Summary of Changes
BMT CTN 1101 Version 7.0 to 8.0
Dated: January 18, 2017

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 (Haplo) for Patients with Hematologic Malignancies.

#	Section title, number and page number	Original text:	Changed to:	Rationale
1.	Throughout the protocol document	*N/A*	Changes to the protocol document were made for consistency and clarity, typos were corrected, and formatting was updated throughout.	Updated for clarity and consistency.
2.	Cover Page	Version 7.0	Version 8.0	Updated for consistent versioning.
3.	Cover Page	N/A	Added the following names to the protocol team: Jamie Garrison, MS and Achintya Jaitly (Emmes) and Nahed El Kassar, MD, PhD (NHLBI).	Updated protocol team information for accuracy.
4.	Cover Page and throughout the protocol document	N/A	Updated protocol to be reflective of changes in protocol team institutional affiliations.	Updated protocol team members' institutional affiliations for accuracy.

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5.	Page i	N/A	List of participating centers was updated.	Updated list of participating centers for accuracy.
6.	Protocol Synopsis – Study Design Page ii	1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, or Burkitt's lymphoma in remission. 2) Lymphoma, including marginal zone lymphoma, follicular lymphoma, or chemotherapy-sensitive large-cell, Hodgkin or mantle cell lymphoma.	1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, dendritic cell leukemias, natural killer cell malignancies or Burkitt's lymphoma in remission. 2) Lymphoma, including marginal zone lymphoma, follicular lymphoma, or chemotherapy-sensitive large-cell, Hodgkin or mantle cell lymphoma, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma.	Clarification for the inclusion of eligible diseases to the study design to be consistent with new protocol language.
7.	Background and Rationale Section 1.1 (NEW) Page 1-6	N/A	*Extended Family Members as Haploidentical Donors* Preliminary data (Fuchs E, et al., unpublished) in which 10 patients with high-risk hematologic malignancies received HLA-haploidentical transplants from extended family donors (aunt, uncle, niece, nephew, cousin, grandchild) showed no negative impact on transplant outcomes compared to results using first degree family donors. Use of extended family members as potential donors when a suitable first degree relative is unavailable or unsuitable is supported by	Added discussion of data along with supporting figure showing no negative impact of extending eligibility to extended family members who are haplos, as defined in the protocol.

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			another Johns Hopkins study which used the 1101 haploidentical transplantation protocol for recipients of grafts from 20 heavily HLA-mismatched unrelated donors (Kasamon Y, et al. presented at ASH 2015 and submitted for publication) where genetic heterogeneity would be expected to be much greater between donor and recipient than in transplants using family donors. In this study, there was a median of 2 HLA mismatches and included three 7/10 matches, one 6/10 match and one 5/10 match. Full CD3 chimerism was 93% at day 60 and there was no grade 3 acute GVHD. The cumulative incidences of grade 2 acute GVHD and any chronic GVHD were 19% and 7%, respectively. Data from both extended family donors and HLA-mismatched unrelated donors showed high rates of engraftment and acceptably low incidences of acute or chronic GVHD and non-relapse mortality.	
8.	Inclusion Criteria Section 2.2.1 Page 2-1	2. Patients must have available both: a. One or more potential related mismatched donors (biologic parent (s) or siblings (full or half) or children). At least low resolution DNA based typing at HLA-A, -B and –DRB1 for potential haplo-identical sibling donors	2. Patients must have available both: a. One or more potential related mismatched donors (biologic parent (s) or siblings (full or half), children or other extended family members). At least low resolution DNA based typing at HLA-A, -B and–DRB1 is	Addition of extended family members as potential donors since some patients share haplotypes with extended

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		is required pre-randomization. HLA typing of biological parents and children as potential haplo-identical donors is not required pre-randomization	required pre-randomization for potential haplo-identical donors other than biological parents and children.	family members either because they have a common haplotype or from consanguinity in the family.
9.	Inclusion Criteria, Section 2.2.1 Page 2-2	3. Acute Leukemias (includes T lymphoblastic lymphoma): b. Acute Myelogeneous Leukemia (AML) in first complete remission (CR1) (see remission definition in Chapter 3) that is NOT considered as favorable-risk. iii. Normal karyotype with mutated NPM1 and not FLT3-ITD	3. Acute Leukemias (includes T lymphoblastic lymphoma): b. Acute Myelogeneous Leukemia (AML) in first complete remission (CR1) (see remission definition in Chapter 3) that is NOT considered as favorable-risk. iii. FLT3 ITD and TKD mutations without concurrent mutations in NPM1 or core-binding factors (inv(16) and t(8:21)).	Clarification to include all FLT3 ITD AND FLT3-TKD abnormalities as non-favorable/high risk, not just FLT3-ITD.
10.	Inclusion Criteria, Section 2.2.1. Page 2-2	3. Acute Leukemias (includes T lymphoblastic lymphoma): d.Biphenotypic/Undifferentiated/Prolymphocytic Leukemias in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR	3. Acute Leukemias (includes T lymphoblastic lymphoma): d.Biphenotypic/Undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR	Addition of high risk hematologic malignancies in first complete remission as eligible diseases as they are treated with allogeneic transplant.

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11.	Inclusion Criteria, Section 2.2.1 Page 2-2	N/A	5. High risk lymphomas in first CR, including, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma	Clarification regarding the inclusion of high risk lymphomas in first complete remission.
12.	Patient Exclusion Criteria Section 2.2.2 Page 2-3	*9. German centers only:* Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half lives or 4 weeks prior to enrollment, whichever is longer, or participation in any other interventional clinical study.	(REMOVED LANGUAGE)	Removed references to participation of German centers in protocol.
13.	Donor Inclusion Criteria Section 2.4.1 Page 2-5	1. Donors must be HLA-haploidentical first-degree relatives of the patient. Eligible donors include biological parents, siblings or half siblings, or children.	1. Donors must be HLA-haploidentical relatives of the patient. Eligible donors include biological parents, siblings (full or half), children or extended family members.	Addition of extended family members as potential donors since some patients share haplotypes with extended family members either because they have a common haplotype or from consanguinity in the family.
14.	Donor Inclusion Criteria,	2. For donors < 18 years, the maximum recipient weight (actual body weight)	2. For donors < 18 years, the maximum recipient weight (ideal body weight in kg)	Clarification that the recipient's IBW

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	Section 2.4.1 Page 2-5	should not exceed 1.25 times the donor weight (actual body weight).	should not exceed 1.25 times the donor weight (actual body weight in kg).	should be used in this eligibility criterion because IBW is used to calculate the stem cell dose, not ABW.
15.	Pre-transplantation Cyclophosphamide, Section 2.6.1.2 Page 2-7	Cyclophosphamide 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion on Days –6 and –5. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see above for formulas). Uroprotection can be administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation Cy, but is not required.	Cyclophosphamide 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion on Days –6 and –5. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see above for formulas). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW) and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW. Uroprotection can be administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation Cy, but is not required.	Clarification for pre-transplant cyclophosphamide dosing if ABW < IBW.

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16.	Post-transplant cyclophosphamide, Section 2.6.1.5 Page 2-8	Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6).	Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW) and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW.	Clarification for pre-transplant cyclophosphamide dosing if ABW < IBW.
17.	Cyclophosphamide, Section 2.6.2.2. Page 2-10	Cyclophosphamide 50mg/kg x 1 day to be administered on Day -6. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6)	Cyclophosphamide 50mg/kg x 1 day to be administered on Day -6. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW)	Clarification for cyclophosphamide dosing if ABW < IBW.

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			and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW.	
18.	Additional Supportive Care Section 2.7 (NEW) Page 2-12	N/A	2.7.1. Post Transplant Maintenance Therapy Plans for the use of post transplant maintenance therapy must be disclosed prior to randomization, and must be used irrespective of the outcome of the randomization.	Clarifying language noting that post transplant maintenance therapy must be declared prior to randomization, and given irrespective of the treatment assignment.
19.	Screening and Eligibility Procedures Section 4.1.1.2 Page 4-1	2. Upon successful completion of the Segment 0 HLA forms, an authorized user at the transplant center will enter the remainder of the eligibility criteria required prior to randomization on the Segment A enrollment form.	2. Upon successful completion of the Segment 0 HLA forms, an authorized user at the transplant center will enter the remainder of the eligibility criteria required prior to randomization on the Segment A enrollment form. In addition, the transplant center must commit to using or not using post transplant maintenance therapy, irrespective of the treatment assignment.	Added clarifying language enrollment procedures, noting that post transplant maintenance therapy must be declared prior to randomization, and given irrespective of the treatment assignment.
20.	Record Retention Section 4.2.2.3. Page 4-3	"…In order to comply with the German Transfusion Law requirements, all participating German centers must ensure that the information and documents	(REMOVED LANGUAGE)	Removed references to participation of German centers in protocol.

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		relating to the traceability for all the stages from donation of the hematopoietic cells to infusion into the recipient (including blood products and the graft [bone marrow or UCB]) are archived in safe custody for a minimum of 30 years, even if the patient withdraws consent."		
21.	Adverse Event Reporting Section 4.2.4.1 Page 4-5	German Centers: The site PI is also required to notify the DCC by fax (240-306-0963) of Unexpected Grade 3-5 AEs.	(REMOVED LANGUAGE)	Removed references to participation of German centers in protocol.
22.	Pre-transplant evaluations Section 4.2.5.1 Page 4-10	N/A	9. Declaration of post transplant maintenance therapy, if intended and independent of randomization assignment.	Added clarifying language noting that post transplant maintenance therapy must be declared prior to randomization, and given irrespective of the treatment assignment.
23.	German Transfusion Law Section 6.6 Page 6-4	To comply with the German Transfusion Law requirements, German centers must ensure that the information and documents relating to the traceability for all the stages from donation of the HSC units to their	(REMOVED LANGUAGE)	Removed references to participation of German centers in protocol.

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		infusion into the recipient (including information about the blood product) are archived in safe custody for a minimum of 30 years, even if the patient withdraws consent.		
24.	Appendix A Abbreviations Page A-3	N/A	FLT3-TKD – FLT3 - Tyrosine Kinase Domain	Added definition of FLT3-TKD for clarification.
25.	Appendix B, Patient Consent Page B-2 and B-26; Donor Consents Page B-29 and B-38	Paul O'Donnell, M.D., Ph.D. Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North/LM-200 Seattle, WA 98109-1023 Phone: 206-667-1968 Email: podonnel@fhcrc.org	Paul V. O'Donnell, MD., PhD Massachusetts General Hospital Cancer Center 55 Fruit St. Boston, MA 02141 Phone: 508-274-7430 Email: pvodonnell@mgh.harvard.edu	Updated affiliation and contact information of study chair Paul V. Donnell, MD, PhD for accuracy.
26.	Appendix B, Patient Consent Page B-21	**For more information:** Lederle Tenney, Fred Hutchinson Cancer Research Center, Seattle (855) 267-9045 or email: ltenney@fhcrc.org.	**For more information**: Jordan Steelquist, Fred Hutchinson Cancer Research Center, Seattle (206)-267-7438 or email: jsteelqu@fredhutch.org.	Updated main CEA study contact information for accuracy.