NCT02081248

BMT CTN #1205 Statistical Analysis Plan (SAP)

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

Protocol Synopsis:

The BMT CTN protocol #1205 titled "Easy-to-Read Informed Consent (ETRIC) for Hematopoietic Cell Transplantation Clinical Trials" is a randomized, multicenter, prospective comparative study of ETRIC or standard consent form to improve patient comprehension of BMT CTN parent clinical trials. The primary objective 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 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 score, (4) time taken for information location, and (5) patient consent rates on parent clinical trials. Per the original study design, the target sample size was 160 patients with 80 on each arm ensuring 64 patients per arm to complete Quality of Informed Consent part A comprehension survey. An interim analysis revealed that the survey completion rate was lower than expected, and then the target sample size was increased to 198 with expected 99 patients per group and 64 per arm to complete the Quality of Informed Consent part A questionnaire.

Study Status and Publication Plan:

The study opened enrollment in November 2013 and closed in August 2016 when the targeted sample of 198 patients was enrolled. Two manuscripts are anticipated from this trial. The first manuscript will describe the qualitative study and will detail the barriers and facilitators that were identified on semi-structured interviews of participating site research and IRB personnel. The analysis for this manuscript has been completed. The second manuscript will present the analysis of the randomized study that is detailed in this statistical analysis plan. We plan to circulate the first draft of the manuscript to the protocol team for review within 6 weeks after the analysis has been reviewed.

Survey instrument scoring:

- The Quality of Informed Consent Parts A and B will be scored as described in (Joffe et al, 2001)
- The Rapid Estimate of Adult Literacy Revised (REALM-R, a health literacy measure) will be scored as described in (Bass et all, 2003): words "fat", "flu", and "pill" will not be scored.
- The New Vital Sign (a health literacy measure) will be scored as described in (Weiss et al, 2005)
- The State-Trait Anxiety Inventory (STAI) will be scores as described in its manual (Spielberger et al, 1983)

- The Consent Form Satisfaction Survey will be summarized by its total score as the sum of responses to its seven Likert questions (0-4).
- The Deaconess Informed Consent Comprehension Test will be scored as described in (Miller et al, 1996). The total score ranges between 0-28.

Primary Endpoint and Data Analysis:

The primary endpoint of BMT CTB 1205 is the mean comprehension score on the Quality of Informed Consent (part A) instrument.

The primary analysis will be performed using all patients who completed the Quality of Informed Consent (Part A) and will be based on the two sample t-test or, if the t-test assumptions are violated, with Mann-Whitney test. The statistical significance will be declared if the P-values of a *two-sided* test <0.05.

The following non-primary analyses will use all randomized patients with possible exclusion of clinical trials protocols with high missing data rates. Non-primary analysis will rely on linear regression models with multiple imputations to address missing data issues.

Analysis of interactions between the randomized assignment and (1) the trial protocol, (2) literacy level (REALM-R), (3) income, (4) age groups, (5) education level. The statistical significance of interactions will be declared at ALPHA 0.01 (Bonferroni adjustment for 5 tests). If the interaction test is significant then post-hoc comparisons between the ETRIC and standard consent groups will be performed for each level of a categorical variable.

Data preparation: We will investigate functional forms of continuous predictor variables, such as “literacy level” (assessed via NVS or REALM-R) and “age” and the use of appropriate transformations of continuous predictors to make the associations with the outcome more linear and the distributions of model residuals closer to normal. We will also consider grouping continuous variables into three categories by tertiles if the linear association with the outcomes is not adequate. The categories of variables with multiple levels, such as “Education level” or “Income”, will be grouped into wider categories.

The adjusted analysis of the primary endpoint will be based on the linear regression model. Potential confounding variables to include in the model are (1) the trial protocol, (2) literacy level (NVS or REALM-R, whichever is more predictive), (3) income, (4) gender, (5) age, (6) categorized race (WHITE vs OTHER). Forward stepwise variable selection will be used to find a parsimonious linear regression model with significant at ALPHA = 5% predictors.

Missing data: Since only near two thirds of all study participants are expected to complete the Quality of Informed Consent (Part A) questionnaire, we will develop an imputation model and use multiple imputations to fill-in missing values. The imputation model will use the information at baseline when the participant is enrolled into the study. Then, we will use Little and Rubin’s approach (Little & Rubin, 2002) to combine the results of multiple imputations for estimating model parameters, variance covariance matrices, and P-values. To investigate the possibility of missing data which are not missing at random (NMAR), we will use tipping-point

approach and find the ranges of the imputation model parameters when the inference on the effect of ETRIC consent does not change.

Dependence within data: The linear mixed models will be used to explore whether there is a need to control for clinical trial site or clinical trial site by protocol, both or neither.

Alternative analyses: To satisfy model assumptions we will consider the use of monotone variance-stabilizing transformations for continuous variables. If, however, the model specification continuous being inadequate (non-Gaussian distribution of model residuals, outliers, etc.), we proceed with generalized estimating equations (GEE) instead of the mean linear regression. To accommodate potential dependence of responses within clinical trial sites "leave-one-site-out" cross-validation will be used to estimate robust standard errors of the test statistic (the regression coefficient of the ETRIC effect in either mean or median regression models).

Secondary Endpoints and Final Analysis:

Secondary continuous endpoints are subjective comprehension, anxiety, satisfaction, and information location. The only *secondary binary endpoint* is the consent rate for the parent clinical trial.

Analysis of secondary endpoints: By analogy with the primary endpoint, the *secondary endpoints* (1) subjective comprehension scores on the Quality of Informed Consent (part B) instrument, (2) the modified Deaconess Informed Consent Comprehension Test instrument, (3) state anxiety scores on State Trait Anxiety Inventory instrument, (4) overall satisfaction score will be analyzed using t- or Mann-Whitney tests as appropriate. The analysis of *time to information location* will be performed with generalized linear models (GLM) models using the LOG link function if nonlinearity needs to be accounted for. The comparison of *consent rates* between ETRIC and standard consent forms will be performed with GEE using the LOGIT link. The GEE model will control for the fixed effect of trial protocol and for the dependence within the clinical trial site. The statistical significance of the ETRIC intervention on each of the secondary endpoints will be declared if the P-values of *two-sided* Wald test with robust standard errors <0.05. Missing data will be treated by analogy with the primary outcome using multiple imputations and tipping-point analysis.

Patients to Include:

All patients who completed the Quality of Informed Consent (part A) survey will be included in the primary data analysis. All enrolled patients will be included in the data analysis of secondary endpoints.

Content of Tables

Tables:

Table 1: Demographics and baseline characteristics by treatment arm

Table 2: Study endpoints by treatment arm

Table 3: Interaction analyses for the Quality of Informed Consent (part A)

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Table 4: Adjusted analysis of Quality of Informed Consent (part A) instrument

Figures:

Figure 1: CONSORT diagram (a separate file is attached for a template)

Figure 2: Bar graphs of means and standard errors for the primary and secondary endpoints in ETRIC and Standard consent forms (below is an example).

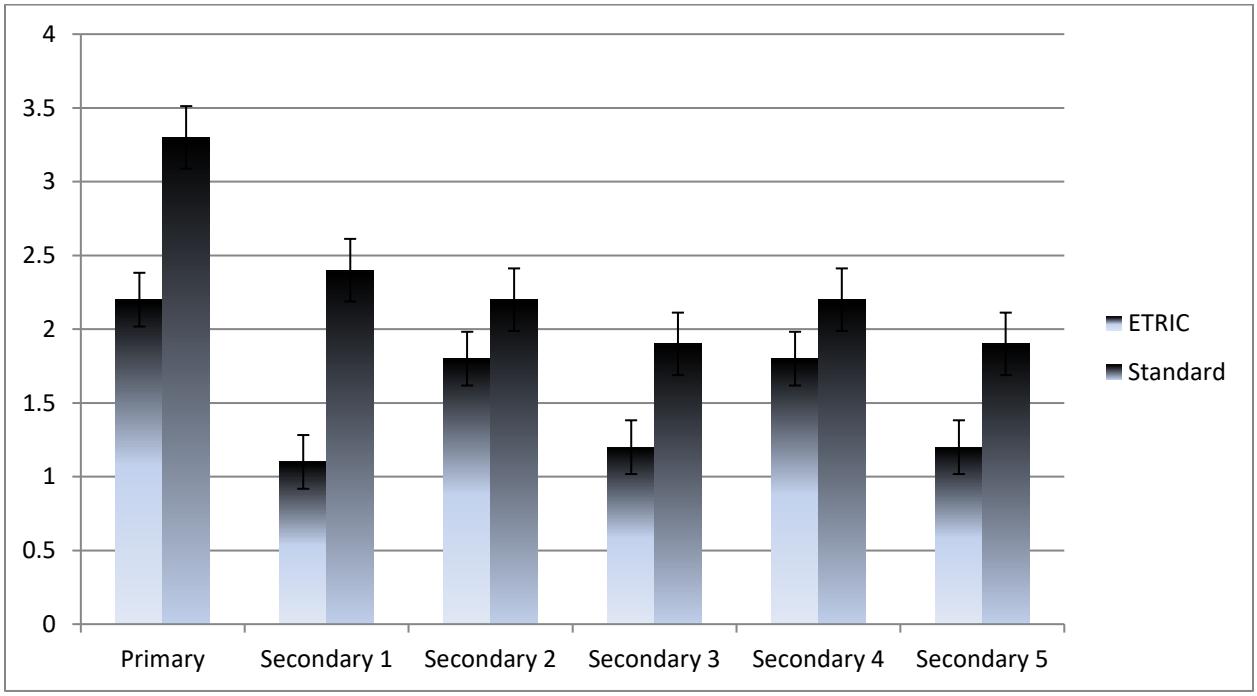

Table 1: Demographics and baseline characteristics by treatment arm

	Treatment Arm		
	ETRIC N(%) or N(M+/-SE)	Standard N(%) or N(M+/-SE)	P-value
Gender - Female (N) - Male (N)			
Hispanic/Latino - Yes (N) - No (N) - Missing (N)			
Race - White (N) - Black (N) - Other (N) - Missing (N)			

The Trial Protocol - BMT CTN 0901 (N) - BMT CTN 1101 (N) - BMT CTN 1203 (N) - BMT CTN 1301 (N)			
Income ($) - <20,000 (N) - 20,000-39,999 (N) - 40,000-59,999 (N) - 60,000-79,999 (N) - 80,000-99,999 (N) - 100,000+ (N) - Missing (N)			
Age (years)			
Education Level - Education Group 1 (N) - Education Group 2 (N) - Education Group 3 (N) - … - Missing (N)			

Table 2: Study endpoints by treatment arm

	Treatment Arm		
	ETRIC N(%) or N(M+/-SE)	Standard N(%) or N(M+/-SE)	P-value
Quality of Informed Consent (part A)*			
Quality of Informed Consent (part B)			
Modified Deaconess Informed Consent Comprehension Test			
The State Trait Anxiety Inventory Score			
Overall Satisfaction Survey			
Averaged Time to Information Location (sec) - Where can you find the main goal of the study? - Where can you find who to contact if you have questions about the study? - Where can you find the risks to taking part in the study - Where can you find how to leave the study? - Where can you find what you will have to do in the study?			
Consent Rate of Parent clinical Trial (Y/N)			

- BMT CTN 0901 (N) - BMT CTN 1101 (N) - BMT CTN 1203 (N) - BMT CTN 1301 (N)			

*primary outcome

Table 3: Interaction analyses for the Quality of Informed Consent (part A)

	Treatment Arm		
	ETRIC (N) M +/-SE	Standard (N) M +/-SE	P-value
The Trial Protocol - BMT CTN 0901 (N) - BMT CTN 1101 (N) - BMT CTN 1203 (N) - BMT CTN 1301 (N)			
Literacy level (REALM-R) - Missing (N)			
Income ($) - <20,000 (N) - 20,000-39,999 (N) - 40,000-59,999 (N) - 60,000-79,999 (N) - 80,000-99,999 (N) - 100,000+ (N) - Missing (N)			
Age (years)			
Education Level - Education Group 1 (N) - Education Group 2 (N) - Education Group 3 (N) - … - Missing (N)			

* P-values column will provide global interaction tests and P-values for post-hoc comparisons between the regression coefficients ETRIC and standard consent groups (Missing Data group will be excluded from calculations).

Table 4: Adjusted analysis of Quality of Informed Consent (part A) instrument

Table will report the results of a parsimonious regression model

	Regression coefficient (+/-SE)	P-value
(Model intercept)	Coef (SE)	
ETRIC	Coef (SE)	
Covariate 1 - Category 1	Coef (SE)	

- Category 2 - … - Reference Category	Coef (SE) 0 (-)	
Covariate 2 - Category 1 of Covariate 2 - Category 2 of Covariate 2 - … - Reference Category of Covariate 2	 coef (SE) coef (SE) 0 (-)	
…		

P-values column will provide global P-values and P-values of post-hoc comparisons between versus the reference category. Indicator of ETRIC will always be included in the regression model; inclusion of other variables will depend on their significance level (<0.05).

References:

1. Steven Joffe, E. Francis Cook, Paul D. Cleary, Jeffrey W. Clark, Jane C. Weeks Quality of Informed Consent: a New Measure of Understanding Among Research Subjects *Journal of the National Cancer Institute, Vol. 93, No. 2, January 17, 2001*
2. Roderick Little and Donald Rubin. Statistical Analysis of Missing Data, 2002, 2nd ed., Wiley
3. Bass PF, Wilson JF, Griffith CH. A Shortened Instrument for Literacy Screening. Journal of General Internal Medicine. 2003;18(12):1036-1038. doi:10.1111/j.1525-1497.2003.10651.x.
4. Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.
5. Weiss BD, Mays MZ, Martz W, et al. Quick Assessment of Literacy in Primary Care: The Newest Vital Sign. Annals of Family Medicine. 2005;3(6):514-522. doi:10.1370/afm.405.
6. Miller CK, O'Donnell DC, Searight HR, Barbarash RA. The Deaconess Informed Consent Comprehension Test: an assessment tool for clinical research subjects. *Pharmacotherapy*. 1996 Sep-Oct;16(5):872-8.
7. Little R. and Rubin D, Statistical Analysis with Missing Data. 2nd ed, 2002, Wiley