Ancillary Cost-Effectiveness Analysis to:

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-BM) for Patients with Hematologic Malignancies

BMT CTN PROTOCOL 1101
CEA VERSION 4.0

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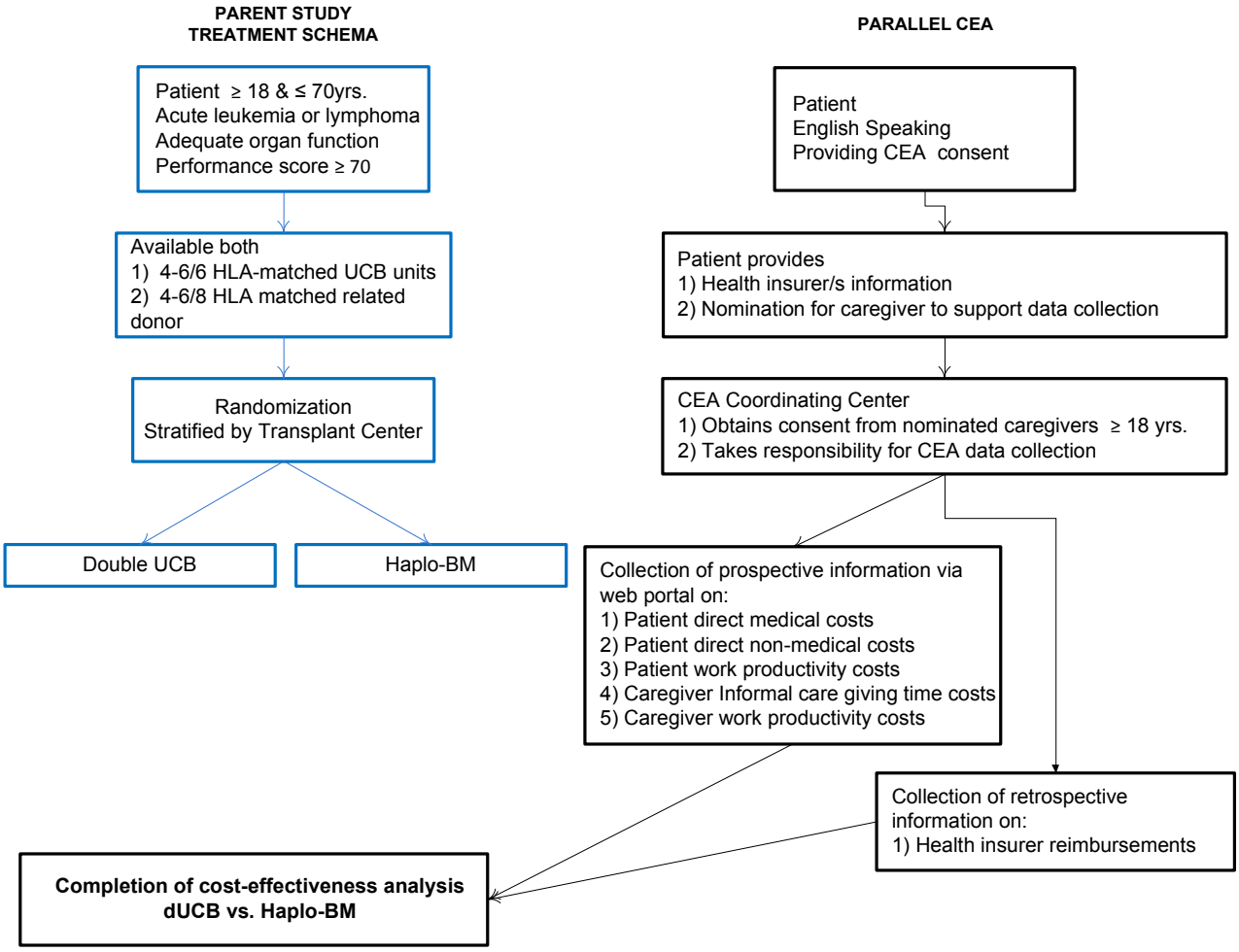
PROTOCOL SYNOPSIS

Ancillary Cost-Effectiveness Analysis to:

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-BM) for Patients with Hematologic Malignancies BMT CTN 1101

Principal Investigator:	Scott Ramsey, M.D., Ph.D.
Study Design:	This study is a parallel cost-effectiveness analysis (CEA) to the multi-center, Phase III, randomized, trial BMT CTN 1101.
Primary Objective:	To determine the cost-effectiveness of dUCB versus haplo-BM as donor cell sources for reduced intensity conditioning blood or bone marrow transplantation in patients with select hematological malignancies, expressed as the cost per quality adjusted life year (QALY) gained.
Secondary Objective:	To examine the out-of-pocket costs, the cost of informal caregiving, and the impact on workplace productivity, for both patients and caregivers, associated with dUCB vs. haplo-BM.
Accrual Objective:	Patients: All participants in the parent trial (target sample size = 410) that meet language eligibility criteria and provide consent to participate in the ancillary cost-effectiveness study. Caregivers as available: Patient nominated caregivers for each CEA participant to support cost data collection and provide additional caregiving related data.
Accrual Period:	The accrual period for the parallel economic evaluation matches the parent study target accrual period of 4 years.
Eligibility Criteria:	All English speaking patients eligible for the parent study. Additionally, all English speaking patient nominated caregivers ≥ 18 years of age.
Study Duration:	Participants (patients and their nominated caregiver) in the ancillary economic evaluation will be followed for two years after transplantation or until patient death.


PARENT STUDY
TREATMENT SCHEMA
Patient ≥ 18 & ≤ 70yrs.
Acute leukemia or lymphoma
Adequate organ function
Performance score ≥ 70
Available both
1) 4-6/6 HLA-matched UCB units
2) 4-6/8 HLA matched related donor
Randomization
Stratified by Transplant Center
Double UCB
Haplo-BM
PARALLEL CEA
Patient
English Speaking
Providing CEA consent
Patient provides
1) Health insurer/s information
2) Nomination for caregiver to support data collection
CEA Coordinating Center
1) Obtains consent from nominated caregivers ≥ 18 yrs.
2) Takes responsibility for CEA data collection
Collection of prospective information via web portal on:
1) Patient direct medical costs
2) Patient direct non-medical costs
3) Patient work productivity costs
4) Caregiver Informal care giving time costs
5) Caregiver work productivity costs
Collection of retrospective information on:
1) Health insurer reimbursements
Completion of cost-effectiveness analysis dUCB vs. Haplo-BM

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1. BACKGROUND AND RATIONALE

1.1. The Parent Study

BMT CTN 1101 is a Phase III, randomized, open label, multicenter, prospective, comparative trial of double unrelated umbilical cord blood (dUCB) versus HLA-Haploidentical related bone marrow (haplo-BM) transplantation after reduced intensity conditioning (RIC) in patients with hematologic malignancies. These alternative sources of donor cells for RIC blood or marrow transplantation (BMT) effectively extend this treatment option to patients who lack other donors[1-6] however, concern remains about the durability of remissions, especially in myeloid malignancies, after RIC haploidentical BMT as well as differences between dUCB and haplo-BM in platelet engraftment, treatment related mortality (TRM), and serious infection.[7] Thus, BMT CTN 1101 has been designed to determine the best graft source for adult patients requiring alternative donor BMT. The central hypothesis is that progression-free survival (PFS) at two years after RIC haplo-BM transplantation is similar to the PFS after RIC dUCB transplantation.

The findings of BMT CTN 1101 have the potential to fundamentally change practice for patients who could benefit from BMT but are unable to proceed due to a lack of suitable related or unrelated donor cells. Any change in practice will also have important economic implications for patients, the health care system, and society.

1.2. Rationale for Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) provides information to help health care payers manage the use of costly medical technologies with the aim of maximizing the health of their patient populations when facing constrained budgets. It also provides information to clinicians and patients to help guide treatment decisions based on CEA's unique endpoints, perspectives, and time horizon.

While the progression-free survival of these two options may be similar, there may be significant differences in the costs and quality of life experienced by patients receiving dUCB or halpo-BM. Preliminary analysis of charges for 19 adult patients receiving dUCB (Mean=$650,000 per transplant, SD=$310,000) and 23 receiving haplo-BM (Mean=$460,300, SD=$290,000) at the Seattle Care Alliance between January 2007 and December 2009, indicate that the cost of dUCB transplantation is 1.4 times greater than haplo-BM transplantation (Difference=$190,000; 95% CI: $3,000 to $377,000; t[40]=2.05, p=0.047). Additionally, there is evidence that the quality of life of patients receiving dUCB may be inferior due to slower platelet engraftment, a higher rate or treatment-related mortality (TRM), and delayed immune recovery leading to increased serious infections in older adults.[8-10]

The potential high cost of dUCB, the hypothesized but unproven similarity in progression-free survival, and the potential differences in quality of life of patients receiving dUCB and haplo-BM, provides a compelling rationale for this parallel cost-effectiveness study.

In addition, although it is one of the costliest procedures in all of medicine, patient out of pocket medical expenditures for BMT are unknown. This issue is important because even modest

copays can be substantial to families given the total costs of transplantation. Significantly, patients undergoing BMT may exceed their lifetime insurance caps exposing them to the full cost of care thereafter.

The personal and family financial burden of BMT direct medical costs is an important area that can be directly addressed by this study.

Finally, because BMT requires substantial hospital stays, nonmedical costs for patients and their families can be substantial. Although many BMT centers provide subsidized housing to families, costs associated with transportation and living away from home, plus associated work loss, may pose significant burdens for patients and families.

This will be the first study to comprehensively study the impact of BMT on non-medical costs for patients and families.

The BMT CTN clinical trial of dUCB versus haplo-BM presents a time sensitive opportunity to comprehensively determine the cost-effectiveness of these two alternative options.

2. STUDY DESIGN

2.1. Study Overview

This is a parallel cost-effectiveness analysis (CEA) to determine the incremental cost per quality adjusted life years (QALYs), of dUCB versus haplo-BM. This specific type of CEA, with outcomes measured as quality-adjusted life years using health state utilities rated on a scale from 0 (death) to 1 (ideal health), is recommended by numerous groups, including the US Preventive Services Task Force on Cost-Effectiveness in Health and Medicine.[11]

2.1.1. Hypotheses and Specific Objectives

2.1.1.1. Hypotheses

Primary Hypothesis: Haplo-BM type transplantation improves quality-adjusted survival and is less costly than dUCB, both from the third party payer perspective and the societal perspective.

Secondary Hypothesis: Patient out-of-pocket costs, the cost of informal care giving, and indirect costs (lost earnings due to illness and its treatment) will be significantly greater for patients who receive bone marrow transplants using dUCB compared to those who are transplanted using haplo-BM donor cells.

2.1.1.2. Study Objectives

The primary objective is to determine the incremental cost-effectiveness of using dUCB vs. haplo-BM as donor cell sources for reduced intensity conditioning (RIC) blood or bone marrow transplantation in patients with select hematological malignancies. The study's secondary

objective is to examine the out-of-pocket costs, the cost of informal caregiving, and the impact on workplace productivity associated with dUCB vs. haplo-BM.

2.2. Eligibility Criteria

2.2.1. Patient Inclusion Criteria

All patients enrolled in the parent study are eligible for the CEA

2.2.2. Patient Exclusion Criteria

Primary language spoken: Languages other than English

2.2.3. Caregiver Inclusion Criteria

CEA participating patient nominated caregivers

2.2.4. Caregiver Exclusion Criteria

1. Primary language spoken: Languages other than English
2. Age <18 years at time of enrolment as caregiver participant

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary end-point for the analysis will be the cost per quality adjusted life year (QALY) from the third party payer perspective with two time horizons: (1) within trial, and (2) lifetime using economic modeling.

3.2. Secondary Endpoints

The secondary end-point includes costs from a broader societal perspective (incorporating health insurer direct medical care costs and patient out-of-pocket direct medical and direct non-medical costs).[12,13] Patient productivity costs (captured as part of QALY calculations) and the value of informal caregiving will be reported separately.

4. ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

1. Eligible patients presented with the option of participating in BMT CTN 1101, will at the same time be given the option to participate in the parallel economic evaluation.

2. For participants providing consent to participate in BMT CTN 1101 and the CEA, the Transplant Center Study Coordinator will:
    a. Complete the **HIPAA Authorization Form** and **Patient Consent Form** (See Appendix B) with patients interested in participating in the economic evaluation substudy.
    b. Complete the **Patient** and **Caregiver Contact Information Form** (See Appendix C) with the patient and/or caregiver.
    c. If the patient nominates a caregiver accompanying the patient, ask the caregiver if they would be willing to help the patient complete the cost diary survey and have them sign the Caregiver Consent Form (see Appendix D) if the caregiver is interested in participating. If the nominated caregiver is not accompanying the patient the Caregiver Consent Form will be mailed to the caregiver or the caregiver will be called by the FHCRC team.
    d. Copy the parent study **Patient Consent Form** and the Economic Evaluation Patient Consent Form to keep on file.
    e. Prepare a fax cover letter indicating the study site and contact person sending the fax (this information will be used to make follow-up phones calls to the contact person if data is missing from either CEA form).
    f. Fax documents a - e to the CEA Coordinating Center at the Fred Hutchinson Cancer Research Center.
        i. Aligning with the parent study, patients should be registered for the CEA study as close as possible and not more than 30 days prior to the initiation of the conditioning regimen. The eligibility screening (Segment A) includes a question confirming that the patient (or legal guardian) has signed the Economic Evaluation component of the informed consent.
    g. Fax immediate notification to the CEA Coordinating Center at the Fred Hutchinson Cancer Research Center if the patient withdraws from the study or dies.

3. CEA Coordinating Center staff will:

    a. Approach nominated caregivers directly by telephone to discuss their nomination and involvement in the Economic study.

    b. Provide a link to the **Named Caregiver Informed Consent to Participate in Research Form** (See Appendix D) for caregivers who confirm their willingness to participate.

    c. Place a follow-up telephone call within 7 days to caregivers who have not provided consent via the electronic consent form to provide support or to confirm unwillingness to participate.

    d. Be responsible for collecting all CEA data upon receipt of the electronic **Named Caregiver Informed Consent to Participate in Research Form** by the CEA Coordinating Center.

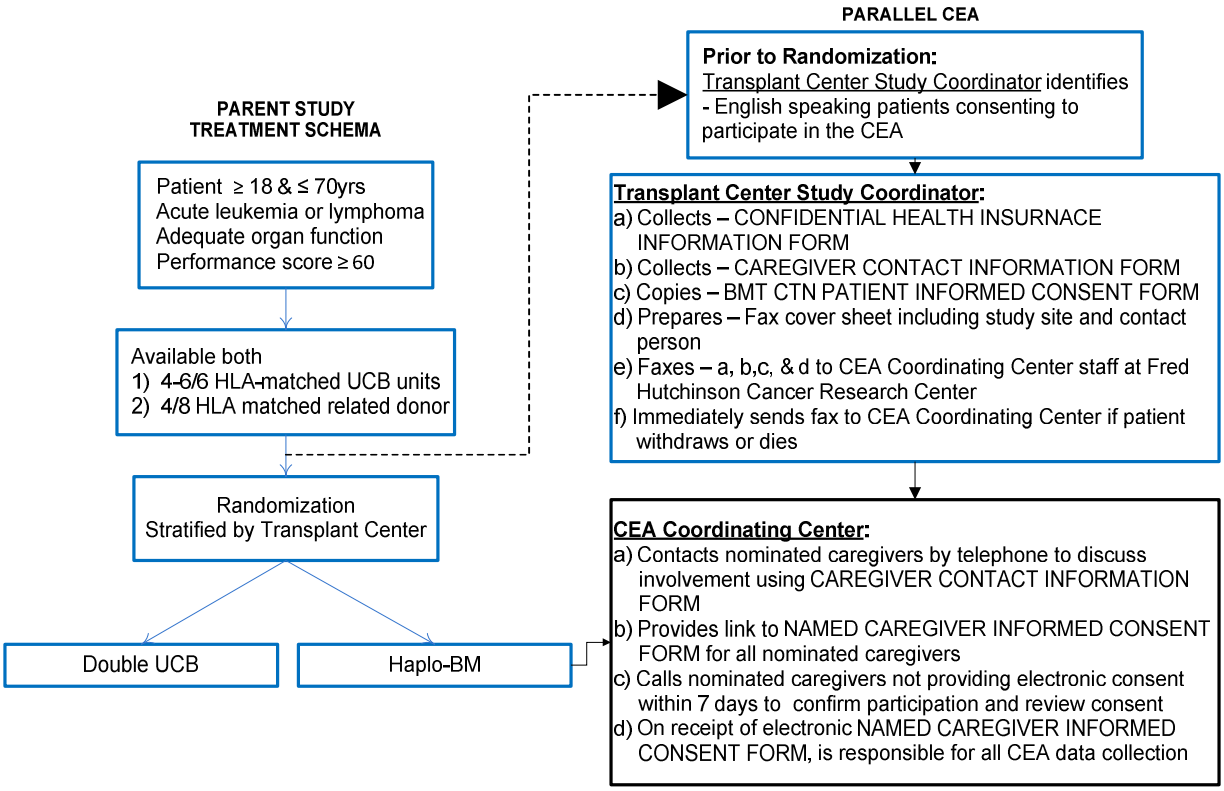

Figure 1 Summary of Enrollment Procedures

4.2. Data Collection

4.2.1. Collection of costs data

To comprehensively evaluate the cost-effectiveness of dUCB versus haplo-BM, information will be collected on both the costs and outcomes for each of the alternative donor cell sources. Cost information will be collected in four distinct areas (**Table 1**).

Table 1 Summary of Cost Information to be Collected

Cost Category	**Description**	
1. Direct medical care costs payer	Health insurance reimbursements	The cost of medical care paid by the patient's health insurer
2. Out-of-pocket costs		
Direct medical care costs patient	Copays, deductibles, uncovered medical bills	The cost of medical care not paid by the patient's health insurer
Direct non-medical costs	Transportation, accommodation, child care	The cost of accessing medical care born by the patient and their family
3. Indirect costs		
Patient	Lost productivity	Lost earnings for the patient, and the family/friends caring for them, due to the patient's illness and its treatment
Caregiver/s		
4. Cost of informal care	A valuation of informal care provided to patient that would otherwise be a real cost (i.e. home nursing care)	

4.2.1.1. Direct Medical Care Costs Payer: Health Insurance Reimbursements

Participants who consent to participate in CTN 1101 (or their legal guardians) will be given the option to participate in the parallel economic analysis. Those providing consent will be asked to provide the name(s) of their health insurer(s), the policy holder's name and date of birth, the health insurance group number(s) and policy identification number(s) (we anticipate that some patients will have multiple insurance plans).

This information will be used to request health care claims records from insurers for the period beginning 12-months prior to the date of BMT, through 2-years following transplantation. To account for administrative delays in claims data processing, requests will be made at least 30-months following the date of transplantation. Claims will be requested from health insurers in batches with batch size dependent on patient accrual to the parent study and subsequent accrual into the CEA. Requests will be made regardless of outcome (i.e. for patients who remain in remission, who relapse, and who die).

4.2.1.2. Out-of-Pocket Costs

In addition to health insurance information, information will be collected directly from patients and/or the caregivers nominated by the patient, to capture the out-of-pocket medical care costs of BMT. Patients and caregivers are asked to participate jointly because: there may be periods where patients are unable to provide information due to illness; patients usually have a team of caregivers supporting them in different capacities and at different time; and to encourage discussion, recall, and reconciliation of potential expenses. These costs will include direct medical care costs for patients (e.g. copays, deductables and uncovered medical bills) and direct non-medical patient costs: transportation costs, travel time and distance, accommodation costs, child care costs and telecommunication costs (additional costs that may be incurred to stay in contact with family and friends using local or long-distance telephone calls or other online

media). This information will be collected using an online adaptation of the cost diary method used by Goossens and colleagues.[14]

4.2.1.3. Indirect costs: Work Loss Related to Illness and Treatment (Productivity Costs)

Patient and caregiver time spent away from work will be estimated using the Work Productivity and Activity Impairment Questionnaire (WPAI). The WPAI measures work time missed as well as work and activity impairment due to a specific health issue.[15] The WPAI's validity has been established in a number of diseases[16-23] and has proven a useful tool for measuring relative differences between treatment groups in clinical trials,[24-28] including cancer,[29] in patients with and without disease.[30,31] Separate WPAI forms will be filled out for patients and the designated caregiver.

4.2.1.4. Caregiving time

Time spent in caregiving will be collected from nominated caregivers using the method of Dumont *et al*.[32] This approach asks the caregiver to provide information on the amount of time they spent on a typical day, before the patient's illness, on various care giving tasks (household duties, providing personal care, feeding, running errands, etc.). The caregiver is then asked to repeat this exercise in reference to a typical day in the last two weeks (while the patient is unwell or undergoing treatment).

The time reported in the baseline response provides a reference for all subsequent responses. The difference in time between baseline and each subsequent measurement is then used to estimate the additional care giving time resulting from the patient's illness. This also allows for changes in care giving tasks to be accounted for as the patient's condition and informal care giving needs change. Over the entire collection period, the total care giving time is calculated by adding the extra time spent on all types of tasks.

For the this study, participating caregivers will be asked to characterize their care giving activities in the period before the patient's illness as well as the period directly prior to transplantation. The pre-transplant estimate will be used as the reference for subsequent surveys while the pre-illness measure will be used as a covariate in multivariate analysis to control for any preexisting care giver dependency the patient may have had.

4.2.1.5. Valuing Patient Work Loss and Caregiver Time

The value of hours recorded for patient work loss and caregiver time will be estimated using wages from the Bureau of Labor Statistics for the sex and age of patients and caregivers, respectively.

4.2.1.6. Cost Data Collection Mechanism

Information on costs may be quite complex and thus will be collected prospectively from both haplo-BM and dUCB BMT participants using an online portal. The portal will be used to collect information on out-of-pocket costs (using a cost dairy), work productivity losses (using WPAI)

and informal caregiving time (using Dumont method). Participants will be prompted to complete information and forms noted above one-month after transplantation, and again 4-months and 7-month post transplant. (**Table 2**) (i.e. 3 data collection points over a period of 7 months dependent on survival).

Table 2 Cost Data Collection

Instrument	N items	Pre-transplant	Month Post-transplant											
			1			4			7					
Cost diary	12	X	X			X			X					
Patient WPAI	6	X	X			X			X					
Caregiver WPAI	6	X	X			X			X					
Caregiver time	14	X	X			X			X					
TOTAL N ITEMS		38												
ANTICIPATED TIME PATIENT		15-30 min												
ANTICIPATED TIME CAREGIVER		15-30 min												

Based on previous experience, we anticipate each entry to take between 15 and 30 minutes dependent on the volume of information to be entered. Following consent, each participant (including the patient and their nominated caregivers) will be provided with a web link for the portal, a unique user name and password to access the portal (both in writing and via email). The option to complete a mail-out version of the surveys will also be available. Depending on each participant's preference, email and/or telephone reminders will be used to prompt data entry into the system at the required time points. A toll free number with trained facilitators will be available during business and early evening hours to assist participants with filling out the survey materials.

The portal will present web-based versions of the WPAI questionnaire, the informal caregiving time questionnaire and cost diary. Prior to the use of the portal with study participants, the portal will be tested with a cohort of 10 consenting transplant inpatients, and their nominated caregivers, recruited from the Seattle Cancer Care Alliance. As far as is possible, patients will be selected to match the expected age and racial characteristics of BMT CTN 1101 participants. As changes to the questionnaires will be minor (non substantive changes in instructions and one item per screen rather than multiple items on paper) only cognitive debriefing and usability testing will be completed (a sample size of 10 is deemed sufficient for this level of testing).[33]

4.2.2. Quality of Life (Health State Utilities)

4.2.2.1. Instruments

As part of a comprehensive suite of patient reported outcomes, two quality of life instruments have been incorporated into BMT CTN 1101, the SF-36 and EQ-5D. The SF-36 takes 6 minutes to complete, and is being used to collect HQL data in BMT CTN protocols 0801 and 0901. The EQ-5D contains a five item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D takes approximately 1 minute to complete (Agency for Healthcare Research and Quality, 2005). EQ-5D scores will be used to calculate health state utilities for use in the cost-utility analysis. SF-36 scores will also be converted to health state utilities using the SF6D algorithm.[34] We will estimate and compare

results using the utilities from both instruments. Because there is no single agreed upon "best" way to measure health state utilities, this will allow us to evaluate the stability of estimates as a function of survey instrument selection.

4.2.2.2. Administration

EQ-5D and SF-36 self-report questionnaires will be completed as part of the suite of patient reported outcomes integrated into BMT CTN 1101 prior to transplantation and subsequently at 12 months, and 24 months from randomization or until death (Table 3). Only patients able to read and speak in English or Spanish are eligible to participate in the HQL component of this trial. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. The method of survey completion, the date, and the language will be recorded in the database. Surveys may not be completed by surrogates.

Table 3 Quality of Life Data Collection

Instrument	N items	Pre-transplant	12 months	24 months
Socio-demographics	8	X		
Global quality of life	4	X	X	X
FACT-BMT	37	X	X	X
MOS SF-36	36	X	X	X
Occupational functioning	6	X	X	X
Chronic GVHD	2		X	X
EQ-5D	5	X	X	X
Alternative contacts	2	X	X	X
TOTAL N ITEMS		98	92	92
ANTICIPATED TIME		30 min	30 min	30 min

5. STATISTICAL CONSIDERATIONS

5.1. Conceptual Overview

Cost-effectiveness analysis is a comparison of alternatives and is measured as the difference in the costs of care between alternative options relative to the change in effectiveness of the alternative options. The *incremental cost-effectiveness* of one alternative over another is derived using the following formula:

$$\text{Incremental cost-effectiveness}_A = (C_A - C_B)/(E_A - E_B)$$

Where C_A and C_B refer to average total costs of each alternative and E_A and E_B refer to average total effectiveness for each alternative, respectively. The resulting incremental cost-effectiveness ratio (ICER) can then be used to make a judgment on the value provided by alternative A when compared to alternative B as it represents the investment required for each additional unit of effect gained.

For this parallel CEA, the costs and outcomes of dUCB versus haplo-BM as alternative donor sources will be compared (

Figure 2).

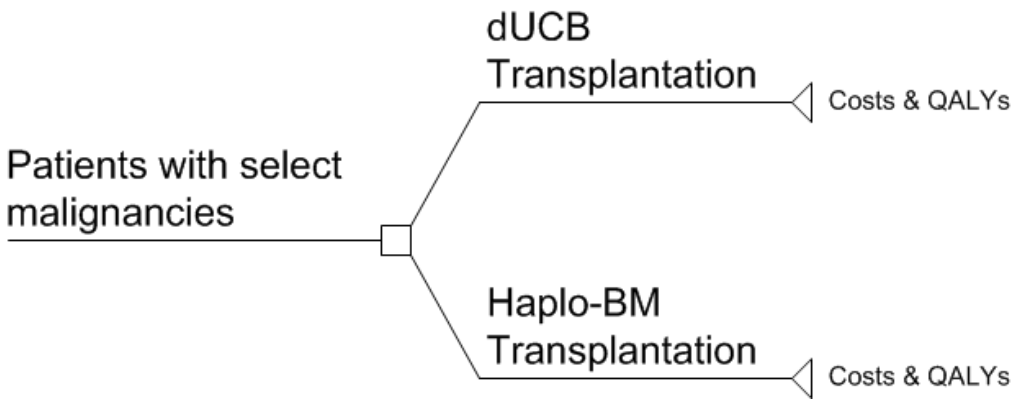

Figure 2 Schematic of the alternatives being compared

Correspondingly, the primary hypothesis of the economic evaluation, that haplo-BM will be less costly and more effective than dUCB, will be tested by comparing the arithmetic mean difference in cost (Δ_c) and the arithmetic mean difference in quality-adjusted survival (Δ_e) between each alternative:

$$\Delta_c = C_{dUCB} - C_{haplo\text{-}BM}$$

$$\Delta_e = E_{dUCB} - E_{haplo\text{-}BM}$$

Where C_{dUCB} and $C_{haplo\text{-}BM}$ refer to average total costs and E_{dUCB} and $E_{haplo\text{-}BM}$ refer to average total effectiveness for each alternative, respectively.
All analyses of cost and effectiveness will be completed on an intent-to-treat basis.

5.2. Analysis of Costs

5.2.1. Study Perspective and the use of Health Insurer Reimbursements

It is recommended that the analysis of costs in CEAs be conducted from both a health system perspective and a broader societal perspective.[12,35] For the evaluation of the costs of dUCB and haplo-BM, the primary analysis will take the third party payer perspective comprising of direct medical payer costs alone.

$$C_{Total} = C_{Direct\ Medical\ Care\ Payer}$$

Reimbursements from insurers will be the basis of estimating costs for the treatments (as study sites are nationwide and we expect a large number of payers to participate including Medicare and Medicaid, we believe that the estimate will be representative of BMT costs nationwide, subject to the limitations of the sample).

A secondary analysis will take the broader societal perspective including direct medical care costs for health insurers, direct medical care costs for patients, direct non-medical costs for patients, and indirect caregiver productivity costs.

$$C_{Total} = C_{Direct\ Medical\ Care\ Payer} + C_{Direct\ Medical\ Care\ Patient} + C_{Direct\ Non\text{-}Medical\ Patient} + C_{Indirect\ Caregiver}$$

To avoid double counting, indirect productivity costs for patients and the value of caregiving will not be included in the ICER calculations but recorded separately (patient indirect productivity costs are captured in the QALY).

5.2.2. Direct Medical Care Costs Payer

The null hypothesis is that there is no difference between the total costs of direct medical care for patients who receive dUCB vs. haplo-BM.

Insurance reimbursement records from each participant providing health insurance information will be reviewed and aggregated into two time horizons for the cost analysis; (1) pre-transplant (conditioning and attainment of donor cells), and (2) after-transplant care (the time following infusion of donor cells). For the base case analysis, the mean difference in disaggregate costs and total cost between patients (i.e. the incremental cost) who receive dUCB and haplo-BM will be analyzed using the Kaplan-Meier sample average estimation (KMSA) technique.[36,37] This technique minimizes bias in estimates due to: (1) the problem of censoring; and (2) that a number of patients will incur extremely high costs of care resulting in skewed data. Both censoring and skewedness are addressed by the KMSA. Using cost histories from the patients in each study arm, the KMSA technique determines the mean cost (*M*) over the time period of interest as:

$$M = \sum_i \widehat{S}_i \widehat{C}_i$$

where S_i denotes the probability of the event occurring in the i[th] month and $\hat{C}_i$ is the average cost among patients who are alive at the beginning of the i[th] month and $\hat{S}_i$ is the estimated survival probability obtained from the Kaplan-Meier curve. Specifically, $\hat{S}_i$ is the estimated probability of being alive at the beginning of the i[th] month. Lin *et al*.[38] demonstrate that the KMSA estimator is unbiased and consistent as long as (1) censoring is independent in time and (2) the time intervals for the cost analysis are sufficiently narrow.[38] The design of the treatment trial is consistent with independent censoring and the time intervals incorporated into cost data collection provide appropriately narrow time intervals. Lin *et al*. also show that the KMSA estimator is asymptotically normal with easily estimated variances, permitting standard two-sample parametric testing.[38]
Finally, a regression-based KMSA model developed by Lin will be used account for baseline patient characteristics that could influence costs, to account for clustering within study centers, and to evaluate the uncertainty provided by the use of these different analytic techniques as an analytic sensitivity analysis.[39-41]

5.2.3. Out-of-pocket and Personal Costs

The null hypothesis is that there is no difference between direct non-medical, indirect, and informal caregiving costs for patients who receive dUCB vs. haplo-BM.

The same analytic approach will be used for out-of-pocket and indirect costs. Direct medical costs paid by patients will be based on records provided by patients and caregivers. Direct non-medical costs will be disaggregated into transportation, accommodation, telecommunication, and other costs. These costs will then be combined to calculate the total out-of-pocket costs incurred. Indirect costs for patients and their nominated caregivers will be presented separately as will cost related to informal caregiving. Time spent by family caregivers to provide support to patients will be valued initially using the opportunity cost method, with subsequent valuation using the proxy-good method in sensitivity analyses.[42]

5.3. Analysis of Effectiveness: Quality Adjusted Life Years

The null hypothesis is that there is no difference between the quality adjusted life for patients who receive dUCB vs. haplo-BM

Health state utilities derived from the EQ-5D and SF-36 (using the SF-6D algorithm)[34,43] collected by CTN 1101, will be combined with survival data to calculate quality adjusted life years (QALYs) using the area under the curve method.[39] The same analytic approach used for the analysis of costs will be used for the analysis of QALYs; using KMSA for the base case followed by mixed effects modeling. Baseline health state utilities will be included as a covariate in multivariate analysis of the difference in QALYs between dUCB and haplo-BM to account for possible differences in baseline utility between groups.[44]

5.4. Analysis of Incremental Cost-Effectiveness

We will analyze costs from both a societal and health insurer perspective.[12,35]. The insurer perspective considers only reimbursable direct medical care costs. The societal perspective includes direct medical care costs for health insurers, direct medical care costs for patients, direct non-medical costs for patients, and indirect caregiver productivity costs:

$$C_{Total} = C_{Direct\ Medical\ Care\ Payer} + C_{Direct\ Medical\ Care\ Patient} + C_{Direct\ Non\text{-}Medical\ Patient} + C_{Indirect\ Caregiver}$$

To avoid double counting, patient productivity costs other than the time spent in treatment (indirect productivity) and the value of caregiving will not be included in the ICER calculations but recorded separately (patient indirect productivity costs are captured in the QALY).

If Aims 1 and 3 show that haplo-BM is less costly and more effective (greater QALYs) than dUCB, haplo-BM is said to *dominate* dUCB and no numerical estimate of incremental cost-effectiveness is required. Instead the estimated reduction in cost and improvement in quality adjusted survival, and the associated uncertainty in these estimates, will be reported. If Haplo-BM is less costly and have equal or non-inferior effectiveness to dUCB (as determined by the difference in QALYs), the estimated reduction in cost, equivalence or non-inferiority in QALYs, and the associated uncertainty in these estimates, will be reported. If Halpo-BM is more costly and more effective than dUCB, incremental cost-effectiveness ratios and will be reported, with uncertainty characterized (see below).

5.5. Lifetime Horizon and Economic Modeling

Mean costs and mean QALYs for dUCB and haplo-BM patients, as estimated using data collected by the parallel CEA, will be used as input in a health economic model. We will compute within-trial and projected (lifetime) results, the latter using modeling. To extend the analysis of the observation period for this study to a lifetime horizon, overall survival (OS) beyond the observation period will be extrapolated using different parametric survival functions (Weibull, Gompertz, exponential, log-normal and generalized gamma distributions)[45] with the base case survival function selected using the Akaike Information Criterion (AIC).[46] Cox-Snell residuals will be plotted as a confirmatory test to identify the function with the best fit to the observed data.[47] The mean number of life-years for patients in each group will be estimated as the area under the OS curve.[48] QALYs will be estimated from OS by weighting with utility values obtained from the analysis of utility data. Projected utility weights for long term survivors will be based on monthly trends in utility as observed for those who survive the year following transplantation. Projected utility weights for the last 6 months of life will be based on utilities for the last 6 months of life for persons who die during the year following transplant. In the case where insufficient numbers of persons have died within 6 months of their survey, we will use patient's pre-transplant utility scores as an estimate for quality of life in the last 6 months of life.

Similarly, for those who survive through the end of the study observation period, we will project costs over a lifetime horizon modeled as described above, dividing costs into two periods: continuing care and death costs. Continuing care costs will be based on monthly trends in costs observed for those who have survived the year following transplant. Death costs, defined as costs of care during the last 6 months of life for persons who have died, will be based on costs of care observed for those who die during the year following transplant. Costs will be modeled based on projected survival (see above).

5.5.1. Uncertainty Analysis

One-way and multi-way analyses will be conducted to characterize uncertainty around the base results. Probabilistic uncertainty analysis will be completed to explore the joint uncertainty of all model parameters. Distributions will be defined for all of the input parameters in the model including cost, QALY, OS, and utility values. One thousand Monte Carlo simulations will be run and results plotted on the cost-effectiveness plane.

In the case where an incremental cost-effectiveness ratio is computed (higher costs, higher QALYs), cost-effectiveness acceptability curves will be created to characterize the level of probability that the intervention is cost-effective at different willingness-to-pay thresholds (e.g., $50,000, $100,000 per QALY).[49]

One-way sensitivity analyses will be conducted on all parameters to determine their individual impact on results with parameters varied within one standard deviation or error from their base case value. Additional one-way sensitivity analyses will be completed around the method used to value caregiving.

5.6. Base Year Cost Conversion and Discounting

All costs will be converted to base year costs (the base year being the year BMT CTN 1101 commences). Direct medical costs will be converted using the medical consumer price index[50] and non-medical costs will be converted using the US Consumer Price Index for All Urban Consumers.[51] Costs and outcomes incurred beyond 12-months form randomization, will be discounted at a rate of 3% annually with sensitivity analyses completed with discount rates of 1% and 5%.[35]

5.7. Missing data

While missing direct medical care costs (payer) data is not anticipated, missing quality of life, out-of-pocket, productivity and caregiving cost data may be encountered. In a longitudinal study, missing data for a particular subject may be missing from a certain time during follow-up onward (dropouts), or it may be intermittently missing. While tests for completely random dropouts are available, such tests do not carry over for assessing intermittently missing data. Furthermore, it is possible to incorporate a model for the mechanism of missingness for dropouts, but not so for intermittently missing data[80]. We will explore the mechanism of missingness if the amount of missing data is substantial. Assuming completely missing at random data in the presence of informative missingness can result in substantial bias. We will address this issue if necessary using random effects models.80 While analyses using mixed effects (subject-specific) models and generalized estimating equations (population average models) allow all observed data to be included in the analysis under the assumption that the data are MAR,[52] if substantial missing data occurs and MAR is tenable, we will impute missing data using multiple imputation. Multiple imputation can be thought of in a Bayesian context as using the posterior predictive distribution to draw samples to impute missing values. Often, 5 imputed values are drawn for each missing value, thus forming 5 complete data sets. Analyses are performed on each data set and the results are appropriately combined to account not only for uncertainty in parameter estimates, but uncertainty due to imputation.[77]

5.8. Sample Size and Power Calculations

The targeted sample size for the parent study is 410 patients, 205 per treatment arm. Because participants in the parent study have the option not to participate in the ancillary CEA, the sample size for the CEA analyses may be less than the complete cohort of patients in the parent study.

Table 4 presents the power associated with each specific aim and the final CEA with different sample size assumptions (proportions of the parent study sample). Power calculations have been estimated under four scenarios: (1) haplo-BM dominates dUCB (i.e. is both less costly and more effective than dUCB), (2) haplo-BM is equivalent to dUCB (i.e. where the difference in quality adjusted survival between haplo-BM and dUCB does not exceed a defined upper and lower bound), (3) haplo-BM is non-inferior to dUCB (i.e. the difference in quality adjusted survival between haplo-BM and dUCB does not exceed a defined lower bound), and (4) haplo-BM is more costly and more effective than dUCB.

In alignment with BMT CTN 1101, we allow for 5% censoring due to loss to follow-up in addition to administrative censoring and anticipation that up to 5% of patients randomized do not make it to the assigned transplant. Parameters used in these calculations: difference in mean direct medical care costs (payer) between dUCB and Halpo-BM (ΔC = \$142.5K, SD: \$300K) - three quarters of the difference and the same variability in costs seen in our preliminary analysis of 42 Seattle Care Alliance transplant patients; difference in mean out-of-pocket and indirect costs for families between dUCB and haplo-BM (ΔC = \$2.6K, SD: \$1.1K) - half the difference and the same variability in costs seen in a pilot study exploring the out-of pocket costs associated with hematopoietic-cell transplantation;[53] for superiority testing, minimally clinically important difference (MCID) in QALYs (E_{MCID} = 0.147) based on MCID estimates of utility values provided by the EQ-5D and SF-6D[54], standard deviation (SD) two times the MCID in QALYs (SD: E_{MCID} = 0.294); an equivalence margin equal to plus and minus half the MCID in QALYs ($E_{MCID}/2$ = 0.074) with a standard deviation two times this value (SD: $E_{MCID}/2$ = 0.147); a similar negative non-inferiority margin ($-E_{MCID}/2$ = -0.074) and variance (SD: $E_{MCID}/2$ = 0.147); and, for ICER power calculations, a correlation between cost and effect of 0.25.

Estimates of the power for ICERs are derived from the statistical test of whether net monetary benefit (NMB) is significantly different from zero with NMB calculated as the willingness to pay (WTP) threshold times the difference in QALYs minus the difference in cost ($[WTP.\Delta E]- \Delta C$).[39]

Table 4 Power Calculations

Scenario	Hypotheses	CEA Sample Size	Power for Costs	Power for QALYs*	Power for ICERs	WTP Threshold/QALY
Specific Aim 1 – Costs Direct Medical Payer (CDMP)						
	H_o: $CDMP_{dUCB} = CDMP_{haplo\text{-}BM}$ H_a: $CDMP_{dUCB} \neq CDMP_{haplo\text{-}BM}$	410 (100%)	0.993			
		308 (75%)	0.969			
		205 (50%)	0.876			
Specific Aim 2 – Costs Out-of-Pocket and Indirect (COOPI)						
	H_o: $COOPI_{dUCB} = COOPI_{haplo\text{-}BM}$ H_a: $COOPI_{dUCB} \neq COOPI_{haplo\text{-}BM}$	410 (100%)	0.999	-		
		308 (75%)	0.999			
		205 (50%)	0.999			
Specific Aim 3 – Effectiveness: QALYS (E)						
	H_o: $E_{dUCB} = Eh_{aplo\text{-}BM}$ H_a: $E_{dUCB} \neq E_{haplo\text{-}BM}$	410 (100%)	0.996			
		308 (75%)	0.981			
		205 (50%)	0.906			
Specific Aim 4 - CEA						
1- haplo-BM *dominates* dUCB	H_o: $C_{dUCB} = C_{haplo\text{-}BM}$ H_a: $C_{dUCB} \neq C_{haplo\text{-}BM}$ H_o: $E_{dUCB} = Eh_{aplo\text{-}BM}$ H_a: $E_{dUCB} \neq E_{haplo\text{-}BM}$	410 (100%)	0.993	0.996	-	-
		308 (75%)	0.969	0.981		
		205 (50%)	0.876	0.906		
2- Equivalent QALYs	H_o: $\Delta E > \frac{E_{MCID}}{2}$ H_a: $\Delta E < \frac{E_{MCID}}{2}$	410 (100%)	-	0.997		
		308 (75%)		0.983		
		205 (50%)		0.899		
3- Non-inferior QALYs	H_o: $\Delta E < -\frac{E_{MCID}}{2}$ H_a: $\Delta E > -\frac{E_{MCID}}{2}$	410 (100%)	-	0.997		
		308 (75%)		0.982		
		205 (50%)		0.910		
4- haplo-BM more costly and effective than dUCB	H_o: $NB = 0$ H_a: $NB \neq 0$	410 (100%)	-	-	0.989	$50,000
		308 (75%)			0.958	
		205 (50%)			0.852	
		410 (100%)			0.988	$62,000
		308 (75%)			0.954	
		205 (50%)			0.844	
		410 (100%)			0.982	$100,000
		308 (75%)			0.940	
		205 (50%)			0.818	

CEA = Cost-Effectiveness Analysis; **QALYs** = Quality Adjusted Life Years; **ICERs** = Incremental Cost Effectiveness Ratios; **WTP** = Willingness-to-pay; *The power reported for the equivalence and non-inferiority tests is the probability that the confidence interval is within defined limits

APPPENDIX A

HUMAN SUBJECTS

APPPENDIX A

HUMAN SUBJECTS

1. Subject Consent

For the parent study, a conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principle investigator or other designated physician. A discussion on the cost-effectiveness study will be included in this conference.

2. Confidentiality

Maintaining confidentiality
For the parent study, 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 CEA will involve cost data collection independently to the parent study. In order to combine these data with outcome data collected during BMT CTN 1101, linkage will be required. To ensure the confidentiality of BMT CTN CEA participant is maintained, data sharing and security protocols will be established as outlined here. Similarly, transfer and linkage of health insurance reimbursement data will be covered under the same protocols.

All linkage between CEA data, BMT CTN 1101 clinical outcome data and health insurance reimbursement data will be completed by CEA Coordinating Center Staff on-site at the Fred Hutchinson Cancer Research Center. All data transfers will be encrypted using 256-bit encryption with a 64 character password, with passwords following these guidelines:

- Contain a mixture of letters (upper and lower case), digits, and punctuation.
- Do not use names, birthdays, social security numbers, addresses, telephone numbers, or any other easily guessed items.

  A good resource for password generation is https://www.grc.com/passwords.htm. Note that the 63-character passwords for printable-ASCII and alpha-numeric characters are acceptable exceptions of the 64-character guideline.

Secure transfer methods to be used for data transfer include in-person transfer to study staff, mail with a tracking number, or a secure FTP site. In all cases the password to decrypt the data will be transferred in an alternative method to the transfer of data. Transfer file passwords **will not** be sent in the same email or package as the data.

BMT CTN 1101 clinical outcome data and the code relaying patient identity to the CEA Coordinating Center, will be transferred separately. Identifying code and corresponding data for CEA participants only will be transferred. Health insurance reimbursement data form health insurers will require similar separation between code relaying patient identity and linkage variables and reimbursement data. Packages sent through the mail will be required to be

traceable and must be signed for by a member of the CEA Coordinating Center team. All removable data storage will be physically kept in a locked storage location while not in use

On receipt of identity and linkage variable files, CEA Coordinating Center Staff will complete all linkages before creating a final analysis dataset. This file will be a limited dataset striped of all protected health information (PHI) other than dates (birth, death, diagnosis, treatment, medical service, etc.) and geographic subdivision (zip code, census tract, city, etc.). Any removable data storage will be destroyed after linkage and verification are deemed complete. Datasets will be destroyed per schedules specified by data sharing agreements.

Risks to confiedentiality
The risk associated with this study is considered to be minimal. The primary risk is breach of confidentiality (e.g. brass key lost/stolen or unauthorized electronic access of patient data).

If a brass key is lost or stolen, it will be reported immediately to FHCRC security (with immediate request for locks to be changed), the FHCRC IRB, the EMMES corporation (as the part responsible for trial oversight, monitoring and data management for the study) and CTN principle investigators. Similarly, any unauthorized electronic access of patient data will be reported to FHCRC security, FHCRC IT department, FHCRC IRB, the EMMES corporation and CTN principle investigators.

3. Participation of Women and Minorities

Women and ethnic minorities and other populations will be included in the main study and cost-effectiveness study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of leukemia and lymphoma in these groups.

APPENDIX B-1

HIPAA AUTHORIZATION

APPENDIX B-1

HIPAA AUTHORIZATION FOR THE USE OF MEMBER PROTECTED HEALTH INFORMATION FOR RESEARCH

Title of Research Study: *Ancillary Cost-Effectiveness Analysis to: A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUBC) versus HLA-Haploidentical Related Bone Marrow (haplo-BM) for Patients with Hematologic Malignancies*

The research study named above and described more fully in the informed consent form that you sign ("Research Consent") requires that the researchers have access to health insurance information about you (also called "Protected Health Information" or "PHI"). By law, your health insurance provider (the "Insurer") must protect the confidentiality of your PHI. The researchers can obtain your PHI from the Insurer and use it for research **only if you authorize and direct the Insurer to share it with them.**

This authorization form ("form") describes what types of PHI the researchers need and what they will do with it as part of the research study. Please read it carefully. If you agree with it, please sign your name at the bottom. You will be given a copy of this form after you have signed it.

If you sign this form, your PHI will be shared with Fred Hutchinson Cancer Research Center, its staff, and others who work with them. In this form, the term for all these people is "Researchers" and they are described more fully in the Research Consent. The Researchers will use the PHI only for the purposes described in the Research Consent and in this form.

1. The protected health information to be obtained and used by the Researchers for the Study includes:

- All health insurance information including the type of health insurance, provider, policy number, group number and the policy holder's name and date of birth. It also includes information about health care costs and health care claims information as well as reimbursements made by your health insurer(s).

- The specific protected health information that will be obtained from the Insurer and used for the Research is described below:

    - Dates and codes associated with medical service and diagnoses
    - Location of medical service
    - Provider of medical service

2. What the Researchers will do with your Protected Heath Information.

The Researchers will use your PHI only in the ways described in the Research Consent form that you sign and as described here. They may also share your PHI with certain people and groups. These may include:

- The sponsor of the Study, The National Heart, Lung and Blood Institute. The sponsor reviews the Study. Government agencies, review boards, and others who watch over the safety, effectiveness and conduct of the research

- Others, if the law requires.

By law, the Researchers are required to protect the confidentiality of your PHI. The Research Consent form you sign describes in more detail how your PHI will be protected. You may ask questions about what the Researchers will do with your information and how they will protect it. Privacy laws do not always require the receiver of your information to keep your information confidential. After your information is given to others, there is a risk that it could be shared without your permission.

You are free to refuse to allow the Researchers access to your PHI. If you refuse, you will not be able to participate in this research study but your refusal will not affect your health insurance eligibility or coverage.

3. How long the permission will last?

The permission for the Researchers to obtain and use your protected health information will end when the Researchers complete the research study AND any review of the research study is completed.

4. Canceling your permission.

You may change your mind and take back your permission anytime. To take back your permission, please send a written request to the research study coordinator, Lisel Koepl, at Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, M/S M3-B232, Seattle, Washington 98109-1074. If you do this, you may no longer be allowed to be in the research study. The Researchers may still keep and use any Protected Health Information they already have. But they can't obtain more PHI about you for the research study unless it is required by a federal agency that reviews the research.

5. Giving permission

You give your permission for the use of your protected health information by signing this form.

Signature

I authorize and direct the Insurer to provide access to my protected health information to the Researchers as described in this authorization form.

_____	_____
Signature of participant or participant's Legal Representative	Date
_____	_____
Printed name of participant or participant's Legal Representative	Representative's relationship to participant

Primary insurance (if any):
Health Insurer: _____ Type of Insurance: _____
Policy Number: _____ Group Number: _____
Policy Holder's Name: _____Policy Holder's Date of Birth: _____

Additional insurance (if any):
Health Insurer: _____ Type of Insurance: _____
Policy Number: _____ Group Number: _____
Policy Holder's Name: _____Policy Holder's Date of Birth: _____

If more than 2 insurance providers, please add additional insurance information below:

Health Insurer:_____ Type of Insurance: _____

APPENDIX B-2

PATIENT INFORMED CONSENT

APPENDIX B-2

PATIENT INFORMED CONSENT INFORMATION

(To be included in Parent Study Consent Form once funding of the proposed ancillary study has been confirmed)

19. Cost-effectiveness Research (Optional)

An additional part of this study is to look at cost-effectiveness.

Why look at cost-effectiveness? To help doctors and patients understand the costs and effects of the two transplant types.

In the future, this may help with decisions on which treatments to use based on both the cost involved and how well the treatments work.

Who is doing this research? Dr. Scott Ramsey of the Fred Hutchinson Cancer Research Center in Seattle is leading the cost-effectiveness research team. Dr. Ramsey is a doctor and well known health economist.

What information do I need to give? We need to know about your health insurance including the type, provider, policy number, group number, and the policy holder's name and date of birth.

We also know that health care costs are not the only costs involved in intensive medical treatments. The costs you and your family have to cover are also very important so we want to collect information on these costs as well, for example; out-of-pocket medical costs, travel and accommodation costs and the cost of time off work for both you and your caregivers (family and friends).

How will my health insurance information be used? After you have finished the transplant study, we will use the health insurance information you have given us to get information on the reimbursements made by your health insurer to calculate the cost of your transplant. Knowing that illness and transplant related costs occur before the actual transplant itself and for a number of years after the transplant, we will get information on reimbursements made for the 12-months before, and the 2-years after, your transplant.

Only research staff from the Fred Hutchinson Cancer Research Center will have access to this information. Confidentiality will be maintained using standard data security procedures including a pledge of confidentiality signed by all research staff, data encryption, storage of all digital/electronic data under network and password protection, storage of all physical files (paper or other media such as CDs) in secure facilities (i.e. on-campus locked offices and locked filing cabinets).

How will my personal and family costs be collected? We are asking you to name the person/s who will give the day-to-day help you need during and after your transplant, such as your spouse, partner, parent, grown child or sibling, and friends. We will help you and the person you nominate (using email reminders plus telephone support) to give us information on your costs using an online questionnaire and cost diary. A user identification number and password will be provided to access the system which has been designed to be as simple as possible while at the same time giving the chance to provide complete cost information.. The option to complete a mail-out survey will also be available.

How often will the questionnaire and cost diary need to be completed and how long will it take? We would like to collect personal cost information 1 month after your transplant, and again 4 and 7 months after your transplant date. We think this will take between 15 and 30 minutes for each entry depending on how much there is to enter.

Why do I need to name my caregivers? You may not feel like using the cost diary while you recover from your transplant. Your caregiver/s may be the one(s) arranging travel and accommodation and looking after bills.

We are also interested in the time they spend caring for you after your transplant and the time – off work they may take. *Please talk to your caregivers about this research before nominating them.*

If you do give us the name of your caregiver/s, we will give them information on what the research involves and what they would need to do before getting their personal consent to participate.

Are there any risks? We will make every effort to keep your health insurance and personal information private. We will use this information only to get reimbursement information for the cost-effectiveness research. A possible risk is the loss of confidentiality about your medical information although the chance of this happening is very small.

What will I receive for my involvement? You will not get paid for your involvement in the cost-effectiveness research nor will there be any cost to you to be involved.

If personal cost information is provided, we will give you a summary of these costs at the end of the study. This may be helpful information for taxation purposes.

Do I have to be involved in the cost-effectiveness part of the study? No, you do not have to be part of the cost-effectiveness research. Your involvement is totally voluntary and you can leave at any time. Leaving or deciding not to be part of the cost-effectiveness component will not change the care or services you receive in any way.

Who can I speak to about the cost-effectiveness research? Contact Lederle Tenney, Fred Hutchinson Cancer Research Center (855) 267-9045 or email ltenney@fhcrc.org

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 be involved in the cost-effectiveness research. If I decide to not be involved, it will not affect my medical care in any way.

.

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

Participant Name _____

Signature_____ Date_____

APPENDIX C

PATIENT AND CAREGIVER CONTACT INFORMATION

APPENDIX C

Patient and Caregiver Contact Information

Ancillary Cost-Effectiveness Study to:

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

Your Name: _____

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

Protocol: BMT CTN #1101 Ancillary CEA

Principal Investigator: Scott Ramsey, MD, PhD

Principal Co-Investigator:

Paul O'Donnell, MD, PhD

Parent Study Collaborators: Paul O'Donnell, MD, PhD
Ephraim Fuchs, MD
Claudio Brunstein, MD, PhD
Mary Eapen, MD, MS

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).

Best contact telephone number for you:_____
Best Email for you:_____

I also provide the name(s), telephone contact number and email of my **caregivers** to help me give personal cost information using the online questionnaire and cost diary linked with this study and to provide additional caregiving information.

Caregiver 1full name: _____
Relationship to you: _____
Best contact telephone number:_____
Email:_____

Caregiver 2 full name: _____
Relationship to you: _____
Best contact telephone number:_____
Email:_____

APPENDIX D

NAMED CAREGIVER INFORMED CONSENT

APPENDIX D

Named Caregiver
Informed Consent to Participate in Research

Ancillary Cost-Effectiveness Study to:

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

Your Name: _____

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

Protocol: BMT CTN #1101 Ancillary CEA

Principal Investigator: Scott Ramsey, MD, PhD

Principal Co-Investigator: Mark Bensink, PhD, MSc, MEd
David Blough, PhD
Paul O'Donnell, MD, PhD

Parent Study Collaborators: Paul O'Donnell, MD, PhD
Ephraim Fuchs, MD
Claudio Brunstein, MD, PhD
Mary Eapen, MD, MS

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

You have been named by a participant in a research study as someone who could assist with the collection of out-of-pocket and personal cost information as part of a cost-effectiveness study.

2. Background

We know that health care costs are not the only costs involved in intensive medical treatments. Personal costs covered by patients and their family are also very important.

As part of cost-effectiveness research being completed alongside a main transplant research study, we would like to collect information on these costs, for example; out-of-pocket medical costs, travel and accommodation costs, the cost of time off work for the person getting the transplant, and your time, as the person caring for them during and after the transplant.

3. Purpose

We are inviting you to help with the collection of this information as part of the cost-effectiveness study.

Information on out-of-pocket and personal cost information will, on its own, be helpful for future patients and their families. When linked with health care cost information, the cost-effectiveness study will give information that may help doctors and patients in the future understand the costs and effects of the treatments being studied and to help with decisions on which treatments to use based on both the cost involved and how well the treatments work

4. How will personal and family costs be collected?

We will help you, as the caregiver named by the person getting the transplant, to give us information on out-of-pocket and personal costs using an online questionnaire and cost diary. We will give you email reminders plus telephone support to do this. You will be provided with your own user identification number and password to access the system which has been designed to be as simple as possible while at the same time giving the chance to provide complete cost information. The option to complete a mail-out survey will also be available.

Only research staff from the Fred Hutchinson Cancer Research Center will have access to this information. Confidentiality will be maintained using standard data security procedures including a pledage of confidentiality signed by all research staff, data encryption, storage all all digital/electronic data under network and password protection, storage of all physical files (paper or other media such as CDs) in secure facilities (i.e. on-campus locked offices and locked filing cabinets).

5. Why am I being asked to participate?

The person getting the transplant may not feel like using the cost diary while they recover from the transplant. You, as the person's caregiver, may be the one arranging travel and accommodation and looking after bills. We are also interested in the time you spend caring for the person getting the transplant and the time –off work you may take.

6. How often will the questionnaire and cost diary need to be completed and how long will it take?

We would like to collect personal cost information 1 month after your transplant, and again 4 and 7 months after your transplant date.We think this will take between 15 and 30 minutes for each entry depending on how much there is to enter.

7. Who is doing the cost-effectiveness research?

Dr Scott Ramsey of the Fred Hutchinson Cancer Research Center in Seattle is leading the cost-effectiveness research team. Dr Ramsey is a doctor and well known health economist.

8. Are there any risks?

We need no more personal information than we have used to provide you with this study information (your name, relationship to the person getting the transplant, your address and telephone number). We will make every effort to keep the information we do have private only to be used to help with the cost-effectiveness research study. A possible risk is the loss of confidentiality about your information although the chance of this happening is very small.

9. What will I receive for my involvement?

You will not get paid for your involvement in the cost-effectiveness research nor will there be any cost to you to be involved. If personal cost information is provided, we will give the person getting the transplant a summary of these costs at the end of the study. This may be helpful information for taxation purposes.

10. Right to Ask Questions and/or Withdraw

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

Lederle Tenney Fred Hutchinson Cancer Research Center, Seattle (855) 267-9045 or email: ltenney@fhcrc.org

If you choose not to take part or leave this study, it will not affect the medical care received by the person who named you as their caregiver in any way.

Statement of Consent to Support the Collection of Out-of- pocket and Personal Cost Information as the Named Caregiver of a Person Participating in a Cost-effectiveness Study Being Conducted Alongside a Clinical Trial

The purpose of collecting out-of-pocket and personal costs information, 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 copy of this consent form to keep.

I understand that I do not have to be involved in this research. If I decide to not be involved, it will not affect the medical care received by the person naming me as their caregiver in any way.

❑ I voluntarily agree to participate in the collection of out-of- pocket and personal cost information as a caregiver of person participating in an ancillary cost-effectiveness study.

❑ I do not agree to participate in the collection of out-of- pocket and personal cost information as a caregiver of person participating in an ancillary cost-effectiveness study.

Participant Name_____

Signature_____ Date_____

APPENDIX E

REFERENCES

APPENDIX E

REFERENCES

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