



# Biology of Blood and Marrow Transplantation

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## Easy-to-Read Informed Consent Form for Hematopoietic Cell Transplantation Clinical Trials: Results from the Blood and Marrow Transplant Clinical Trials Network 1205 Study

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### ABSTRACT

Because of the complexity of hematopoietic cell transplant trial treatments, informed consent forms are often long and difficult to read. We evaluated a 2-column easy-to-read informed consent (ETRIC) form that incorporates elements of health literacy and readability in participants and centers participating in Blood and Marrow Transplant Clinical Trials Network (BMT CTN) clinical trials. In a randomized study 198 adult patients from 25 centers potentially eligible to participate in 4 BMT CTN interventional trials were randomized to the ETRIC form or a standard consent form for that trial. Both forms were written at no more than an eighth-grade reading level. The primary endpoint was objective comprehension score on the Quality of Informed Consent, part A (QuIC-A) instrument. In a parallel evaluation study, 2 moderators conducted semistructured interviews of 49 investigators, research staff, and institutional review board (IRB) members at 9 BMT CTN trial sites. The mean QuIC-A scores were comparable in 152 patients (77%) assessable for the primary endpoint (ETRIC form, 80.5; standard form, 81.8;  $P = .37$ ). In regression analysis there was no significant association between the consent type and QuIC-A score. In the evaluation study dominant themes identified on qualitative analyses included general comfort and willingness to use the ETRIC template and that its formatting and layout enhancements would offer additional value to research participants, investigators, and IRBs. IRB language preferences and requirements, length, and prior experience with alternative consent formats were perceived as barriers. Among patients considering participation in BMT CTN clinical trials, the formatting enhancements of the ETRIC form did not alter comprehension of the trial. Despite local challenges to implementation, trial sites generally viewed the ETRIC form favorably and expressed willingness to use it over standard consent form.

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### INTRODUCTION

Obtaining voluntary informed consent is the cornerstone of the ethical conduct of research. Improvements to the informed consent process that enhance participant understanding are essential, both to promote respect for autonomy and because increased comprehension leads to better

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protocol compliance and lower attrition [1,2]. Many cancer clinical trial participants have misconceptions about the trials in which they participate, such as overestimation of benefits, underestimation of the unproven nature of the study intervention, and failure to recognize the primary purpose of the trial [3-7]. One key component of the informed consent process is a clear written consent form. Especially for cancer clinical trials, however, written consents have become longer, difficult to read, and more complex. Complex and lengthy written consents can compromise participant comprehension of clinical trials [8-11].

Research to improve the consent process has included enhanced consent form interventions (eg, shortening length, revising content, improving formatting, and adding graphics). Results of such interventions have been mixed with generally limited efficacy in enhancing participant understanding of clinical trials or increasing trial participation [12,13]. Few studies, however, have evaluated interventions to enhance consent forms for multicenter cancer clinical trials [14,15]. A nonrandomized study assessing a standard Southwestern Oncology Group consent form or a simplified booklet form in 183 healthy individuals and cancer patients showed a significantly higher proportion preferred the simplified form, although no difference in their understanding of the information on the 2 forms was observed [14]. In an Eastern Cooperative Oncology Group study, 226 patients in lung and breast cancer trials were randomized to a standard consent form or a consent form with readability adjusted to the seventh- to eighth-grade level [15]. Participants reported reduced anxiety and increased satisfaction with the easier-to-read consent form, yet there was no difference in comprehension of the consent form.

Participant decision-making and the informed consent process for hematopoietic cell transplantation (HCT) clinical trials present unique challenges because HCT is a complex, "high-stakes" medical treatment for life-threatening hematologic malignancies and other diseases where the potential for cure has to be balanced against the possibility of developing significant morbidity and mortality from the procedure itself [16,17]. Simplification of the consent process has been identified as a putative intervention to improve participant comprehension of HCT clinical trials [16,18]. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) previously proposed an easy-to-read informed consent (ETRIC) form template that follows evidence-based recommendations for health literacy, readability and processability, and the use of plain language specifically targeting specialized terminology related to HCT while including all federally required elements for research informed consent [19]. BMT CTN 1205 was a 2-part study composed of (1) a randomized study comparing the effects of the ETRIC form and standard consent form templates on understanding and other outcomes among patients approached for enrollment on select BMT CTN clinical trials and (2) a qualitative evaluation study to understand the barriers and facilitators to implementation of the ETRIC form template at BMT CTN clinical trial sites.

## METHODS

### BMT CTN ETRIC Form Template

The ETRIC format was developed by a multistakeholder BMT CTN task force with expertise in institutional review board (IRB) regulations and procedures, research ethics, clinical trial design, health services research, health literacy, and patient advocacy. Existing BMT CTN clinical trial consent forms were reviewed for completeness, readability, length, and format, and based on guidance from the literature and feedback from BMT CTN investigators,

coordinators, and site IRBs, recommendations were provided for an ETRIC form template [19]. The overarching intent of the template was to simplify the process for development and review of informed consent documents, enhance potential participants' understanding of their trials, and improve participant satisfaction with the informed consent process. An innovative feature was the layout of the consent document, with information provided in a 2-column format and recommendations for layout, organization of text, typography, and plain language that can facilitate information location, comprehension, and identification of target words (Supplementary Figure 1) [19].

## Randomized Study

### Study design

We conducted a randomized multicenter study comparing the ETRIC and standard consent forms to improve participant comprehension of BMT CTN clinical trials (protocol available at [bmtctn.net](http://bmtctn.net) [BMT CTN 1205 trial]). Patients who were potentially eligible for BMT CTN 0901, 1101, 1203, or 1301 (parent) clinical trials were first approached for participation on the ETRIC form study. These trials reflect common indications and/or complications of HCT and the diversity and complexity of transplantation approaches and supportive care treatments (protocol details available at [bmtctn.net](http://bmtctn.net)). Participants who provided consent to BMT CTN 1205 were randomized 1:1 to the ETRIC form or the standard consent form arms and provided the study-assigned written consent form for participation on the parent clinical trial. Participants who declined participation on the 1205 study could still undergo consent discussion and participate on the parent clinical trial using the standard consent form.

The study was conducted under the guidance and approval of participating center IRBs. A waiver of the requirement to document consent to BMT CTN 1205 was obtained from site IRBs, where the informed consent for participating could be obtained verbally; however, participants signed informed consent forms (ETRIC or standard) before enrollment on the parent clinical trial. Participants were enrolled between November 2013 and September 2016. The study was registered on [ClinicalTrials.gov](http://ClinicalTrials.gov) (clinical trial registration number: NCT02081248).

### Participants and interventions

Participants had to meet the eligibility criteria for the parent clinical trial for which they were being considered. In addition, they had to be adults (age  $\geq 18$  years) with adequate speaking and reading proficiency in English to complete the study assessments. The intervention arm received the ETRIC form described above [19]. The standard consent form had a single-column format and lacked the formatting and readability enhancements of the ETRIC form. Of note, both the ETRIC and standard consent forms were written in plain language (eighth grade or lower reading level). The content of both forms was similar and contained all federally required elements of informed consent.

### Assessments and endpoints

Supplementary Table 1 describes the BMT CTN 1205 study assessments. Participants were asked to complete them within 7 business days after the consent discussion for the parent clinical trial irrespective of enrollment on the parent trial. Assessments included the following: (1) health literacy (Rapid Estimate of Adult Literacy in Medicine [20] and Newest Vital Sign [21]), (2) actual and perceived comprehension of the clinical trial presented (Quality of Informed Consent [QuIC] [22] and modified Deaconess Informed Consent Comprehension Test [23]), (3) anxiety related to the consent process (State Trait Anxiety Inventory [24]), (4) satisfaction with the consent process (QuIC supplement and study-specific questionnaire), and (5) information location (study-specific instrument). The QuIC incorporates basic elements of informed consent specified in federal regulations, assesses therapeutic misconception, and measures actual (part A) and perceived (part B) understanding of cancer clinical trials [22]. This instrument has been developed specifically for assessing subject comprehension of cancer clinical trials, has good test-retest reliability (interclass correlation coefficient, .66 to .77), and has been well validated in the literature.

The primary endpoint for the study was objective comprehension score on the QuIC part A (QuIC-A) instrument. Secondary endpoints included subjective comprehension of the clinical trial (QuIC, part B and modified Deaconess Informed Consent Comprehension Test), anxiety and satisfaction with the consent process, time taken to locate selected information in the consent form, and consent rates to parent clinical trials.

### Statistical analysis

The study was designed to detect a 4-point difference in the mean QuIC-A comprehension scores between the study arms; this represents a .5 standard deviation and meaningful difference in comprehension [11,22,25]. Based on a 2-sided *t*-test, a sample size of 64 participants per arm was required to have sufficient power to detect this difference in group means ( $\alpha = .05$ ;

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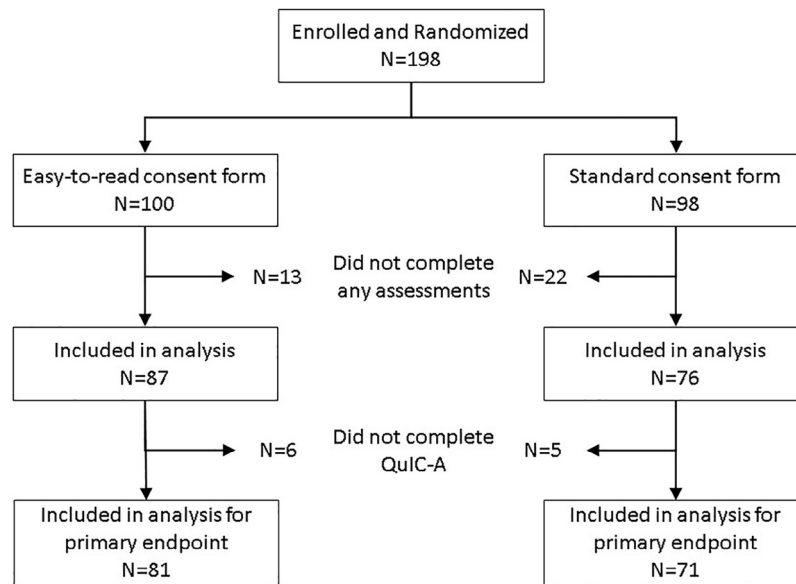


Figure 1. Participant flow diagram for randomized study.

power, 80%; standard deviation, 8). The sample size was inflated by 25%, resulting in 80 participants per group to account for potential violation of the normality assumption under the Mann-Whitney test and also for possible dropouts. At a scheduled Data Safety Monitoring Board review, it was observed that the levels of missing assessments and dropouts (ie, participants who consented for the 1205 study but did not complete the consent process for the parent clinical trial or the 1205 study assessments) were higher than anticipated. To account for these levels, the final sample size was increased to 198 participants (99 in each arm).

Analysis was performed using the intention-to-treat approach, and all participants who completed sufficient questions of QuIC-A ( $\geq 7$  of 13 domains) were included in the primary analysis. QuIC-A scores were compared using the 2-sample *t*-test after verification of normality. Secondary endpoints were analyzed using the Mann-Whitney test, except for consent rates, which were compared using Fisher's exact test. Regression analyses were used to control the effects of potentially confounding variables (age, gender, race/ethnicity, annual household income, education level, health literacy, and parent clinical trial). Analyses were also performed to test for interactions between QuIC-A and age, parent clinical trial, health literacy, household income, and education level. Analyses were performed with and without imputations for missing data; only the former are presented as the results were similar. All *P*-values were 2-sided. Analyses were performed using SAS software v9.4 (SAS Institute, Cary, NC).

### Evaluation Study

#### Study design

A qualitative study was also conducted to understand clinical trial site-specific barriers and facilitators to implementing the ETRIC form. Centers were recruited from BMT CTN clinical trial core and affiliate sites, representing a diversity of geographic location and center size and a mix of centers that did and did not elect to participate in the 1205 randomized study. During a 1-day visit, 2 trained moderators conducted 4 to 6 semistructured interviews of investigators and research personnel involved in HCT trials and of IRB administrators and staff. Interviews lasted 30 to 45 minutes and examined (1) willingness to use and acceptability of the ETRIC form 2-column format, (2) perceived barriers to implementation, (3) previous experience with alternative format informed consent forms or novel methods of obtaining consent, (4) perception of value of ETRIC form, and (5) helpfulness of sample resources to facilitate implementation of the ETRIC form. Discussions were facilitated by an interview guide and audio recorded. Notes were taken during the interviews to record nonverbal behavior of participants and to provide a "back-up" record. Study participants were not provided any incentive to participate. The study had undergone review by the National Marrow Donor Program IRB and was determined to be exempt human subjects research as defined by the Common Rule. Verbal informed consent was obtained from each participant before the interview.

### Qualitative data analysis

Sequential, transcript-based analysis was performed using NVivo 10 software [26]. Two experienced reviewers familiar with the area of study and preliminary research independently analyzed the data. First, a codebook was developed and textual data was coded line by line (ie, segmenting the data into meaningful analytical units). Reliability and validity of the coded data were assessed through inter- and intracoder agreement measures [27]. To correct for the possibility that coders might agree by chance, the kappa statistic was calculated [28]. A  $\kappa > .90$  indicates agreement in the way codes are assigned [27]. Coded textual data were explored inductively using content analysis to generate categories and explanations. This identified hierarchical relationships among codes; families of codes were created and were aggregated, reviewed, and analyzed at an increasingly general level [29]. This process is referred to as content analysis for saturation of themes. Participant quotes are used to support key themes and to show the diversity of opinions gathered during the interviews.

## RESULTS

### Randomized Study

Twenty-five BMT CTN centers participated in the study and enrolled 198 patients (Figure 1). Thirty-five patients did not complete any study assessments (24 declined study assessments, 15 of whom also declined enrollment in or were ineligible for the parent trial, and consent discussion did not occur because of closure of parent trial for 1 participant). Among the remaining 163 participants who completed some assessments, 152 provided sufficient information on the QuIC-A and were included in the analysis for the primary endpoint. Participant demographics including annual household income, education level, and health literacy scores were well balanced between the 2 arms (Table 1).

There was no significant difference in the mean QuIC-A scores between the 2 study arms (80.5 for ETRIC form versus 81.8 for standard consent,  $P = .37$ ; Table 2). In unadjusted analyses that evaluated the association of the primary outcome with potential confounding variables, only the parent clinical trial was observed to be significantly associated with the QuIC-A score ( $P = .046$ ). In subsequent multivariate analyses adjusted for the parent trial, there was no significant association between consent type and QuIC-A score ( $P = .57$ ). We also did not find any difference between arms in

**Table 1**  
Demographics of Participants Enrolled on the Randomized Study

Characteristic	ETRIC Form (n = 100)	Standard Consent Form (n = 98)	P*
Median age, yr (range)	61 (21-76)	61 (27-73)	.5093
Gender			.7750
Female	43 (43)	45 (46)	
Male	57 (57)	53 (54)	
Ethnicity			.3187
Hispanic/Latino	2 (2)	5 (5)	
Not Hispanic/Latino	94 (94)	87 (89)	
Declined/missing	4 (4)	6 (6)	
Race			.8954
White	88 (88)	85 (87)	
Black	8 (8)	7 (7)	
Other	2 (2)	2 (2)	
Declined/missing	2 (2)	4 (4)	
Annual household income			.3446
<\$40,000	19 (19)	11 (11)	
\$40,000-\$79,999	20 (20)	25 (26)	
≥\$80,000	26 (26)	22 (22)	
Declined/missing	35 (35)	40 (41)	
Education level			.1872
High school or less	35 (35)	20 (20)	
More than high school but less than graduate degree	27 (27)	29 (30)	
Graduate degree or more	11 (11)	15 (15)	
Other	6 (6)	5 (5)	
Declined/missing	21 (21)	29 (30)	
Health literacy, REALM			.3967
Score < 8	17 (17)	15 (15)	
Score 8	69 (69)	62 (63)	
Declined/missing	14 (14)	21 (21)	
Health literacy, NVS			.3837
Score < 4	16 (16)	11 (11)	
Score 4	52 (52)	53 (54)	
Score 5	18 (18)	13 (13)	
Declined/missing	14 (14)	21 (21)	
Parent clinical trial <sup>†</sup>			.9188
BMT CTN 0901	11 (11)	10 (10)	
BMT CTN 1101	22 (22)	25 (26)	
BMT CTN 1203	51 (51)	50 (51)	
BMT CTN 1301	16 (16)	13 (13)	

Values are n (%) unless otherwise indicated. REALM indicates Rapid Estimate of Adult Literacy in Medicine; NVS, Newest Vital Sign.

\* Fisher exact test P with the exception of age, which represents P-value from 2-sample t-test with pooled variance.

<sup>†</sup> Parent clinical trials were as follows: BMT CTN 0901, phase III randomized trial of full vs. reduced-intensity conditioning regimens in myelodysplastic syndromes and acute myeloid leukemia; BMT CTN 1101, phase III randomized trial of double unrelated umbilical cord blood versus HLA-haploidentical related bone marrow for hematologic malignancies; BMT CTN 1203, phase II randomized trial of novel approaches for graft-versus-host disease prevention; BMT CTN 1301, phase III randomized trial of calcineurin inhibitor-free interventions for prevention of graft-versus-host disease (all trial protocols are available at [bmtctn.net](http://bmtctn.net)).

subjective comprehension, anxiety, satisfaction, information location, or consent rates on parent clinical trials (Table 2). A priori, we tested for and found no significant interactions between the consent type and age, household income, education level, health literacy scores, or parent clinical trial protocol. Similarly, there was no significant random center effect on QuIC-A scores, and we did not find any significant nested random effect of center within clinical trial protocol on the QuIC-A.

### Evaluation Study

Nine BMT CTN transplant centers participated in the qualitative study; among these, 5 participated in the ETRIC randomized study and 4 elected not to participate. Overall, 49 semistructured interviews were conducted among site investigators (n = 13), research staff (n = 27), IRB members (N = 5), legal/regulatory staff (n = 3), and a patient advocate (n = 1), who collectively had a median of 13 years (range, .5 to 38) of experience working within the area of informed consent. A large proportion of interviewees were familiar with the ETRIC format (33/49 [67%]), which reflects their famil-

arity with BMT CTN trials and initiatives. On content analysis, dominant themes focused on five main areas: (1) a willingness to use and acceptability of the ETRIC form template; (2) perceived value of the ETRIC form template, including usefulness in facilitating informed consent for study staff and principle investigators; (3) perceived barriers to implementation, such as concerns about implementation and whether IRBs would accept this template; (4) previous experience with alternative consent formats; and (5) educational resources for clinical trial researchers, staff, and IRB members (Table 3 and Supplementary Table 2).

### DISCUSSION

There is general agreement about the critical need for reforming the informed consent process for cancer clinical trials by making it more patient-centric. However, studies investigating novel consent form interventions and generating high-quality evidence in this area are generally lacking. Compared with prior studies, our study was innovative in that it was a mixed methods study with both quantitative and qualitative methods. With this approach we addressed



**Table 2**  
Study Endpoints by Treatment Arms

Endpoint	ETRIC Form		Standard Consent Form		P
	N	Estimate	N	Estimate	
Objective comprehension					
Mean QuIC-A (standard deviation)	81	80.5 (8.7)	71	81.8 (9.5)	.3681 <sup>†</sup>
Subjective comprehension					
QuIC, part B	81	96.4 (89.3-100.0)	71	98.2 (91.9-100.0)	.3893 <sup>‡</sup>
Modified Deaconess	84	15 (14-17)	73	15 (13-17)	.1660 <sup>‡</sup>
Informed Consent					
Comprehension Test					
Anxiety					
State anxiety score on STAI	80	2.5 (2.3-2.6)	72	2.5 (2.3-2.6)	.2085 <sup>‡</sup>
Trait anxiety score on STAI	80	2.3 (2.1-2.5)	72	2.4 (2.2-2.5)	.2474 <sup>‡</sup>
Satisfaction					
Study-specific survey	82	4.1 (3.9-4.7)	72	4.2 (3.7-4.9)	.8035 <sup>‡</sup>
Information Location <sup>§</sup>					
Finding main goal for study	85	30 (11-63)	76	22 (11-60)	.7333 <sup>‡</sup>
Finding who to contact for questions)	85	20 (10-45)	76	15 (7-34)	.2641 <sup>‡</sup>
Finding risks and benefits section	85	20 (10-40)	76	20 (14-30)	.7368 <sup>‡</sup>
Finding how to leave the study	85	30 (11-60)	76	24 (15-60)	.5638 <sup>‡</sup>
Finding study procedures	85	36 (18-96)	76	43 (21-83)	.7934 <sup>‡</sup>
Consent rate on parent trial					
BMT CTN 0901, %	11	27.3	10	20.0	1.0000 <sup>#</sup>
BMT CTN 1101, %	22	45.5	25	52.0	.7726 <sup>#</sup>
BMT CTN 1203, %	51	49.0	50	44.0	.6914 <sup>#</sup>
BMT CTN 1301, %	16	43.8	13	69.2	.2642 <sup>#</sup>

Values are median (interquartile range) unless otherwise indicated. STAI indicates State Trait Anxiety Inventory.

\*Primary endpoint for the study.

<sup>†</sup> Based on t-test.

<sup>‡</sup> Based on Wilcoxon-Mann-Whitney test.

<sup>§</sup> Reported as seconds; participants who were not able to identify a given section were assigned the maximum time allotted to find each section (180 seconds).

<sup>#</sup> based on Fisher exact test.

the impact of our ETRIC form both on participants enrolling on BMT CTN-sponsored HCT clinical trials and institution-specific stakeholders whose engagement is essential for successfully implementing any interventions related to the informed consent process. Overall, the randomized study demonstrated no statistical improvement in understanding, anxiety, time to information location, and consent

rates among participants assigned to the ETRIC form versus standard format consent form. On the other hand, considering the impact that the ETRIC form template had on all stakeholders in the informed consent process, including study staff, our qualitative data suggest that the ETRIC form represents an improvement in the informed consent process.

**Table 3**  
Themes Related to Barriers and Facilitators to Use of ETRIC Format Identified on Evaluation Study\*

Interview Domain	Themes
Willingness to use and acceptability of ETRIC form	<ul style="list-style-type: none"> <li>• Researchers and IRBs are generally comfortable in using the ETRIC (2-column) form</li> <li>• Local IRB-related factors can influence use of ETRIC form (eg, flexibility in incorporating local IRB-specific language, challenges in having several consent formats within an institution, feedback and comfort level of IRB members)</li> </ul>
Perceived value of ETRIC form	<ul style="list-style-type: none"> <li>• Formatting and layout enhancements will help research participants better locate information</li> <li>• Will help health professionals and IRBs better explain trial (eg, objectives, risks, benefits) to research participants</li> <li>• ETRIC form will meet institutional standards for informed consent</li> </ul>
Perceived barriers to implementation of ETRIC form	<ul style="list-style-type: none"> <li>• Some center factors may hinder its use (eg, length of consent form, local IRB and legal requirements, ability to use specific institutional language)</li> <li>• Barriers specific to use by research participants (eg, need for more graphics, consent length, use of plain language that is specific for hematopoietic cell transplantation)</li> <li>• Barriers specific to use by health professionals and IRBs (eg, consent length, duplication/redundancy of information, not familiar with 2-column format, use of specific language)</li> <li>• Failure to meet institutional standards (eg, preference for single-column format, IRB requirements around specific consent sections)</li> </ul>
Previous experience with alternative consent forms	<ul style="list-style-type: none"> <li>• Variability in how participants review consent documents</li> <li>• Variability in awareness of ETRIC form</li> <li>• Variability in previous experience with using alternative consent forms</li> </ul>
Educational resources for implementing ETRIC	<ul style="list-style-type: none"> <li>• Educational resources on ETRIC form will generally be helpful for research participants, research personnel, and IRBs</li> </ul>

\* See [Supplementary Table 2](#) for Representative Quotes from Interviewees to Support Themes.

There are several potential reasons for not finding an association between the ETRIC form and participant comprehension and other endpoints on the randomized study. As noted above, the lay language enhancements of the ETRIC template had already been adopted by the BMT CTN. Thus, the main difference between the standard consent template and the ETRIC form were the formatting enhancements such as more white space, layout that was more readable, and the 2-column format. Furthermore, the trial was conducted at BMT CTN participating sites that are accustomed to educating and counseling participants about complex HCT clinical trials and, hence, the consent form itself did not have a major impact on our study endpoints. Also, the health literacy scores of our study population were relatively high, and participants reviewing the consent form may not have benefitted as much from the formatting enhancements of the ETRIC form. We do acknowledge this as a limitation of the study as well, and we did not have data on health literacy scores for patients who did not enroll on our study to compare and determine generalizability of our findings. It is clear, however, that the formatting elements of the ETRIC form template did not improve understanding and the other domains of interest.

That IRB chairs, IRB staff, and site investigators and research staff perceive the ETRIC form template as helpful for not just participants but researchers as well is an important and novel finding not only for the ETRIC form template but for informed consent research in general. Discussions of informed consent often focus on the entire consent process, not merely the signing of the piece of paper, and rightly so. However, discussions of informed consent for research have thus far focused on the research participants in that process, ignoring the other stakeholders. Because principle investigators, study staff, and IRB chairs and staff are all involved in the consent process, it is essential to better understand their roles and their preferences in the informed consent process. To be clear, research participants are the most important stakeholders in the informed consent process, but they are not the *only* stakeholders.

In conclusion, the ETRIC form template did not influence understanding, anxiety, time to information location, and consent rates for patients considering enrollment on BMT CTN clinical trials. However, it was viewed favorably by IRB chairs, staff, principle investigators, and study staff and may facilitate their roles in the consent process. The BMT CTN is transitioning toward a central IRB mechanism that will facilitate implementation and use of the ETRIC form. In the meantime, continued research is needed to investigate alternative interventions to enhance participant understanding of HCT clinical trials.

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#### SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at [doi:10.1016/j.bbmt.2018.04.014](https://doi.org/10.1016/j.bbmt.2018.04.014).

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