acute and chronic. Acute GVHD usually develops within the first 3 months after transplant. Chronic GVHD usually develops later and lasts longer.

GVHD can cause:

- Skin rash
- Stomach (or intestinal) problems like nausea (feeling sick to your stomach), vomiting (throwing up), or diarrhea (loose stool)
- Damage to your liver
- Hepatitis or jaundice (yellowing of the skin)
- Increased risk of infection

Chronic GVHD can affect many organs and greatly impact your quality of life.

(See **Section 6: Risks and Discomforts** for more information on the side effects of GVHD, and GVHD prevention drugs.)

3. Study Purpose

We are inviting you to take part in this study because you have acute leukemia or myelodysplasia, and an allogeneic transplant is a treatment option. We are doing this research to compare 3 different treatment combinations to see if 1 or more is better than the standard treatment for preventing **chronic GVHD**. The treatments are listed below (**Table 1):**

Table 1: Treatment Groups

Group A:	CD34 Selected Peripheral Blood Stem Cells (new treatment)
Group B:	Bone Marrow Transplant followed by Post-Transplant Cyclophosphamide (new treatment)
Group C:	Bone Marrow Transplant with Tacrolimus and Methotrexate as GVHD Prevention (standard treatment)

Doctors are mostly interested in learning how Groups A and B compare to Group C. The study will help doctors decide which treatment is best at preventing chronic GVHD. We also want to learn how much GVHD is affecting your quality of life, if at all.

(See **Section 5: Study Tests and Treatments** for more information on the treatment groups.)

4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, during your treatment, and for **2 years** after transplant. All patients in this study need to have a matched donor.

Before You Start Your Treatment

Before you begin, you will need to have several exams (tests) and checkups to find out if you can be in the study. These exams and checkups are part of regular cancer care. They would be done even if you don't join the study. The exams include:

- Medical history
- Physical exam, including height and weight
- Blood and urine tests
- Heart function tests, including EKG and ejection fraction
- Lung (pulmonary) function tests
- Tests to see how much cancer is in your body (cancer re-staging). This might include a bone marrow aspirate or biopsy. This is where samples of your bone marrow are taken from your hip bone with a large needle.
- Chest X-ray or chest CT
- A pregnancy test if you are a woman and able to have children. If you are pregnant, you will not be able to take part in this study.
- Health quality of life surveys

We will also talk with you about providing extra blood samples for future research (see **Section 17: Blood Samples for Future Research**). This is completely optional.

The quality of life surveys are for study participants who are:

- Children and teenagers, 8 – 18 years old, who speak English, and
- Adults, 18 or older, who speak English or Spanish

The survey will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

We will ask you to fill out paper surveys at the clinic or hospital. The surveys will take less than 30 minutes to finish. If you need to take the survey by phone, an interviewer will contact you before your transplant. You may skip any questions you wish.

<u>Randomization</u>

We will use a computer to randomly assign you to 1 of 3 treatment groups (A, B, or C). You will have an equal chance of being

placed in 1 of the 3 groups. You, your doctor, and the study researcher won't have any control over which treatment group you're assigned.

During Your Treatment

The tables below describe the 3 treatment groups that will be used in this study. Each treatment includes a conditioning regimen (chemotherapy and/or radiation), allogeneic transplant, and GVHD prevention. Your doctor will decide on the conditioning regimen. You will be given the chemotherapy drugs by mouth or by IV (through your vein). The amount of chemotherapy drugs you receive will be based on your weight. The chemotherapy and radiation may cause side effects. Some of these side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

Some of the treatment groups include a medicine called Mesna. Mesna helps prevent bladder discomfort and hemorrhaging (bleeding).

<table>
<tr><td colspan="3">Group A: CD34 Selected Peripheral Blood Stem Cells</td></tr>
<tr><td>Your doctor will choose 1 of 2 conditioning regimens <u>before transplant</u>:</td><td>Graft (source of donor cells) for <u>transplant</u>:</td><td>GVHD prevention treatment:</td></tr>
<tr><td>1. Total Body Irradiation (TBI), Chemotherapy drugs (3), and Mesna:
TBI, given 3 times a day for 4 days (11 doses total), starting 9 days before transplant
Thiotepa, given once daily for 2 days, starting 5 days before transplant
Anti-Thymocyte Globulin (rATG), given over 6-8 hours, once daily for 2 days, starting 4 days before transplant
Cyclophosphamide (Cy), given once daily for 2 days, starting 3 days before transplant
Mesna – your doctor will decide how many doses based on Cy dose</td><td rowspan="2">Peripheral blood stem cells</td><td rowspan="2">The donor cells will be put through a device, CliniMACS, that removes the immune cells responsible for causing GVHD.</td></tr>
<tr><td>2. Chemotherapy drugs (4):
Busulfan, given over 2 hours, 4 times each day for 3 days, starting 9 days before transplant
Melphalan, given over 30 minutes, once daily for 2 days, starting 6 days before transplant
Fludarabine, given over 30 minutes, 5 times a day for 5 days, starting 6 days before transplant
Anti-Thymocyte Globulin (rATG), given once daily for 2 days, starting 3 days before transplant</td></tr>
</table>

Group B: Post-Transplant Cyclophosphamide (Cy)

We'll give you medicines to kill the donor cells that are attacking your body after your transplant.

Your doctor will choose 1 of 3 conditioning regimens before transplant:	Graft source for transplant:	GVHD prevention drugs:
1. Chemotherapy drugs (Busulfan and Cy) and Mesna: • **Busulfan,** given for 4 days. Your doctor will decide when you will start taking this drug and how many doses you will get every day. • **Cyclophosphamide (Cy),** given once daily for 2 days, starting 3 days before transplant • **Mesna** – your doctor will decide when you will start taking this drug and how many doses you will get every day.	Bone marrow	**Cyclophosphamide** will be given by IV (through your vein), over 1-2 hours, on Days 3 and 4 after your transplant.
2. Chemotherapy drugs (Busulfan and Fludarabine): • **Busulfan,** given for 4 days. Your doctor will decide when you will start taking this drug and how many doses you will get every day. • **Fludarabine,** given 4 times a day for 4 days, starting 5 days before transplant. Each dose will take about 30 minutes.		
3. Total Body Irradiation (TBI) and Chemotherapy drugs (Cy): • **TBI –** your doctor will decide how many doses, for 4 days, starting 7 days before transplant • **Cyclophosphamide (Cy),** given once daily for 2 days, starting 3 days before transplant • **Mesna** – your doctor will decide when you will start taking this drug and how many doses you will get every day.		

Group C: Tacrolimus and Methotrexate (standard treatment)

We'll give you medicines to prevent the donor cells from attacking your body before your transplant.

Your doctor will choose 1 of 4 conditioning regimens <u>before transplant</u>:	Graft source for <u>transplant</u>:	GVHD prevention drugs:
1. Chemotherapy drugs (Busulfan and Cy) and Mesna **a. Busulfan,** your doctor will decide when you will start taking this drug and how many doses you will get every day. ▪ **Cyclophosphamide (Cy),** given over 1-2 hours, once daily for 2 days, starting 3 days before transplant ▪ **Mesna** – your doctor will decide when you will start taking this drug and how many doses you will get every day.	Bone marrow	<u>Before your transplant</u>: **Tacrolimus** will be given as a pill by mouth or by IV (through your vein) 2 times every day, starting 3 days before transplant. The amount will slowly be lowered and eventually stopped. This process will take place over several months. <u>After your transplant</u>: **Methotrexate** will be given by IV (through your vein) on Days 1, 3, 6 and 11 after your transplant.
2. Chemotherapy drugs (Busulfan and Fludarabine): **a. Busulfan,** your doctor will decide when you will start taking this drug and how many doses you will get every day. **b. Fludarabine,** given 4 times a day for 4 days, starting 5 days before transplant. Each dose will take about 30 minutes.		
3. Total Body Irradiation (TBI) <u>and</u> Chemotherapy drugs (Cy) <u>and</u> Mesna: **a. TBI –** your doctor will decide how many doses, for 4 days, starting 7 days before transplant ▪ **Cyclophosphamide (Cy),** given once daily for 2 days, starting 3 days before transplant ▪ **Mesna** – your doctor will decide when you will		

start taking this drug and how many doses you will get every day.		
4. Total Body Irradiation (TBI) <u>and</u> Chemotherapy drugs (Etoposide): **a. TBI –** your doctor will decide how many doses, for 4 days, starting 7 days before transplant ▪ **Etoposide,** given one time, 3 days before transplant		

Treatment Groups A and B don't require long-term use of GVHD prevention drugs. If you're assigned to Treatment Group A or B and you develop GVHD, your doctor will give you drugs to treat the GVHD. Your doctor will determine your treatment (drugs) and the amount based on your signs and symptoms.

<u>Your Transplant (Peripheral blood stem cells (PBSCs) or bone marrow)</u>

On your transplant day, we will give you the donated PBSCs or bone marrow through your catheter. It works just like a blood transfusion. The cells will travel to your bone marrow where they will start to make healthy, new blood cells after several weeks.

After Your Transplant

We'll evaluate (test) your health after your transplant. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

<u>Health evaluations after transplant:</u>

See Table 1: Timeline of Exams After Your Transplant for a schedule of when we will give you these exams.

Quality of life surveys (see Before You Start Your Treatment earlier in this section). We will ask you about your general health and how well you feel while you're in this study. Even though different treatments may treat a disease equally well, there might be differences in how patients feel or the side effects they have after their treatment. This is important information for when we evaluate the treatments in this study. You will take the surveys at the clinic or hospital on Days 100, 180, 365 and 730.

1) Optional blood samples for future research (see **Section 17: Blood Samples for Future Research**).

Table 1: Timeline of Exams After Your Transplant

Exams	Day After Transplant						
	Weekly until Day 63	**100**	**150**	**180**	**270**	**365**	**730**
Tests for toxicities, and infections	✓	✓	✓	✓	✓	✓	✓
Monitoring for CMV, EBV	✓	(Weekly until Day 100) ✓	✓	✓			
Tests for GVHD	✓	✓	✓	✓	✓	✓	✓
Blood tests for cell counts, liver and kidney function	✓	✓		✓		✓	✓
Tests to see how much cancer you still have		✓		✓		✓	✓
Quality of life surveys		✓		✓		✓	✓
Optional blood samples for research (if you consent)	(Day 35 only) ✓	✓		✓		✓	

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to serious.

The risks and discomforts of allogeneic transplant are the same if you join this study, or if you don't join this study. You might do better or worse with a standard transplant. Your healthcare team may give you medicines to help with side effects like nausea (feeling sick to your stomach). In some cases, side effects can last a long time or may never go away.

Risks of Medications

The risks of the chemotherapy drugs, and/or radiation you get as part of the treatment are listed below. How often patients get each of side effects are shown in **Table 2**.

Table 2: Risks And Side Effects

Likely	What it means: This type of side effect is expected in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected in 20% of patients or fewer. This means that 20 or fewer patients out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect is expected in fewer than 2% of patients. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect. It doesn't happen very often, but is serious when it does.

Busulfan (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in fewer than 20% of patients)	**Rare, but Serious** (May happen in fewer than 2% of patients)
▪ Upset stomach or pain in the belly ▪ Constipation ▪ Diarrhea (loose stool) ▪ Feeling dizzy ▪ Water retention (storing extra water) ▪ Headache ▪ Heartburn ▪ Insomnia (not able to sleep) ▪ Loss of appetite ▪ Mouth sores (mucositis) ▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Runny nose ▪ Skin rashes ▪ Irregular or no menstrual periods in women ▪ Tachycardia (fast heart beat)	▪ Cough ▪ Hepatic Veno-occlusive disease (type of liver disease) ▪ High blood pressure ▪ High magnesium and phosphorus levels in the blood ▪ High sugar levels in the blood ▪ Infertility ▪ Low blood pressure ▪ Seizures ▪ Dyspnea (shortness of breath)	▪ Cataracts ▪ Lung fibrosis (scarring of lungs)

Cyclophosphamide (Cytoxan®) (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Sores in mouth or on lips ▪ Loss of appetite ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Diarrhea (loose stool) ▪ Water retention ▪ Temporary hair loss ▪ Damage to male (testes) and female (ovaries) sex glands ▪ Infertility (inability to have children) ▪ Irregular or no menstrual periods in women ▪ Neutropenia (low white blood cell count and increased risk of infection) ▪ Thrombocyotpenia (low platelet count and increased risk of bleeding)	▪ Bleeding in bladder ▪ Anemia (low red blood cell count) ▪ Damage to the fetus if you become pregnant while taking drug ▪ Stomach pain ▪ Skin rash	▪ Allergic reaction ▪ Scarring of lung tissue with cough and shortness of breath ▪ Serious skin rash ▪ Severe heart muscle injury and death (at very high doses) ▪ Second (new) cancers

If you are taking cyclophosphamide, your doctor may also prescribe you a medicine called **Mesna**. Mesna helps prevent bladder discomfort and bleeding that can occur from taking cyclophosphamide.

Etoposide (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Diarrhea ▪ Hair loss ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up)	▪ Mouth sores (mucositis) ▪ Constipation ▪ Upset stomach or pain in the belly	▪ Allergic reaction ▪ Peripheral neuropathy (numbness and tingling in hands and/or feet)

Fludarabine (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Diarrhea (loose stool) ▪ Mouth sores ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Suppressed immune system (immune system not able to fight off infection as normal)	▪ Fever ▪ Numbness and tingling in the hands and/or feet ▪ Feeling sleepy or tired ▪ Changes in vision ▪ Weakness	▪ Coma ▪ Cough ▪ Inflammation (swelling) of the lungs ▪ Interstitial Pneumonia (type of lung disease) ▪ Skin rash

Melphalan (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Constipation ▪ Diarrhea(loose stool) ▪ Temporary hair loss ▪ Mouth sores (mucositis) ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up)	▪ Abnormal heart beat ▪ Increased risk of Hepatitis ▪ Kidney failure	▪ Allergic reaction ▪ Interstitial Pneumonia (type of lung disease) ▪ Seizure ▪ Scarring of lung tissue

Total Body Irradiation (TBI)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Diarrhea ▪ Nausea (feeling sick to stomatch) ▪ Vomiting (throwing up) ▪ Stomach cramps ▪ Temporary hair loss ▪ Cataracts ▪ Stunted growth ▪ Low platelet count with increased risk of bleeding ▪ Low white blood cell count with increased risk of infection ▪ Pain and swelling of the parotid gland (salivary glands under the ears) ▪ Anemia ▪ Infertility (inability to have children) ▪ Endocrinopathies (such as thyroid disease or diabetes) ▪ Mouth sores (mucositis)	▪ Lung inflammation and pneumonia ▪ Redness of the skin ▪ Liver problems	▪ Second (new) cancers ▪ Difficulty swallowing ▪ Back problems ▪ Kidney problems

Thiotepa (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare , but Serious** (May happen in less than 2% of patients)
▪ Low white blood cell count with increased risk of infection ▪ Diarrhea (loose stool) ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Liver damage ▪ Low sperm production in men ▪ Temporary hair loss ▪ Loss of appetite ▪ Missing or no menstrual period in women ▪ Mouth and throat sores ▪ Infertility (inability to have children)	▪ Liver abnormalities ▪ Skin rash ▪ Change in skin coloring ▪ Low platelet count with increased risk of bleeding	▪ Confusion ▪ Disorientation

Rabbit Anti-Thymocyte Globulin (rATG)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare , but Serious** (May happen in less than 2% of patients)
▪ Fever ▪ Shaking chills ▪ Low blood pressure ▪ Skin rash ▪ Itching ▪ Decreased platelet counts ▪ Decreased white blood cell counts	Serum sickness, consisting of : ▪ Severe skin rashes ▪ Mouth sores ▪ Vaginal sores ▪ Pain/swelling of joints ▪ Kidney damage	Severe allergic reaction which may cause: ▪ Life-threatening drop in blood pressure ▪ Wheezing ▪ Difficulty breathing ▪ Severe hives

Risks of Drugs Used to Prevent GVHD

If you're assigned to Treatment Group C you will get medicines to help prevent GVHD after your transplant. The side effects of the GVHD drugs usually stop when you're done taking them.

Cyclosporine (Gengraf® or Neoral®) (GVHD prevention drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
▪ Kidney problems ▪ Loss of magnesium, calcium, and potassium ▪ High blood pressure	▪ Liver problems ▪ Unwanted hair growth ▪ Growth of extra tissue on the gums (inside mouth) ▪ Burning, tingling or numbness in the hands, arms, feet or legs	▪ Seizures ▪ Changes in vision ▪ Formation of very small blood clots

Methotrexate (GVHD prevention drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
▪ Low white blood cell count with increased risk of infection ▪ Feeling tired ▪ Infections	▪ Nausea(feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Irritation or sores in the throat or mouth (mucositis) ▪ Diarrhea (loose stool) ▪ Upset stomach or pain in the belly ▪ Fever ▪ Chills ▪ Anemia (low red blood cell count) ▪ Abnormal liver tests ▪ Kidney failure	▪ Feeling dizzy ▪ Lung fibrosis (scarring of the lungs)

Tacrolimus (FK506, Prograf®) (GVHD prevention drug)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors (shaking) ▪ High cholesterol and triglyceride ▪ Low blood platelet count with increased risk of bleeding ▪ Infections	▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Unwanted hair growth ▪ Liver problems ▪ Insomnia (not able to sleep) ▪ Foggy thinking ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Feeling dizzy ▪ Red blood cell damage

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

Risks of Transplant

The following problems may happen after transplant. These problems might happen if you have a transplant as part of the study or as standard care:

<u>Graft-Versus-Host Disease (GVHD)</u>

GVHD develops when the donor's white blood cells attack your body. White blood cells are also called T cells. You are more likely to get GVHD if your donor's tissue type does not closely match your tissue type. There are 2 kinds of GVHD: acute and chronic.

<u>Acute GVHD</u>

Acute GVHD usually develops within the first 3 months after transplant.You may experience these side effects with acute GVHD:

- Skin rash
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Abdominal (stomach area) pain
- Problems with your liver (your doctor will run tests for this)
- Infection

Chronic GVHD

Chronic GVHD usually develops later and lasts longer. You may experience these side effects with chronic GVHD:

- Skin rashes
- Hair loss
- Thickened skin
- Dry eyes
- Dry mouth
- Liver disease (your doctor will run tests for this)
- Weight loss
- Diarrhea
- Infection

We don't know for sure if you will develop acute or chronic GVHD. Your doctor will watch you closely for GVHD and treat it if it happens.

To know for sure if you have acute or chronic GVHD, we may do a biopsy of your skin. A biopsy involves taking a small piece of your skin to look at it under a microscope. There's a small chance that we might also do a biopsy of your intestine and liver. Risks of biopsy may include pain, infection, or bleeding.

In most cases, GVHD can be treated with drugs. In some cases, GVHD can be very hard to treat. It might also cause death.

Slow recovery of blood counts

The red blood cells, white blood cells, and platelets can be slow to recover after transplant. Until your blood counts recover, you will need blood and platelet transfusions. You'll be at risk for bleeding and infections. We might give you a drug called **Filgrastim** (G-CSF; Neupogen®) to speed up the recovery of the white blood cells as much as possible and lower the chance of bleeding and infections.

Graft (donor cells) failure or rejection

The PBSCs or bone marrow (the "graft") might not grow inside your body. There can be a 10 - 15% chance of graft failure. If graft failure happens, this may result in low blood counts for a long period of time. If your counts don't recover, you may need to get a second transplant. Graft failure can be fatal.

Damage to the vital organs in your body

Your vital organs include your heart, lungs, liver, intestines, kidneys, bladder and brain. The chemotherapy and GVHD drugs may hurt these organs. You may develop lung

problems from chemotherapy or an infection.

If there is serious damage to your vital organs, you may have to stay in the hospital longer or return to the hospital after your transplant. Many patients get better, but these complications can cause permanent damage to your organs or death.

Serious infections

It may take many months for your immune system to recover from the chemotherapy and the transplant. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infection, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Return (relapse) of disease or a new blood cancer

Your disease may come back even if the transplant is successful at first. In rare cases, a new blood cancer may develop from the donor cells.

Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic transplant is less than 2% (1 or 2 patients (or fewer) out of 100). If cancer develops in your donor's blood cells, you may need more chemotherapy or another transplant.

Lymphoproliferative Syndrome

Patients in treatment Treatment Group A (CD34 Selected Peripheral Blood Stem Cell Graft) have an increased risk of developing post-transplant lymphoproliferative disorder (PTLD) or lymphoma caused by a virus called EBV. They can develop symptoms like fevers and enlarged lymph nodes. Your doctor may use scans and biopsies to confirm the diagnosis. Your blood will be monitored to check if you have signs of EBV in the blood. In many patients EBV can be treated at that stage before it ever progresses to lymphoma. EBV in the blood or EBV lymphoma often responds to treatment with rituximab, a drug commonly used in other lymphomas.

Risk to the Unborn

The treatments in this study have not been proven safe at any stage of pregnancy. If you are pregnant or nursing, you can't join this study. Women who can become pregnant must use effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD, and for 1 year after transplant. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (abstinence)
2. Consistent use of birth control pills
3. Injectable birth control methods (Depo-Provera, Norplant)

4. Tubal sterilization or male partner who has undergone a vasectomy

5. Placement of an IUD (intrauterine device)

6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children, or cause birth defects if you take them while you are pregnant. It is important that females who aren't pregnant or breast-feeding don't become pregnant while part of the study.

Both women who can become pregnant and their male partners should use birth control for 1 year after transplant while on this study.

- Females who join the study

  If you are female and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you're in the study. Women who have gone through puberty might experience irregular menstrual cycles or their cycle might stop forever. This doesn't mean that you can't become pregnant. You must still use an effective form of birth control during your transplant and continue with it until you are finished with GVHD prevention treatment.

Be sure to talk with your doctor about options for fertility planning, like storing your eggs, before starting chemotherapy and radiation treatment.

- Males who join the study

  If you are male, your body may not be able to produce sperm (become sterile). Be sure to talk with your doctor about options for fertility planning, like banking your sperm, before starting chemotherapy and radiation treatment.

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things that might make you want to stop being in the study. If this happens, we will let you know so you can decide if you want to continue in the study.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study. For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you can still receive an allogeneic transplant to treat your disease. The treatment and tests could be very similar to what you'd receive if you're part of the study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant.
- An allogeneic transplant that is not part of the study, or another type of transplant
- Participation in another research study, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

We don't know if taking part in this study will make your health better. The information from this study will help doctors learn more about drugs used to prevent GVHD. This information could help people with a blood cancer who may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

10.Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *[Name of Transplant Center]* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to these agencies or organizations:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC), including The Emmes Corporation
- BMT CTN Data and Safety Monitoring Board (DSMB)
- Miltenyi Biotec, makers of the device that removes cells that are associated with the development of GVHD (used in Treatment Group A)
- Study investigators

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at

www.ClinicalTrials.gov. Federal law requires clinical trial information for certain studies to be submitted to the data bank.For questions about access to your medical records, please contact /name/ at /number.

11. Ending Your Participation

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time. If you choose not to take part or leave this study, your regular medical care will not be affected in any way.

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs too soon after transplant (see **Section 6: Risks and Discomforts**), your body could reject the donor stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

If you decide to leave this study after getting the study treatment, or are asked to leave by your doctor for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to seek payment by signing this Consent Form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

14. Costs and Reimbursements

Most of the visits for this study are standard medical care for your allogeneic transplants and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for optional blood samples for research on this study. You will not pay for any extra tests that are being done for the study.

Some health plans will not pay the costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact */Center/ Financial Counselor at /Number/*.

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.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

The ethical aspects of this study have been reviewed and approved by *[name of IRB]*.

For questions about your rights while taking part in this study, call the *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at *(telephone number)*.

17. Blood Samples for Future Research (Optional)

This section of the Consent Form is about future research studies. This research will use blood samples from people who are taking part in the main study. You may choose to give blood samples for these research studies if you want to. You can still be a part of the main study even if you say 'no' to give blood samples for immune recovery research studies.

Researchers are trying to learn more about why patients develop side effects after transplant, such as infections and graft-versus-host-disease (GVHD).This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood samples, here is what will happen:

a.) We'll collect 5 blood samples from your catheter or a vein in your arm. These samples will probably be collected at the same time as your other blood draws. We'll take about 2 teaspoons (or 6 mL) before you begin the conditioning regimen for your transplant, and about 20 teaspoons (or 86 mL) at each time: 35 days, 100 days, 6 months, and 1 year after your transplant.

These samples will only be collected from patients who are more than 66 pounds (30 kg).

b.) The blood samples for future research will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples. A link to this code does exist. The link is stored at the Data and Coordinating Center for the BMT CTN DCC. The staff at the repository where your samples are being stored does not have a link to this code. Your research samples will continue to be stored at the BMT CTN Repository until they are used up for research.

c.) Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

d.) Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

e.) DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples, although the results of genetic studies could theoretically include identifying information about you.

Things to Think About:

- The choice to let us have blood samples 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 blood can be kept for future research, you can change your mind at any time. Just contact your study doctor and let

him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

- In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers 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.

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

Genetic Information Nondiscrimination Act:

- A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research.
- This means that they must not use your genetic information when making decisions about your insurance. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits:
The benefits of research using blood include learning more about how your body's immune system recovers after a transplant, as well as why certain complications like graft-versus-host disease or infections develop.

Risks:
There is a small risk of an infection or fainting from the blood draw.

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

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at *[contact information]*.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Blood Samples for Future Research (Optional)

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this Consent Form to keep. I understand that I do not have to allow the use of my blood and for research. If I decide not to let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my blood samples to be stored for research.
- ❑ I <u>do not</u> agree to allow my blood samples to be stored for research.

_____ _____

Signature Date

Health Insurance Portability and Accountability Act 1 (HIPAA2) Authorization to use and disclose individual health information for research purposes

A. **Purpose**:
As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Phase II Trial of Randomized Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

B. **Individual Health Information to be Used or Disclosed**:
My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. **Parties Who May Disclose My Individual Health Information**:
The researcher and the researcher's staff may collect my individual health information from:
[*List hospitals, clinics or providers from which health care information can be requested*]

D. **Parties Who May Receive or Use My Individual Health Information**:
The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH)
- Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC) , including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP), and the EMMES Corporation.
- BMT CTN 1301 Co-Principal Investigators: Dr. Leo Luznik, Dr. Marcelo Pasquini, and Dr. Miguel Angel Perales.

Other Organizations

- U.S. government agencies that are responsible for overseeing

[2] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Miltenyi Biotec, makers of the device that removes cells that are associated with the development of GVHD (used in Treatment Group A)

E. **Right to Refuse to Sign this Authorization**:
I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:
I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, t he researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:
My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

Title: BMT CTN #1301: A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-Versus-Host-Disease

Principle Investigator:

Name: Email:

Address: Phone:

Fax:

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____

Name of Counseling Physician Date

_____ _____

Signature of Counseling Physician Date

APPENDIX G

BMT CTN 0901 & BMT CTN 1203 CLOSURE DETAILS AND ETRIC

APPENDIX G

BMT CTN 0901 CLOSURE DETAILS AND ETRIC

The BMT CTN 0901 study was a phase III, multicenter, randomized clinical trial investigating allogeneic HCT using standard high dose versus reduced intensity preparative chemotherapy regimens in patients with acute myeloid leukemia or myelodysplastic syndromes. The primary objective was comparison of overall survival at 18-months between the two study arms. Disease-free survival, relapse, non-relapse mortality, complications and toxicities and quality of life were secondary endpoints. The trial opened for enrollment on June 2, 2011 and closed to accrual on April 18, 2014. Approximately 19 potentially eligible 0901 patients enrolled onto the BMT CTN 1205 study between December 2013 and April 2014. Table G-1 outlines the patient reported assessments for the 1205 and 0901 studies.

Table G-1: Patient Assessments in the BMT CTN 1205 and 0901 Studies

Study/Instrument	Administered by	# of items	TIME POINTS (pre and post)							Time Required
			Within 7 business days post-consent*	Pre-HCT*	100 days	12 mos	18 mos	24 mos	5 yrs	
1205										
Health Literacy										
- REALM	Coordinator	11	X							2 minutes
- NVS	Coordinator	6	X							3 minutes
Comprehension										
- QuIC (A and B)	Self	30	X							7 minutes
- Modified DICCT	Coordinator	11	X							5 minutes
Anxiety										
- STAI	Self	40	X							5 minutes
Satisfaction										
- Satisfaction Survey	Self	7	X							5 minutes
Information location										
- Study specific	Coordinator	5	X							5 minutes
0901										
- FACT-BMT	Self	37		X	X	X	X		X	6 minutes
- MOS SF-36	Self	36		X	X	X	X		X	6 minutes
- MDASI	Self	19		X	X	X	X		X	< 5 minutes
- Global HRQoL	Self	4		X	X	X	X		X	< 1 minute
- Occupational Functioning	Self	6		X	X	X	X		X	< 1 minute
- EQ-5D	Self	5		X	X	X	X		X	1 minute

Sample ETRIC Informed Consent Template for BMT CTN 0901 Study

BMT CTN 0901 v5.0

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

Your Name: _____

Study Title: BMT CTN 0901: A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

Protocol: BMT CTN #0901, version 5.0

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Transplant Center Investigator: _____

Sponsor: The National Institutes of Health (NIH) gave financial support for this research study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. The main goals of the study are to:

1. Compare 2 kinds of treatments used to destroy diseased cells and prepare your body for transplant. This process is also called a **conditioning regimen**.
2. Measure how well your disease (acute myeloid leukemia or myelodysplastic syndrome) responds to the treatment.

Combinations of chemotherapy and sometimes radiation are used as a treatment to destroy cancer cells and help donor cells start to grow in your bone marrow. Depending on the combination used, each treatment (or conditioning regimen) can have a different intensity or strength.

- **High intensity treatment** uses high doses of chemotherapy or radiation.
- **Reduced intensity treatment** uses lower doses of chemotherapy or radiation.

Both kinds of treatments are used by stem cell transplant doctors around the world and are not experimental. Our goal is to see if one kind of treatment is better than the other for people who have a stem cell transplant to treat either their acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS).

If you volunteer to join this study, we will randomly assign you to receive either a high intensity or a reduced intensity treatment before you receive the stem cells from your donor.

We believe this study will last about **18 months** for most patients who decide to join. About 356 patients will take part in the study at transplant centers around the United States.

We will explain the 2 different treatments in this consent form. Every participating clinic will report their results, so we can compare and share the results at the end of the study.

This consent form tells you about the study, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take your time to make your decision.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [*insert name of facility or institution*].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and

friends. It is your decision to be in the study. If you decide to take part, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

This research study is sponsored by The National Institutes of Health (NIH) through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Conditioning Regimen

The conditioning regimen is a combination of chemotherapy and/or radiation given to patients before the donor cells are infused. This treatment allows donor cells to engraft and start growing in your bone marrow. The treatment also helps to kill cancer cells that might not be detectable.

Different chemotherapy drugs can be used as part of the conditioning regimen. Some common combinations of chemotherapy drugs used for transplant are:

- Busulfan + cyclophosphamide or fludarabine
- Fludarabine + melphalan
- Radiation + cyclophosphamide

Each combination of chemotherapy drugs or radiation has a different strength. This strength can also be described as the treatment "intensity".

Stem cell transplant destroys cancer in two ways:

1. The treatment (or conditioning regimen) destroys cancer cells.
2. The immune cells from the donor can recognize cancer cells and kill them.

High intensity treatments are also known as **myeloablative conditioning (MAC) regimens**. These treatments work well to destroy cancer cells because they use very high amounts of chemotherapy or radiation. High intensity treatments can also have more side effects during and after transplant.

Using a lower or "reduced" intensity treatment before transplant can have fewer serious problems from the chemotherapy drugs. While the cancer killing effects may also be lower, studies show that immune cells given during the transplant can help destroy remaining cancer cells. Transplants with reduced intensity conditioning (RIC) regimens are often used for people who cannot have high doses of chemotherapy or radiation because of their age or other medical problems.

This study will compare high intensity and reduced intensity treatments used to destroy cancer cells and prepare bone marrow for transplant. Our goal is to see if one kind of treatment is better than the other for people who have a stem cell transplant to treat either their AML or MDS.

3. Study Purpose

You are invited to join this research study because you have AML or MDS and are currently being evaluated for an **allogeneic transplant**. The main goal of this study is to see if patients with AML or MDS have better results with transplants using reduced intensity treatment compared to high intensity treatment.

4. Right to ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*].

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time.

If you choose to not take part or to leave this study, your regular medical care will not be affected in any way. The conditioning regimen of your transplant will be the standard of care. If you decide to leave this study after taking the study treatment, or are asked to leave by your doctor for medical reasons, you will be asked to come back to the doctor's office for tests for your safety and as part of your routine medical care.

- Even if you withdraw from the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.
- Your study doctor and study staff will be available to answer any questions that you may have about your participation in, or your withdrawal from this study.

5. Study Treatment and Tests

Before you join the study, we will evaluate your general health, medical history, and your current medications.

Study Participation

You will need to go to the clinic at least once before the study begins. Your participation in the study starts after you sign this consent form. After your transplant you will have weekly evaluations for the first 3 months of this study. After 3 months, you will have an evaluation at 6, 12 and 18 months after your transplant.

These evaluations will be done if you are in the hospital ward or clinic, or if your disease becomes active again after the transplant.

Before You Start Your Treatment

You will have at least one clinic visit before you begin the study. This visit will collect information about your:

- Physical health (including history, height, weight and temperature)
- Heart, lung and kidney function
- Chest x-ray
- Bone marrow biopsy and aspirate

- Routine blood tests, including cell counts, liver and kidney function
- Routine markers of infectious diseases, including hepatitis, herpes, HIV, syphilis, varicella zoster (shingles) among others
- Pregnancy test (if it applies to you)
- HLA type from you and your donor
- Health quality of life for English speaking patients (see below)

Randomization

We selected 5 different treatment options based on the ones that are most often used by transplant centers. The treatment options are listed in Table 1.

Your doctor will choose 1 reduced intensity treatment (A or B in the table below) and 1 high intensity treatment (C, D or E in the table below) to use for this study. These are often the most commonly used at [*insert Institution name*]. A computer program will then assign you by chance to either the reduced intensity or the high intensity treatment option.

You will have an equal chance of being placed in either group. This means that half of the people in the study will be in the reduced intensity group and half will be in the high intensity group.

TABLE 1: TREATMENT OPTIONS (CONDITIONING REGIMENS)

Reduced Intensity Treatments	
A	Fludarabine + Busulfan (Flu/Bu)
B	Fludarabine + Melphalan (Flu/Mel)

High Intensity Treatments	
C	Busulfan + Fludarabine (Bu/Flu)
D	Busulfan[a] + Cyclophosphamide (Bu/Cy)
E	Cyclophosphamide + Total Body Irradiation (Cy/TBI)

Study Evaluations

We will measure your health at specific times during your study participation. These tests and how often they are scheduled are standard for what we do for all patients receiving an **allogeneic transplant**. We would do them even if you were not part of this study.

a.) History, physical exam and weight: weekly for 3 months, 6, 12 and 18 months.

b.) Routine blood tests, including cell counts, liver and kidney function: weekly for 3 months, 6, 12 and 18 months.

c.) Bone marrow biopsy and/or aspirate: at Day 100 and 18 months.

d.) Graft-versus-host disease (GVHD) and infections monitoring: weekly for 3 months, 6, 12 and 18 months.

e.) Side effects or toxicity: monthly for the first 3 months, then at 6, 12 and 18 months.

f.) Blood or bone marrow tests to find out the proportion of donor cells present in

the recipient (chimerism): at 1, 3 and 18 months.

g.) Health quality of life for English speaking patients (see below): at 3, 12 and 18 months.

Blood Samples for Busulfan Pharmacokinetics

Some transplant centers may be participating in this ancillary study.

Researchers are trying to learn more about how your body breaks down one of the drugs (busulfan) given as part of the conditioning regimen in this study. Samples for this test will be collected from you only if you receive this drug and your transplant center is participating in this ancillary study. These tests measure how much busulfan is concentrated in the blood. Busulfan levels are already done routinely in some settings in order to avoid too high levels. Every patient can have different levels of this drug after receiving the same dose of busulfan.

The goal of this study is to see if these levels can be tied to the success of the transplant. This study will explore the levels of busulfan in these 2 treatment intensities and compare with what happens after transplant.

This study will collect up to several blood samples within 6 to 8 hours after a dose of busulfan was given to you. Each blood sample volume is 3mL (1/2 teaspoon). Once all several blood samples are collected from you, they will be sent to a laboratory for testing. None of your personal information will be shared with the laboratory.

Busulfan blood tests are part of this clinical trial at select centers, but your center may repeat these as part the routine transplant procedure. If this happens, your doctor will either collect 6mL (1 teaspoon) each time as described above, or collect 3mL for research tests on another day that busulfan is given.

Health Quality of Life

We will ask you about your general health and how well you feel while you participate in this study. Even though different treatments may treat a disease equally well, there might be a difference in how patients feel or the side effects they have after their treatment. This is important information for when we evaluate the treatments in this study.

We will collect information by using surveys. The surveys will ask about:

- How you feel
- What symptoms you might have and how they affect you
- How well can you do regular daily activities

You will need to fill out the surveys and each survey should take about 30 minutes to finish. Your answers will help us understand how your transplant treatment affects how you feel, what you can do, and your general quality of life.

6. Alternative Treatment

It is your choice to join this study. If you decide you do not want to participate, you may still receive a transplant for treatment of your disease. It is possible that you may have a treatment and evaluations that are very similar to what would be if you joined this study.

Your study doctor will discuss these choices with you. If you decide you do not want to join this research study, your medical care will not be affected in any way.

7. Risks and Discomforts

The risks and discomforts of stem cell transplant are the same if you join this study, or if you do not join this study. The differences in side effects from medications are because of the different levels of treatment strength.

High intensity treatments usually have more side effects early after transplant compared to reduced intensity treatments. Other problems with transplant, such as graft-versus-host disease (GVHD) and infections happen equally in patients who have high intensity or reduced intensity treatments.

<u>Risks Related to Medications or Irradiation Used in Conditioning Regimens</u>

All chemotherapy and radiation treatments used as conditioning in this study are commonly used in **allogeneic stem cell transplantation**. The side effects can change based on the amount of drug given. This is true for busulfan, which is used for reduced intensity and high intensity treatments but in different amounts.

TABLE B-2 – ADVERSE EVENTS

Cyclophosphamide	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	▪ Damage to male (testes) and female (ovaries) sex glands ▪ Diarrhea ▪ Fluid retention ▪ Hair loss ▪ Infertility ▪ Irregular or no menstrual cycles ▪ Loss of appetite ▪ Nausea, Vomiting ▪ Suppression of the immune system	▪ Bleeding in the bladder ▪ Inflammation of the heart muscle (heart failure) ▪ Shortness of breath	▪ Allergic reaction ▪ Lung fibrosis ▪ Serious skin rashes

Fludarabine	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	▪ Diarrhea ▪ Mouth sores ▪ Nausea and vomiting ▪ Suppression of the immune system	▪ Fever ▪ Numbness in the extremities ▪ Sleepiness ▪ Visual changes ▪ Weakness	▪ Coma ▪ Cough ▪ Inflammation of the lung ▪ Interstitial Pneumonia ▪ Skin rash

Busulfan	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	▪ Abdominal discomfort ▪ Constipation ▪ Diarrhea ▪ Dizziness ▪ Fluid retention ▪ Headache ▪ Heartburn ▪ Insomnia ▪ Lack of appetite ▪ Mouth sores ▪ Nausea and vomiting ▪ Running nose ▪ Skin rashes ▪ Irregular or no menstrual cycles ▪ Tachycardia	▪ Cough ▪ Hepatic Veno-occlusive Disease ▪ High blood pressure ▪ High magnesium and phosphorus levels in the blood ▪ High sugar levels in the blood ▪ Infertility ▪ Low blood pressure ▪ Seizures	▪ Cataracts ▪ Lung fibrosis

Melphalan	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	▪ Constipation ▪ Diarrhea ▪ Hair loss ▪ Mucositis ▪ Nausea and vomiting	▪ Heart rhythm abnormalities ▪ Hepatitis ▪ Kidney failure	▪ Allergic reaction ▪ Interstitial Pneumonia ▪ Seizure ▪ Lung fibrosis

Total Body Irradiation (TBI)

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients)*	**Rare** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur)*
▪ Diarrhea ▪ Nausea ▪ Stomach cramps ▪ Vomiting (throwing up) ▪ Painful swelling of the salivary glands under the ears for a few days ▪ Short-term hair loss ▪ Anemia ▪ Infection ▪ Bleeding ▪ Cataracts ▪ Sterility (inability to have children) ▪ Slow growth ▪ Hormone problems (such as thyroid disease or diabetes) ▪ Mouth sores	▪ Lung inflammation ▪ Pneumonia ▪ Redness of the skin ▪ Serious liver problems	▪ Risk of developing other cancers in the future ▪ Difficulty swallowing ▪ Back problems ▪ Kidney problems ▪ Learning problems

Risks Related to the Medication Used to Help Prevent Graft-versus-Host Disease (GVHD)

Graft-versus-Host Disease (GVHD) is a medical condition that can become serious enough to cause death. GVHD is a common development after **allogeneic stem cell transplant**. It happens when the donor cells attack and damage your organ tissues after transplant. GVHD can cause:

- Skin rashes
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Abdominal pain
- Diarrhea
- Liver damage or jaundice (yellowing of the skin or eyes)

Your doctor will prescribe medication to prevent GVHD. You will start GVHD prevention around the time you get your donor cells, and it can last many months after the transplant. These medications do

not completely prevent GVHD and more drugs might be needed to manage this complication.

Your doctor will decide which GVHD prevention treatment is the best choice for you. This decision is not part of the research study. Your doctor will also decide your medications based on what is regularly used for transplant in this hospital or clinic. Below is a list of commonly-used drugs used to prevent GVHD. Your doctor may choose to use other medications than what is listed here.

a) **Tacrolimus:** This drug is used to try to prevent GVHD. Early side effects you may have include: feeling sick to your stomach (nausea) or throwing up (vomiting) after you swallow. Other side effects include high blood pressure (hypertension), shaking hands (tremor), increased hair growth and possibly how clearly you can think or make decisions (mental function).

   If you have these effects, they generally go away if your doctor lowers the amount of medication you take. A few patients have had a seizure while on these medications.

   Your liver or kidneys might not work as well as they did before. If this happens, your doctor may lower the amount of drug you take or stop giving the drug completely. You might be more likely to have kidney problems if you need to take other medications at the same time. This is especially true for drugs that we know might cause kidney problems, such as antibiotics. Sometimes, the kidney damage caused is serious enough for you to need an artificial kidney machine (hemodialysis).

   Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

   It is very important that you do not eat grapefruit or drink grapefruit juice. Grapefruit has an ingredient called begamottin, which can affect some the treatment drugs, including tacrolimus, used in this study. Common soft drinks that have bergamottin are Fresca, Squirt, and Sunny Delight.

b.) **Methotrexate:** This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells and can affect many different parts of your body. It may cause mouth sores or mouth inflammation. Or if you already have these problems from your treatments and other medications, they can get worse.

   Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can also cause kidney damage. If your kidneys are already damaged for other reasons, it can make your kidneys worse. If kidney damage does happen, your doctor might give you a lower dose of methotrexate, or stop giving it completely.

c.) Tacrolimus and Methotrexate: These medications can affect your body's immune system and make it

easier for you to get infections. Even simple infections can become very serious and even life-threatening. As a result, you might have more infections for several months after transplant, especially viral infections and pneumonia.

Risks Related to the Transplant Procedure

The following risks are part of the transplant process and not connected to any one medication or the transplanted donor cells.

a) **Bleeding:** Platelets help your blood to clot. When you have low amounts of platelets, you may have bleeding problems. Once your new bone marrow starts to grow, your platelets will increase and your blood will start to clot normally again.

   Bleeding problems can range from minor bleeding, such as nosebleeds or bruising, to more serious bleeding in your brain and lungs. Serious bleeding can be very dangerous and can happen if your platelet levels stay low. Usually, we can prevent major bleeding problems with transfusions of platelets. However, if your body does not respond well to transfused platelets, you may be at serious risk for bleeding.

b) **Veno-occlusive Disease (VOD):** High dose chemotherapy, irradiation therapy and medications used to prevent GVHD can cause Veno-occlusive Disease (VOD). VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the belly (abdominal cavity) and other parts of the body. We can usually manage veno-occlusive disease very well, to the point where it goes away. However, complications can happen with VOD that may put your life in danger.

c) **Mouth Sores and Diarrhea:** The large doses of chemotherapy and radiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores, we will give you medicine to help control the pain. If your mouth sores are very bad, you may not be able to eat normally until the sores are healed. Mouth sores get better when your white blood count starts to rise, and your donor cells start to grow (also called engraftment).

d) **Capillary Leak Syndrome:** This can happen from your chemotherapy and radiation treatments. The blood vessels may become 'leaky' and fluid enters your abdomen, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters your lungs and makes it hard to breathe. You may die if fluid continues to build up in your lungs.

e) **Unexpected Organ Damage and Other Side Effects:** You might have unexpected, life-threatening heart, lung, kidney, or liver damage as a result of your transplant. High doses

of chemotherapy and radiation can cause very bad lung damage that may not get better with time or medications. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multiple organ failure (such as lung and kidney failure) can happen, which can lead to death.

f) **Fluid Build-up:** We will give you intravenous (IV) fluids during the transplant process and it can be hard for your body to eliminate this fluid. We will also give you Furosamide, which is a medication that can help your body get rid of the extra fluid. One risk of Furosamide is hearing loss. Some side effects may be loss of body chemicals such as potassium and sodium.

g) **Late Effects:** You may have side effects happen a few months to many years after your transplant.

- You may have problems with your thyroid gland that require you to take thyroid medication.
- You may get cataracts earlier in life compared to a person who has not had a transplant. If you develop cataracts (cloudiness in the eyes) they may need treatment.
- Your kidneys could be affected and cause anemia (low red blood cell count) or high blood pressure.
- You may develop a second cancer as a result of the chemotherapy, radiation and/or underlying disease. If secondary cancers happen they generally do not develop until 10 to15 years after your transplant.
- We do not know the long-term effects of transplant on your heart, lungs and brain.

Unforeseen Risks

New risks might appear at any time during the study that are different from the risks listed in this Consent Form. We will promptly tell you of any new information that may affect your decision to participate.

Risk to the unborn:

The treatments in this study have NOT been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some form of effective birth control while receiving chemotherapy, TBI, and GVHD prophylaxis. Effective birth control is defined as the following:

- Refraining from all acts of vaginal intercourse (abstinence)
- Consistent use of birth control pills
- Injectable birth control methods (Depo-Provera, Norplant)
- Tubal sterilization or male partner who has undergone a vasectomy
- Placement of an IUD (intrauterine device)
- Use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

Sterility and future child bearing potential for men and women.

Chemotherapy and/or sterility or irradiation may affect your ability to have children. Male patients may become sterile (unable to produce sperm) and should discuss with their doctor regarding sperm banking prior to transplantation. Female patients who have attained puberty may find that their menstrual cycle become irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control during transplant and afterwards until you are off GVHD prophylaxis. Damage to reproductive tissue may result in infertility (inability to have children). It is not known if the damage could result in birth defects. You should discuss these risks and options in detail with your doctor before entering this study.

8. Possible Benefits

Taking part in this study may or may not make your health better compared to receiving the transplant through your routine medical care. We do know that the information from this study will help doctors learn more about selection of conditioning regimen intensities. This information could help patients in the future who are in need of an **allogeneic transplant**.

9. What if I Change my Mind

You can change your mind at any time about allowing us to use your samples and health information for research. We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form.

If you withdraw yourself from this protocol, even if you allowed your samples to be used for research, your samples will not be used from that point and they will be discarded. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

10. New Information Available During the Study

During this research study, new information about the study drug or the risks and benefits of the study may become known to the study doctors. If this happens, they will tell you about the new information.

The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study. If this happens, the study doctor will stop your participation in the study and you will be

offered all available care to suit your needs and medical conditions.

11. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record and research records remains confidential. We will not discuss or publish information about your health with any unauthorized person or persons. However, we cannot guarantee total privacy.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your study number is not related to your name, social security number or medical record number at [*insert facility name*].

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

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and
- Other authorized study organizations.

We will not identify you by name in any publications or reports that come from these organizations or groups.

12. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and you may be asked to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment.

The study sponsor may decide to end the study at any time. If you are asked to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.

- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

13. Physical Injury as a Result of Participation

It is important to tell your study doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured from taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study.

You and/or your health plan will be charged for this treatment.

This study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

14. Compensation or Payment

You will not be paid for your participation in the research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

15. Costs and Reimbursement

Most of the visits for this research study are standard medical care for patients undergoing allogeneic transplants and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for the busulfan blood samples required for the study or the optional blood sample for research on this study.

16. Ethical Review

The ethical aspects of this research study have been reviewed and approved by [*name of IRB*].

17. Further Information

If you need any information about this study, or if you have any problems while you are participating in this study you can contact the study doctor or his/her staff. They may be contacted at the telephone numbers listed below.

[*Insert name and contact details*].

Independent Contact

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*].

Health Insurance Portability and Accountability Act 1 (HIPAA3) Authorization to use and disclose individual health information for research purposes

A. **Purpose**:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

B. **Individual Health Information to be Used or Disclosed**:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. **Parties Who May Disclose My Individual Health Information**:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*].

[3] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

D. **Parties Who May Receive or Use My Individual Health Information**:

The individual health information disclosed by parties listed in item C and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff

  Dr. Bart Scott, Co-Principal Investigator

  Dr. Mitchell Horwitz, Co-Principal Investigator

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Study sponsors

  Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data Coordinating Center

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

E. **Right to Refuse to Sign this Authorization**:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

18. Blood Samples for Future Research *(Optional)*

Researchers also want to learn how to better predict possible health problems and how to make transplants more successful. Much of this research is done using human tissue or blood.

We would like to store a sample of your blood for use in future research studies. Your blood would be collected at your transplant center before your transplant. We would keep the sample at a central place called the BMT CTN Research Sample Repository (this will be called the "Repository" in the rest of the consent form). A Repository is a place that protects, stores and sends out samples for approved research studies.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission. You should feel free to talk over your decision with your family, friends, doctor, and health care team. If you decide to not let us store research samples now or in the future, it will not affect your medical care.
- Research is meant to gain knowledge that may help people in the future. You will not get any direct benefit from taking part.
- All testing done on your blood is for research purposes. You or your doctor will not be given results and they will not be added to your medical record.
- You will not get paid for any samples or for any products that may be developed from current or future research.

If you agree to provide a blood sample, here is what will happen:

1. A single 6 mL sample of your blood (approximately 1 teaspoon) will be collected before your transplant and stored solely for research purposes. The collection will be done at the same time as the routine blood collection done for the study.

2. The research sample will be given unique bar code designation that cannot be linked to you by the researcher testing your samples.

3. Researchers can apply to study the materials stored in the Repository.

4. Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the remaining research samples and clinical data will be made available outside of this network. Researchers from other universities, the government, and drug or health-related companies can apply to use the samples and information. Only skilled researchers will be allowed to use the samples and information.

5. The BMT CTN Steering Committee or the BMT CTN Biomarkers Committee must approve each study application before they will share samples or information with researchers. This kind of review is to make sure that the investigators requesting the samples are qualified, and that the research they propose has a high potential of success and for contribution of scientific knowledge.

6. DNA from your stored blood sample might be used in genome-wide association (GWA) or pharmacogenomics studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease. Pharmacogenomics studies are similar genetic tests but look specifically at genes related to how the body breaks down medications.

   If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

7. A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Statement of consent

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood, tissue and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my blood samples to be stored for research.
- ❑ I do not agree to allow my blood samples to be stored for research.

_____ _____

Signature Date

TITLE: A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

PROTOCOL NUMBER: BMT CTN #0901

CO-INVESTIGATOR:
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Phone: (206)

CO-INVESTIGATOR:
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Duke University
2400 Pratt St. DUMC 3961
Durham, NC 27710
Phone: (919) 668-1045

- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.
- I understand that the treatment intensity will be randomly assigned to me.
- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed Consent Form.

_____ _____ _____

Participant Signature Print Name Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____

Signature of Counseling Physician Date

_____

Signature of Interpreter Date

BMT CTN 1203 CLOSURE DETAILS AND ETRIC

The BMT CTN 1203 study was a phase II, multicenter, randomized clinical trial investigating whether any of three new GVHD prophylaxis approaches improved the rate of GVHD and relapse free survival at one year after allogeneic transplant in patients with acute leukemia, chronic myelogenous leukemia, myelodysplasia, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, Hodgkin's Lymphoma, diffuse large B cell lymphoma, or mantle cell lymphoma. The primary objective was comparison of one year GVHD/relapse or progression-free survival (GRFS) after hematopoietic stem cell transplantation (HSCT) between each of three novel GVHD prophylaxis approaches and a contemporary control from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Rates of grade II-IV and III-IV acute GVHD, visceral acute GVHD, chronic GVHD, immunosuppression-free survival at one year, hematologic recovery (neutrophil and platelet), donor cell engraftment, disease relapse or progression, transplant-related mortality, rates of Grade $\geq$ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, incidence of infections, immune reconstitution, and overall survival were secondary endpoints. The trial opened for enrollment on September 17, 2014 and closed to accrual on May 13, 2016. Approximately 100 potentially eligible 1203 patients enrolled onto the BMT CTN 1205 study between November 2014 and May 2016. Table G-2 outlines the patient reported assessments for the 1205 and 1203 studies.

Table G-2: Patient Assessments in the BMT CTN 1205 and 1203 Studies

Study/Instrument	Administered by	# of items	TIME POINTS (pre and post)							Time Required
			Within 7 business days post-consent*	Pre-HCT*	100 days	12 mos	18 mos	24 mos	5 yrs	
1205										
Health Literacy										
- REALM	Coordinator	11	X							2 minutes
- NVS	Coordinator	6	X							3 minutes
Comprehension										
- QuIC (A and B)	Self	30	X							7 minutes
- Modified DICCT	Coordinator	11	X							5 minutes
Anxiety										
- STAI	Self	40	X							5 minutes
Satisfaction										
- Satisfaction Survey	Self	7	X							5 minutes
Information location										
- Study specific	Coordinator	5	X							5 minutes

Sample ETRIC Informed Consent Template for the BMT CTN 1203 Study

BMT CTN 1203, v3.0

A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

Your Name: _____

Study Title: A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

Protocol: BMT CTN #1203

Principal Investigator: *Insert local PI information*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. You are being asked to join because you have a disease that can be treated with an **allogeneic transplant** and you have a matched related or unrelated peripheral blood stem cell donor.

We are doing this study to find a way to prevent **Graft-versus-Host-Disease (GVHD).** GVHD is a possible side effect of allogeneic transplant and can be very serious.

For this study, the type of allogeneic transplant you will get is called a **peripheral blood stem cell (PBSC) transplant**. Your doctor also wants to use a **reduced-intensity or non-myeloablative conditioning regimen** for your transplant.

(See section **2: Study Background** for a definition of the bolded terms.)

We will use 3 drug combinations to see which one, if any, is better at preventing GVHD than the current standard of care. The 3 drug combinations are:

- Tacrolimus, methotrexate, and bortezomib
- Tacrolimus, methotrexate and maraviroc
- Tacrolimus, mycophenolate mofetil and cyclophosphamide

This study will take at least 2 years and will include 270 participants. Your participation will last about **1 year**.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join,

please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

For this study, you will receive a type of allogeneic transplant called peripheral blood stem cell (PBSC) transplant. Your doctor also wants to use a reduced-intensity or non-myeloablative conditioning regimen for your transplant.

An **allogeneic transplant** uses blood-making cells from a family member or an unrelated donor to remove and replace your abnormal blood cells. With a **peripheral blood stem cell (PBSC) transplant**, the donor cells come from his or her blood stream.

The conditioning regimen is the chemotherapy and radiation used to destroy the diseased cells before you get your donor cells. A **reduced-intensity or non-myeloablative conditioning regimen** uses lower doses of chemotherapy or radiation.

Graft-versus-Host-Disease (GVHD) is a common side effect of allogeneic transplant. It is a medical condition that can become very serious.

GVHD happens because of differences between your own immune cells (host) and the immune cells from your donor (graft). Your new immune system, or the donated cells, might see your cells as foreign and attack them.

GVHD can cause:

- Skin rashes
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Liver damage
- Hepatitis or jaundice
- Increased risk of infection

3. Study Purpose

We are inviting you to take part in this study because you have a cancer of the blood or lymph glands and an allogeneic transplant is a treatment option for you. We are doing this study to learn more about preventing GVHD.

We will use 3 drug combinations to see which one, if any, is better at preventing GVHD than the current standard of care **(Table 1)**. The current standard of care is a combination of drugs called tacrolimus and methotrexate.

Table 1: Treatment Groups (Study Drug Combinations)

Treatment Group A	Treatment Group B	Treatment Group C
▪ Tacrolimus ▪ Methotrexate ▪ Bortezomib	▪ Tacrolimus ▪ Methotrexate ▪ Maraviroc	▪ Tacrolimus, ▪ Mycophenolate Mofetil ▪ Cyclophosphamide

The current standard of care for preventing GVHD (tacrolimus and methotrexate) is not available on this study. If you want the current standard of care, be sure to let your doctor know (see **Section 7: Alternative Treatments**).

The study results will be compared to the standard of care. This study will help doctors make the best choices about which drugs work best to prevent GVHD.

4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[insert contact info]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for 1 year after transplant.

Before You Start Your Treatment

You will need to have several check-ups and tests to see if you can be in the study. These check-ups and tests are part of your regular cancer care. They would be done even if you were not part of this study. These tests include:

- Medical history
- Physical exam, height and weight
- Blood and urine tests
- Heart function tests
- Lung (pulmonary) function tests
- Cancer re-staging test to see how much cancer you have (if needed)
- Bone marrow tests if you have acute leukemia, chronic myelogenous leukemia, or myelodysplastic syndrome. These tests are called aspirates or biopsies. Samples of your marrow will be taken from your hip bone with a large needle.
- Imaging studies if you have lymphoma
- Chest X-ray or chest CT
- A pregnancy test (if you are a woman able to have children)

Randomization

We will use a computer program to assign you by chance to 1 of 3 treatment groups. You won't be able to choose your group. Once you are assigned to a group, you can't change to the other groups. The study doctor can't change your group either. You will have an equal chance of being placed in 1 of the 3 groups.

During Your Treatment

Conditioning Regimen Before Transplant

The conditioning regimen is the combination of chemotherapy and radiation you will receive before you get your donor cells. This helps the donor cells start to grow and make new cells in your bone marrow (engraft). It also helps to kill cancer cells. Your doctor will choose from 1 of several conditioning regimens to prepare your body for transplant. The regimens are:

- Fludarabine and busulfan
- Fludarabine and melphalan
- Fludarabine and cyclophosphamide
- Fludarabine and Total Body Irradiation (TBI), or
- Fludarabine, cyclophosphamide, and TBI

Your doctor will decide which conditioning regimen you will receive before you are assigned to one of the three (3) treatment groups (study drug combinations).

Reinfusion of Peripheral Blood Stem Cells (Transplant)

On your transplant day (Day 0), the donor cells (stem cells) will be given to you through your catheter, like a blood transfusion. The cells will travel to your bone marrow where they will start to make healthy, new blood cells.

GVHD Prevention Drugs

You will be given different combinations of drugs to prevent GVHD. Some drugs will be given to you before your transplant and some after. You will be randomized (assigned by chance) to 1 of 3 treatment groups.

Treatment Group A: Tacrolimus, methotrexate and bortezomib

If you are assigned to Treatment Group A, we will give you tacrolimus as a pill or by intravenous infusion (IV) beginning 3 days before your transplant. We will give you less and less until we stop it completely. This can take several months.

After your transplant, we will give you methotrexate by IV on Days 1, 3, 6, and 11.

We will give you bortezomib as a shot (or IV push) on Days 1, 4 and 7 after your transplant.

Treatment Group B: Tacrolimus, methotrexate and maraviroc group

If you are assigned to Treatment Group B, we will give you tacrolimus as a pill or by IV beginning 3 days before your transplant. We will give you less and less until we stop it completely. This can take several months.

After your transplant, we will give you methotrexate by IV on Days 1, 3, 6, and 11.

We will give you maraviroc beginning 3 days before your transplant. It will be given to you as a pill to take 2 times a day. You will continue to take it 2 times every day for 30 days after your transplant.

Treatment Group C: Tacrolimus, mycophenolate mofetil and cyclophosphamide group

If you are assigned to Treatment Group C, we will give you tacrolimus beginning Day 5. It will be given as a pill or by IV. We will give you less and less until we stop it completely. This can take several months.

We will give you mycophenolate mofetil beginning Day 5. It will be given as a pill or by IV 3 times a day. You will continue to take it 3 times a day for 30 days. Your doctor might decide that you have to continue taking this drug if you have signs of GVHD.

On Days 3 and 4 after your transplant, we will give you cyclophosphamide by IV. It will take about 1-2 hours.

Health Evaluations

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They

would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

Health Evaluations After Transplant

- Physical exam to look for toxicities, and infections weekly until Day 63 and then at Days 100, 120, 150, 180, 270 and 365.
- Physical exam to assess GVHD weekly starting Day 7 until Day 63, and then at Days 100, 120, 150, 180, 270 and 365.
- Routine blood tests (cell counts, liver and kidney function) weekly until Day 63 and then at Days 100, 180, 270 and 365.
- Blood or bone marrow tests to find the amount of donor cells in your body on Days 28 and 100. This is also called chimerism.
- Disease evaluation tests to see how much cancer you have after treatment on Day 100, 180 and 365.
- Lung (pulmonary) function tests on Day 365.
- Optional blood samples for future research on Days 35, 100, 180 and 365 (see **Section 18: Blood Samples for Future Research**).

6. Risks and Discomforts

The risks and discomforts of stem cell transplant are the same if you join this study, or if you don't join this study. Your health care team may give you drugs to help ease side effects, such as feeling sick to your stomach (nausea). In some cases, side effects can be long-lasting or never go away.

Risks and Toxicities Related to Medications

All immune suppressive drugs, except for bortezomib and maraviroc, are commonly used in allogeneic transplant.

Table 1- Risks and Side Effects

Likely	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Bortezomib (Velcade®) – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Anemia (low red blood cell count) ▪ Thrombocytopenia (low platelet count and increased risk of bleeding) ▪ Feeling weak and uncomfortable ▪ Feeling tired Fever, with shaking chills ▪ Weight loss because of loss of appetite (not feeling hungry) ▪ Constipation ▪ Diarrhea ▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Stomach pain ▪ Pain , numbness and tingling in hands and feet	▪ Neutropenia (low white blood cell count and risk of infection) ▪ Insomnia (trouble sleeping) ▪ Skin rash ▪ Low blood pressure ▪ Arrhythmia (changes in heart beat) that causes you to feel light-headed, dizzy, faint, or short of breath ▪ Chest pain ▪ Heartburn ▪ Bleeding in stomach or lungs ▪ Blood in urine ▪ Pneumonia and bronchitis (lung infection) ▪ Confusion ▪ Anxiety (feeling worried and nervous) ▪ Painful sores in the mouth or throat ▪ Changes in the way things taste ▪ Abnormal liver tests ▪ Blurred vision ▪ Redness and swelling in the eye ▪ Aches and pain and	▪ Coughing up blood ▪ Posterior reversible encephalopathy syndrome (PRES) (Headache, confusion, seizures and vision loss caused by very high blood pressure that comes on quickly) ▪ Hepatitis (swelling of the liver) and liver failure ▪ Pancreatitis (swelling of the intestines, stomach, or pancreas) ▪ Pleural effusion (swelling and fluid build-up in and around the lungs) ▪ Pericarditis (swelling or fluid build-up in and around the heart) ▪ Hearing loss ▪ Bleeding in the brain ▪ Loss of some or all vision in one or both eyes ▪ Encephalopathy (brain disorder that can lead to death ▪ Allergic reactions that cause swelling of the skin, face or throat ▪ Rash with skin peeling and mouth sores that can lead to death ▪ Pain, redness, swelling and

Likely	Less Likely	Rare, but Serious
	weakness in arms and legs muscles, joints and the bone in the arms and legs ▪ Muscle weakness ▪ Cough ▪ Shortness of breath ▪ Headache ▪ Nose bleeds ▪ Changes in blood sugar ▪ Low potassium and sodium in your blood ▪ Increase in calcium in your blood ▪ Flu-like symptoms such as chills, sore throat, runny nose and sinus and throat infections ▪ Edema (swelling or fluid build-up in the arms and legs, feeling dizzy and gaining weight) ▪ Shingles (Herpes virus) ▪ New or worsening heart failure ▪ Infections of the bladder, sinuses, throat, stomach and intestines and skin ▪ Fungal infections in the mouth and throat ▪ Life-threatening infections in the blood	infection at the injection site for bortezomib ▪ Pain in the mouth and throat when swallowing ▪ Intestinal obstruction ▪ Fast death of cancer cells. This might let toxins (poisons) into the blood and hurt organs such as the kidneys ▪ Severe muscle weakness and paralysis

Cyclophosphamide (Cytoxan®) – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Neutropenia (low white blood cell count and increased risk of infection) ▪ Temporary hair loss ▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Loss of appetite ▪ Sores in mouth or on lips ▪ Diarrhea ▪ Stopping of menstrual periods in women ▪ Low sperm production in men ▪ Thrombocytopenia (low platelet count and increased risk of bleeding)	▪ Anemia (low red blood cell count) ▪ Temporary tiredness ▪ Damage to the fetus if you become pregnant while taking drug ▪ Stomach pain ▪ Skin rash ▪ Bleeding in bladder	▪ Scarring of lung tissue, with cough and shortness of breath ▪ Severe heart muscle injury and death (at very high doses) ▪ Second cancers

Maraviroc (Selzentry®) – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Fever, cough and flu-like symptoms ▪ Rash and redness of the skin ▪ Upper respiratory (lung) infections	▪ Fever ▪ Feeling dizzy ▪ Insomnia (trouble sleeping) ▪ Anxiety (feeling worried and nervous) ▪ Depression ▪ Itching ▪ Benign (not cancer) skin tumors ▪ High blood pressure ▪ Loss of appetite ▪ Constipation ▪ Neutropenia (low white blood counts and increased risk of infections) ▪ Joint pain ▪ Sweating a lot ▪ Nerve damage (causing numbness, tingling, and burning) ▪ Muscle pain ▪ Bladder discomfort ▪ Acne ▪ Abnormal liver tests ▪ Herpes infections ▪ Eye infections or inflammation (redness and swelling) ▪ Trouble breathing ▪ Genital warts ▪ Change in body fat	▪ Loss of consciousness (fainting) ▪ Rash covering the whole body ▪ Allergic reactions that can cause liver damage and jaundice (yellow skin)

Methotrexate – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Neutropenia (low white blood cell count and increased risk of infection) ▪ Feeling tired ▪ Infections	▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Irritation or sores in the throat or mouth ▪ Diarrhea ▪ Stomach pain ▪ Fever ▪ Chills ▪ Anemia (low red blood cell count) ▪ Abnormal liver tests ▪ Kidney failure	▪ Feeling dizzy ▪ Scarring of the lungs

Mycophenolate Mofetil (MMF, Cellcept®) – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Miscarriage (unborn baby dies in uterus) ▪ Birth defects ▪ Damage to unborn baby ▪ Less effective birth control pills (you could get pregnant while taking your birth control pills) ▪ Diarrhea ▪ Stomach pain ▪ Nausea (feeling stick to your stomach) ▪ Vomiting (throwing up) ▪ Headache ▪ Tremors (shaking) ▪ Neutropenia (low white blood cell count and increased risk of infection) ▪ High cholesterol ▪ Thrombocytopenia (low platelet count and increased risk of bleeding) ▪ Swelling of the hands, feet, ankles, or lower legs	▪ Anemia (low red blood cell count) ▪ Body rash ▪ Insomnia (trouble sleeping) ▪ Feeling dizzy	▪ Trouble breathing ▪ Abnormal bruising ▪ Fast heartbeat ▪ Feeling very tired ▪ Weakness ▪ Blood in stool ▪ Blood in vomit ▪ Change in vision ▪ Encephalopathy (brain disorder that can lead to death) ▪ Second cancers

Tacrolimus (FK506, Prograf®) – GVHD prevention drug

Likely	Less Likely	Rare, but Serious
▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors (shaking) ▪ High cholesterol and triglyceride ▪ Thrombocytopenia (low platelet count and increased risk of bleeding) ▪ Infections	▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Liver problems ▪ Foggy thinking ▪ Insomnia (trouble sleeping) ▪ Unwanted hair growth ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Feeling dizzy ▪ Pure red cell aplasia. (Your body stops making red blood cells. This could lead to anemia.)

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

Risks and Toxicities Related to Transplant

The following problems may happen because of your transplant. These risks may happen if a transplant was done as part of the study or not. The risks are:

Slow recovery of blood counts. The red blood cells, white blood cells, and platelets can be slow to recover after blood or marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. To speed the recovery of the white cells as much as possible you will receive Filgrastim.

Graft failure. The stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10-15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. If your counts do not recover, you may need to receive a second transplant. Graft failure can be fatal.

Graft-Versus-Host Disease (GVHD). GVHD results from cells in the graft recognizing your body as foreign and attacking it. In most cases, GVHD can be successfully treated. Sometimes GVHD is

severe or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it.

Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

Other complications may include:

a. **Damage to the vital organs in your body.** The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys and bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections or the chemotherapy and radiation.

b. **Serious infections.** Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will be prescribed certain drugs to reduce the chance of those infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

c. **Relapse of disease or a new blood cancer.** Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases, a new blood cancer may develop from the donor cells. Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic blood or marrow transplant is probably less than 2%. If cancer develops in your donor's blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

d. **Risk to the unborn.** The treatments in this study <u>have not</u> been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must use effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD, and for 1 year after transplant. Effective birth control is defined as the following:

   1. Refraining from all acts of vaginal sex (abstinence)

   2. Consistent use of birth control pills

   3. Injectable birth control methods (Depo-Provera, Norplant)

4. Tubal sterilization or male partner who has undergone a vasectomy

5. Placement of an IUD (intrauterine device)

6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of the study.

It is important that both women who can become pregnant and their male partners use birth control for 1 year after transplant while on this study.

If you are a woman and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use an effective method of birth control during your transplant and continue until you are finished with your GVHD prevention treatment.

If you are a man, your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

Please check with your doctor to understand more about these risks.

Additional Information about Bortezomib (Velcade®)

- The effect of Velcade® on reproduction and its safety in pregnancy are unknown. If you are a woman capable of becoming pregnant [anyone who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row], you must have a negative pregnancy test before beginning treatment. In addition, you must not be breastfeeding a baby during this study.

- If you think that you have become pregnant or may have fathered a child while taking part in this study you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. You should also notify the doctor managing your pregnancy that the mother/father received a study drug called Velcade®.

- If you are a woman and you become pregnant during your participation in this study, your treatment with Velcade® will

be stopped and you may be withdrawn from some of the study procedures but not from follow-up by your study doctor. The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.

- If you are a man and your partner becomes pregnant, the study doctor will ask for your partner's permission to collect information about her pregnancy and the health of the baby.

- Laboratory tests show that Velcade® may damage DNA. Based on this information, it is possible that Velcade® may cause infertility in men and women.

Additional Information about MMF

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.

- MMF can make birth control pills less effective and increase your chances of becoming pregnant while you are taking it.

- If you could become pregnant, you must use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for 1 year after transplant.

- If you think you might be pregnant or could be become pregnant prior to enrollment, you should not join this study.

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about reduced-intensity transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

Other Treatments or Medications

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes over-the-counter drugs, vitamins and herbal treatments.

It is also important that you tell the study staff about any changes to these medications during your participation in the study.

For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- An allogeneic transplant, including the standard drugs that are used to prevent GVHD (standard of care)
- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant
- An allogeneic transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care.

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about drugs used to prevent GVHD. It could also help people with a blood cancer that may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to meet your needs

and medical conditions.

10.Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy.

All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential.

[Name of Transplant Center] and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment, or for required reporting to regulatory authorities (such as to the FDA for serious adverse events). In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Millennium Pharmaceuticals, Inc., supplier of bortezomib

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this clinical trial has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain clinical trials to be submitted to the data bank.

For questions about access to your medical records, please contact:

[Insert name and phone number].

11. Ending Your Participation

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time. If you choose not to take part or leave this study, your regular medical care will not be affected in any way. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

If you decide to leave this study after taking the study treatment, or are asked to leave by your doctor for medical reason, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

13. Compensation or Payment

You will not be paid for your participation in the research study. You will not be compensated or reimbursed for any extra costs (travel, meals, etc.) from taking part in this study. Taking part in this study might help researchers make products to sell.

Millennium Pharmaceuticals, Inc. (manufacturer of bortezomib) or others may profit from these products. You will not have any rights to the patents or discoveries that could happen from this research, and you will not receive any payments from it.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care for your allogeneic transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for tests that are only done for research on this study.

The drug bortezomib is being provided by the manufacturer (Millennium Pharmaceuticals, Inc.), free of charge. The drug maraviroc is being provided by the study, free of charge. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/Financial Counselor at /Number/.

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.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. Ethical Review

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

16. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

17. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]
For questions about your rights while taking part in this study, call the _____*[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

18. Blood Samples for Future Research (Optional)

This section of the Consent Form is about future research studies that will use blood samples from people who are taking part in the main study.

You can choose to give blood samples for the future research studies if you want to. You can still be a part of the main study even if you say "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood samples, here is what will happen:

a) We would like to have five (5) small blood samples for future research. If you agree, these samples will be drawn before you begin the conditioning regimen for your transplant (3 teaspoons or 16 mL), and at 4 different times after your transplant: on Days 35, 100, 180 and 365 (10 teaspoons or 40 mL each). These samples will be kept and may be used in research to learn more about immune reconstitution, GVHD, cancer and other diseases.

b) The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples. A link to this code does exist. The link is stored at the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC). The staff at the Repository where your sample is being stored does not have a link to this code. Your research samples will continue to be stored at the BMT CTN Repository until they are used up for approved research.

c) These samples will be kept and may be used in research to learn more about immune recovery, GVHD, cancer and other diseases. When the samples are given to investigators for research, no information about your name, address, phone number or other information that will let the researcher know who you are will be provided.

   DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes

of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

If your coded samples are used in such a study, the research is required to add your test results and sample information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples, although the results of genetic studies could theoretically include identifying information about you.

Benefits:

The research that may be done with your blood is not designed specifically to help you. The benefits of research using blood include learning more about what causes GVHD, cancer and other diseases, how to prevent them, and how to treat them.

Risks:

There is a small risk of an infection or fainting from the blood draw.

A possible risk is the loss of confidentiality about your medical information. 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.

Some general things to think about when letting us store your blood samples for research are:

1. The choice to let us have blood samples 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 blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

2. In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers 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 blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

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

Genetic Information Nondiscrimination Act:

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research.

This means that they must not use your genetic information when making decisions about your insurance. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Making Your Choice:

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

You can change your mind at any time about allowing us to use your samples and health information for research.

Statement of Consent for Blood Samples for Future Research (Optional)

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep. I understand that I do not have to allow the use of my blood and for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that a blood samples may be collected and that my blood and related information can be stored indefinitely by the BMT CTN Repository for research to learn about, prevent, or treat GVHD, cancer, or other health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I do agree to give blood samples for future research.
- ❑ I do not agree to give blood samples for future research.

Signature _____ Date _____

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. **Purpose**:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

B. **Individual Health Information to be Used or Disclosed**:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. **Parties Who May Disclose My Individual Health Information**:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

D. **Parties Who May Receive or Use My Individual Health Information**:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

Principal Investigator and the researcher's staff:

Dr. Javier Bolaños-Meade
Dr. John Koreth
Dr. Ran Reshef

Study Sponsors:

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data and Coordinating Center
- U.S. government agencies that are responsible for overseeing

research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

- Millennium Pharmaceuticals, Inc., supplier of bortezomib.

E. **Right to Refuse to Sign this Authorization**:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, t he researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

TITLE: BMT CTN #1203: A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

PRINCIPAL INVESTIGATOR(S):

Name: Phone:

Address Fax:

Email:

- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.
- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____
Participant Name Date

_____ _____
Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____
NAme of Counseling Physician Date

_____ _____
Signature of Counseling Physician Date