Title: New Paradigm of Transfusion Decision Support for Patients with MDS: Using Peri-Transfusion Quality of Life Assessments (PTQAs)

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PROTOCOL TITLE:

A New Paradigm of Transfusion Decision Support for Patients with MDS: Using Peri-Transfusion Quality of Life Assessments (PTQAs)

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1.0 Objectives

1.1 Study Aims

The goal of this multi-center study is to determine how to tailor blood transfusion decisions to the quality of life (QOL) changes experienced by individual patients with myelodysplastic syndromes (MDS). We will assess this by piloting a peri-transfusion QOL assessment (PTQA) approach. The PTQA involves administering a QOL questionnaire (see Appendix A) to study participants before and after an upcoming transfusion appointment and comparing QOL scores.

Specific Aim 1

Assess the feasibility of PTQA. We will assess the feasibility of this new paradigm of decision support by determining the enrollment yield as a percentage of all patients approached. We will also assess feasibility by calculating the proportion of enrolled participants who complete both the pre- and post-transfusion the Quality of Life in Myelodysplasia Scale (QUALMS).

Specific Aim 2

Assess the potential usefulness of PTQA in improving clinical and utilization outcomes. We will use medical record review and match our participants to historical controls (matched for transfusion group; IPSS-R; pre-transfusion Hb; and institution) to assess our primary outcomes, which are:

1. The presence of second transfusion after PTQA (for transfusion-naive)
2. The number of red cell units used after PTQA (for transfusion-dependent)
3. The number of hospitalizations after PTQA (for both transfusion groups)
4. The number of clinic visits after PTQA (for both transfusion groups)

Specific Aim 3

Explore the potential impact of PTQA on patient-reported outcomes. At 8 weeks post-transfusion, we will send participants a follow-up questionnaire (see Appendix B) to assess the following secondary outcomes:

1. PTQA utilization
2. Decisional regret
3. Perception of care
4. Perceived stress

1.2 Study Hypothesis

We hypothesize that PTQA may help patients with MDS, primarily by decreasing transfusion use and its attendant iron overload. This includes patients who are starting transfusions (may hold off on additional transfusions if QOL does not improve) and the transfusion-dependent (may extend transfusion interval if QOL does not improve).

2.0 Background

2.1 Overview

The myelodysplastic syndromes (MDS) are bone marrow failure disorders that primarily affect the elderly. Up to 50,000 people are diagnosed with MDS each year in the United States [1,2], making them one of the most common hematologic malignancies. The disease can be clinically devastating, as patients who do not succumb to infections or bleeding often develop acute leukemia. Many also experience a severe decline in their QOL.[3,4] The likelihood of increasing MDS incidence as the population ages has prompted the American Society of Hematology to include "finding an effective and personalized treatment" for MDS as one of its top research priority areas.[5]

While several potentially disease-modifying medications were approved in the mid-2000s, progress has been slower since,[6] and red cell transfusions remain a mainstay of care. Unfortunately, chronic red cell transfusions have many disadvantages, including iron overload,[7] decreased overall QOL among the transfusion-dependent,[8] and increased stress on the national blood supply.[9] Moreover, some patients experience improved QOL after transfusions, others do not.

While compromised QOL is often invoked to justify transfusions for patients with MDS, the question of whether or not QOL improves after transfusion remains unanswered due to several barriers.[10,11] First, until recently, a rigorous tool to assess MDS-specific QOL did not exist. Second, research assessing when QOL concerns might outweigh physiologic ones has been limited by a lack of consensus regarding a minimum hemoglobin (Hb) that is safe for outpatients with MDS. Third, it has been difficult for researchers to systematically identify patients who would benefit from formal QOL assessment, such as those starting transfusions and the transfusion-dependent. Finally, while some patients likely experience improved QOL after transfusion, others do not, even at the same level of Hb. We thus propose that the key question is not whether transfusions improve QOL, **but how to tailor transfusion decisions to the QOL changes experienced by individual patients living with MDS.**

2.2 Relevant Preliminary Data

The QUALMS

From 2011 to 2015, we developed[12] and validated[13] the Quality of Life in Myelodysplasia Scale (QUALMS), a rigorous QOL assessment tool for patients with MDS (see Appendix A and Protocols 10-461 and 13-346). With excellent internal consistency, known groups validity and responsiveness, the QUALMS has rapidly been incorporated into several MDS registries in the U.S., Canada, and Europe. In this current protocol, we will use the QUALMS to implement a new paradigm of transfusion support for patients with MDS that integrates peri-transfusion QOL assessment (PTQA). The PTQA will involve administering the QUALMS before and after red cell transfusions to determine whether the patient experiences any changes in QOL. Pre- and post-transfusion surveys will be scored, compared, and compiled in a report for patients and providers. These PTQA results will help guide future therapy decisions: if QOL post-transfusion is worse for a particular patient, a decrease in transfusions will be encouraged.

Minimum Safe Hb Level

At present, the optimal transfusion strategy for outpatients with MDS remains unknown. While high-quality studies of liberal versus restrictive transfusion practices have been conducted for other patient populations, there are sparse data on the minimum Hb level at which it is safe to forgo transfusions for non-hospitalized patients with MDS.

TRICC, the first of several inpatient studies, demonstrated that a restrictive transfusion strategy (Hb threshold of 7.0 g/dL) was effective and possibly superior to a liberal transfusion strategy (Hb threshold of 10.0 g/dL) in decreasing the 30-day mortality of **critically ill patients** in the intensive care unit, with the possible exception of patients experiencing acute coronary syndromes.[14] A second inpatient study, FOCUS, examined the effects of a restrictive transfusion strategy (triggered by symptoms of anemia or at physician discretion for a Hb of <8 g/dL) versus a liberal strategy (triggered by Hb threshold of 10 g/dL) on **hip surgery patients with high cardiac risk**. This study found that a liberal transfusion strategy did not reduce rates of death or disability with respect to 60-day follow-up.[15] TRACS, an additional inpatient study, found that a restrictive perioperative transfusion strategy (hematocrit less than 24%) was as safe as a liberal strategy (hematocrit less than 30%) in patients undergoing **elective cardiac surgery**.[16]

The above studies focused almost exclusively on inpatients without bone marrow failure or MDS. In contrast, few studies have assessed transfusion strategies in patients with MDS. A 2015 Cochrane review regarding the impact of transfusion practices on patients with bone marrow failure syndromes such as MDS found only one completed randomized trial (13 subjects in the Netherlands, published as abstract only).[11] The quality of the evidence was "very low" across different outcomes according to GRADE methodology, and the study mentioned did not report effects of transfusion on QOL. The reviewers did also identify two ongoing trials specific to MDS (one in Canada [NCT02099669] and the other in the UK [ISRCTN26088319]), each with an accrual goal of less than 40 patients, and both testing different Hb thresholds. The authors firmly concluded that "further randomized trials with robust methodology are required to develop the optimal transfusion strategy for MDS patients."

For patients without MDS, the literature suggests a consensus on hemoglobin thresholds for restrictive versus liberal transfusion strategies. A 2016 Cochrane review of thresholds to guide transfusions found that among 31 trials—mostly of inpatients—about half used a restrictive transfusion threshold of 7 g/dL and the other half used a threshold between 8-9 g/dL. The studies found no evidence that a restrictive transfusion strategy impacted 30-day mortality or morbidity compared with a liberal transfusion strategy, although there was more uncertainty concerning patients with hematologic malignancies and bone marrow failure.[17,18]

In view of the sparsity of data, in March 2018 we conducted a qualitative study with MDS experts (see Protocol 18-064) to determine the lowest Hb level at which, given no end-organ effects of anemia, outpatients with MDS can safely forgo transfusions. We utilized the modified Delphi technique, incorporating elements from the Rand/UCLA Appropriateness method (RAM).[19,20] This is a formal method of working with experts to achieve consensus, involving three rounds of assessments and anonymous feedback from experts to each other between rounds.

Per Protocol 18-604, we convened an expert panel of 13 MDS physicians (12 MDS experts; 1 blood bank physician) at the national AAMDSIF Symposium to determine the minimum safe Hb level. All panel participants received a literature review and questionnaire via email prior to the in-person panel. This questionnaire comprised round one of the modified Delphi. Among several critical questions (see Protocol 18-604), we asked: "*Please mark the lowest hemoglobin at which you think it would be safe to forgo transfusions for patients with MDS given no evidence of end-organ damage.*" Once we received participants' responses, we tabulated them and provided a summary of the results to the experts at our in-person panel. We allowed time for open discussion of each question. Following this discussion, we asked participants to fill out a round two questionnaire, the results of which were compiled and disseminated via email. We then asked the expert panel to fill out a third round of questions via email. While we were unable to reach a consensus threshold of 75% after three rounds, **we did have 100% consensus that the minimum safe Hb level should be no less than 7.5 g/dL**. Accordingly, we will use this threshold to identify eligible patients for our study, meaning patients with an Hb level less than 7.5 g/dL will be ineligible for participation.

Epic Workbench Report

To systematically identify patients who would benefit from PTQA, a member of our study team, Dr. Michael Hassett (Medical Director for Clinical Information Systems at DFCI), is currently working with DFCI's Epic team to create a Workbench report. This report will identify patients with MDS that are facing transfusion decisions. Epic is an EHR that covers 190 million patients in the U.S., including at the three centers participating in this project. Since May 2015, Epic has been the enterprise EHR for DFCI/BWH. It was previously adopted by Yale Cancer Center (YCC; 2013) and Wake Forest Baptist (WFB; 2012), the other two pilot sites.

Recent work has harnessed Epic data capture for cancer staging[21] and surgical metrics;[22] Dr. Hassett is similarly working with the Partners Epic reporting group to create Workbench Reports to use in this current protocol. To ensure high quality care for patients who receive blood products, the Epic team at DFCI/BWH created sophisticated order sets to facilitate transfusion ordering. Using our Workbench Report, data elements from these sets will be mined to identify patients with MDS who might benefit from PTQA.

Our Workbench Reports will identify (1) patients with MDS who have not yet been transfused, but have Hb levels approaching 8.5 g/dL during our study's enrollment period (to identify those heading toward first transfusion); and (2) patients with more than one transfusion during an 8 week period (to identify the transfusion-dependent; we will use the IWG criteria,[23] but not restrict to Hb $\leq$ 9.0]). We are working with the Epic teams at YCC and WFB to ensure that they are able to use an identical report at their institutions to systematically identify patients for PTQA at these sites.

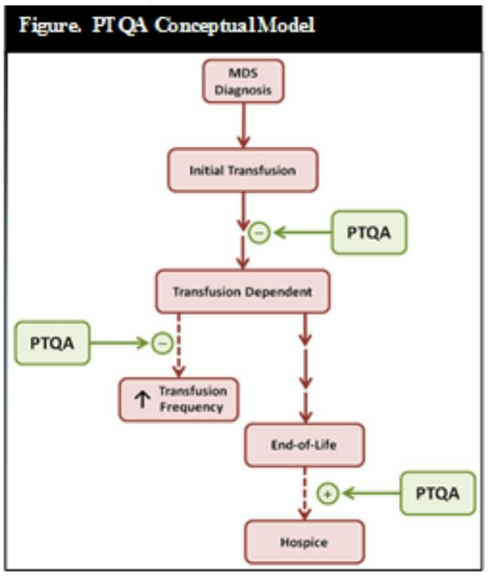
2.3 The Basis for PTQA

Up to 90% of patients with MDS will receive red cell transfusions during the course of their disease, and many will become chronically dependent on them.[8] Chronic transfusions also lead to an accumulation of iron that, in turn, can lead to cirrhosis, cardiomyopathy, and progressive endocrine dysfunction.[24] Thus, potential overuse of red

cell transfusions by patients with MDS not only contributes to critical national blood shortages, such as the one experienced in July 2016,[9] but also can be physiologically damaging. Moreover, transfusion dependency itself can lead to diminished QOL,[25,26] and recent work has shown that MDS patients who are at the end of life often avoid hospice because of the potential difficulty receiving red cell transfusions there.[27,28] One strategy to address these issues is to tailor transfusion only to those patients with MDS who benefit.

During our QUALMS validation study (see Protocol 13-346), we found that while some patients had improved QOL after transfusion, others did not, even at the same level of resulting Hb. We thus propose that a better question than "do MDS patients experience better QOL after transfusions" is "which MDS patients experience better QOL after transfusions." The best way to determine if a specific patient with MDS benefits from transfusions is to measure the patient's QOL, transfuse, and assess whether or not QOL improves. Such "peri-transfusion QOL assessment" (PTQA) is a paradigm shift because physicians would not be basing transfusion decisions on Hb level or prior transfusion history but on whether transfusion has an effect on the QOL of an individual patient at that time in their disease course.

Recent studies have shown it is possible to collect patient-reported outcomes (PROs) such as QOL and use the results to drive clinical care.[29,30] One analysis specifically demonstrated PTQA is possible, measuring the effect of red cell transfusions on PROs in an ambulatory oncology population, including 115 transfusion episodes.[31] Patients were telephoned after 7 days to discuss fatigue, shortness of breath, and overall QOL. Of the total episodes, 71% resulted in at least one improvement, but for 29%, there was none. If there is a similarly sized population of patients with MDS who do not experience improved QOL after transfusions, limiting their transfusion may be of great benefit in terms of reducing ferritin, burden of infusion visits, and overall red cell use.



3.0 Inclusion and Exclusion Criteria

3.1 Research Subject Eligibility Screening

Potential participants will be screened for eligibility using clinic schedule reports or the study-specific Epic Workbench report developed by Dr. Hassett (see above). Members of the study team at all three sites will be trained on the use of the study-specific Epic report. The report will generate a list of potentially eligible participants that will be further screened for eligibility by a designated member of the study team at each site (RA or RPM).

At DFCI, we will ensure eligibility by following the appropriate SOPs (REGIST-100: Internal Eligibility Checklist & REGIST-104: Using the Eligibility Checklist).

3.2 Inclusion/Exclusion Criteria

Inclusion criteria:

1. Age ≥ 18 years of age
2. Patients with MDS, including t-MDS and MDS/MPN
3. Transfusion-naive group: approaching Hb of 8.5 g/dL during enrollment period
    a. Ideally never-transfused (have never received red cell transfusion)
    b. If not never-transfused, participants are also eligible for inclusion in this group if they have not been transfused with red cells within last 8 weeks
4. Transfusion-dependent group: Patients with ≥1 transfusion scheduled during 8-week period prior to enrollment
5. Ability to read and understand English

Exclusion criteria:

1. Age <18 years
2. Cr > 2
3. Known CHF
4. Unstable Angina
5. Hb level below 7.5 g/dL
6. No plans for potential future outpatient transfusion.

3.3 Special Populations

Our study will exclude members of the following special populations:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

4.0 Study-Wide Number of Subjects

4.1 Accrual Goal

Our study-wide accrual goal is 60 evaluable participants. To reach this accrual goal, we will consent and enroll 90 participants as some participants are not able to complete the protocol due to a variety of reasons (e.g., participant does not end up requiring future transfusions). The 60 evaluable participants will be matched 1:1 to historical controls seen between 2015 and 2017, for a total sample size of 120.

5.0 Study-Wide Recruitment Methods

5.1 NA – Our multicenter study will not be employing recruitment methods that are outside the control of the local sites (e.g., call centers, national advertisements).

5.2 NA

5.3 NA

6.0 Multi-Site Research

6.1 Communication Plan

As the lead site, DFCI will communicate study updates to participating sites (YCC and WFB) via phone call or email. For the duration of the study, the Research Project Manager (RPM) will ensure that all sites are using the most current version of the protocol and consent documents. YCC and WFB will be asked to send the DFCI study team all notifications of approval (including IRB approval of initial protocol, continuing reviews, and any study modifications). The DFCI study team will monitor the compliance of participating sites during monthly check-in phone calls. In the event of a study modification, potential modifications to the protocol will be discussed during monthly calls prior to implementation.

The DFCI study team will be responsible for all monitoring activities related to the study across all sites. We will implement a risk-based monitoring approach where monitoring activities will be at the discretion of the sponsor/PI (Dr. Gregory Abel).

We will monitor accrual during our monthly check-in calls. During these calls, we will ensure that all sites are enrolling between 1-2 patients per month. With regards to data monitoring, the DFCI RPM will review the RedCap database for missing/discrepant data every three months. The consent/eligibility for 10% of participants (2 at each site) will be verified with source documentation by the RPM. This will be done remotely and the participating sites will send the RPM the necessary source documentation.

6.2 As this study is minimal risk, we do not anticipate any problems or reportable events. All other problems, interim results, and study updates will be communicated via our monthly study phone call.

6.3 NA

7.0 Study Timelines

7.1 Study Duration

- Individual subjects will participate in the study for approximately 10 weeks from the time of consent. This includes the completion of the pre-transfusion questionnaire, the post-transfusion questionnaire, and the follow-up survey at 8 weeks after transfusion. We will assess the number of hospitalizations and clinic visits for each participant 8 weeks after the index transfusion.
- We anticipate that it will take approximately 18 months to enroll 90 subjects across all three sites.
- The estimated date for the investigators to complete this study is April 30, 2020.

8.0 Study Endpoints

8.1 Study Outcomes

Primary Endpoints

Subjects will be compared with historical controls (matched for transfusion group; IPSS-R; pre-transfusion Hb; and institution) seen between 2015 and 2017. For the transfusion-naive, the primary outcome will be receipt of second transfusion (yes/no) within 8 weeks following the index transfusion. For the transfusion-dependent, the primary outcome will be defined as number of units pRBCs received within 8 weeks following the index transfusion. For both groups, we will also compare the number of hospitalizations and clinic visits during the 8 weeks after index transfusion (Table).

Table. Primary and Secondary Outcomes, Measured at Two Months after PTQA

Primary	**Presence of second transfusion** after PTQA (for those undergoing first transfusion) **Number of red cell units used** since PTQA (for transfusion-dependent) **Number of hospitalizations** since PTQA **Number of clinic visits** since PTQA
Secondary	**Decisional Regret** Decision Regret Scale.[32] 5-item scale provides indicator of health care decision regret; will be tailored to measure regret about transfusion decisions. **Perceptions of Care** "About Your Care" Domain of Prior DFCI Survey. We previously developed[33] a 6-item domain based on the **Consumer Assessment of Healthcare Providers and Systems Survey "**health status" "access," and "communication" domains.[34] **Perceived Stress** PSS-4.[35-37] The PSS-4 was designed for use with patients with at least a junior high school education, and takes 3 minutes to complete. It contains four questions about feelings of control and overall stress, with simple response alternatives.

Secondary Endpoints

Secondary endpoints include decisional regret, perceptions of care, and perceived stress by the associated scales at two months post-transfusion (Table 1).

8.2 Safety Endpoints

NA. There are no primary or secondary safety endpoints in our study.

9.0 Procedures Involved

9.1 Study Design

We propose a prospective cohort pilot study where patients will complete the QUALMS survey before and after their first/next transfusion. We will aim to have two groups of study participants: (1) those that are approaching first transfusion and (2) those that are transfusion dependent (n=30 for each group).

9.2 Study Procedures

Please see study schema (Appendix C) for study flow.

Pre-Transfusion

1. Once identified by Epic scheduling report, provider suggestion, or study-specific Epic Workbench report, eligible patients will be approached for consent discussion at an appointment with their provider.
    - Patients with Hb approaching 8.5 g/dLwill be approached at an appointment prior to an upcoming transfusion.
    - Patients that are transfusion-dependent will be approached at an upcoming appointment with their provider or during a transfusion appointment.
2. During this initial encounter, consenting participants will be given a study packet containing a paper copy of the QUALMS. Study participants will be instructed to fill out the survey on the day before their upcoming pRBC transfusion.

3. Study participants will indicate whether they would like to receive PTQA reports in person, via mail, or via email.
4. Site RAs will call study participants using script (see Appendix D) on the day prior to an upcoming transfusion to remind them to complete the QUALMS and bring it with them to their transfusion.
5. Note: Index transfusion is defined as any upcoming transfusion appointment for which the participant has completed both the pre- and post-transfusion QUALMS questionnaires.
    - If a participant does not complete the pre-transfusion questionnaire for any reason (i.e., participant forgot to complete at home or forgot to bring in), then the RA may ask the participant to complete the questionnaire at home prior to a subsequent transfusion appointment. This subsequent transfusion will become the index transfusion.
    - If a participant does not complete the pre-transfusion QUALMS at home prior to the appointment and there are extenuating circumstances (i.e., participant does not regularly receive transfusions at the site), then the RA may ask the participant to complete the questionnaire in clinic before his/her planned index transfusion.

Post-Transfusion

6. On the day of transfusion, the site RA will collect the completed pre-transfusion QUALMS survey. Study participants will then receive a second paper copy of the QUALMS, along with a stamped envelope addressed to the appropriate site.
7. Participants will be instructed to complete this survey exactly one week after transfusion and return it using the pre-addressed, pre-stamped envelope.
8. Site RAs will call participants using script (see Appendix D) to remind them to complete the QUALMS survey exactly one week after transfusion.
    - The window may increase up to one extra week to accommodate for circumstances where the patient is un unable to complete the post-transfusion QUALMS (i.e., participant does not feel well or participant forgot).

PTQA Report

9. Once received, the second assessment will be scored and compared with the first, and both the patient and provider will be sent a report with the results. The QUALMS validation study suggested that a clinically meaningful difference on the instrument is between 5 and 10 points;[12] For this study:
    - A post-transfusion score that is within 5 points of the pre-transfusion score will indicate a stable QOL
    - A post-transfusion score that increases by 5 or more points will indicate a clinically significant improvement in QOL
    - A post-transfusion score that decreases by 5 or more points will indicate a clinically significant decline in QOL

10. In our report, we will include language that encourages patient and providers to use these results to inform their next transfusion decision, specifically suggesting that transfusion be halted or decreased in frequency if QOL has worsened.

Secondary Outcomes Assessment

11. At 8 weeks post-transfusion, all participants will be sent a survey (Appendix B) to assess the utilization of the PTQA and patients' decisional regret, perceptions of care, and perceived stress.

9.3 Study Risks

As this is a survey study, we do not anticipate any risks due to study participation. The QUALMS survey (see Appendix A) has been extensively vetted to be acceptable to patients during its development and validation phases.[13] Nevertheless, the PIs will be available for consultation if the survey questions make any participant upset and referral to appropriate resources (e.g., social work, counseling) will be made available. In the unlikely event that a patient is made upset or uncomfortable by the QUALMS survey, the study investigators will contact the treating physician to inform him or her of the patient's concerns.

9.4 Data Collection

Data will be collected via medical record reviews, the QUALMS, and several other survey instruments.

Primary medical record review will include:

- Sociodemographic information
- Information regarding patients' MDS diagnosis, including IPSS-R score
- The number/frequency of transfusions prior to index transfusion (for transfusion-dependent patients)
- Hemoglobin level prior to index transfusion

Secondary medical record review will include:

- The presence of a second transfusion since index transfusion (for those who are starting transfusion)
- The number of red cell units used since index transfusion (for those who are transfusion-dependent)
- The number of hospitalizations since index transfusion
- The number of clinic visits since index transfusion

Survey instruments will include:

- The QUALMS to assess pre- and post-transfusion MDS-related QOL (see Appendix A)
- The Decision Regret Scale, "About Your Care" domain of prior DFCI survey, and the PSS-4 to assess secondary outcomes related to decisional regret, perception of care, and perceived stress (see Appendix B)

10.0 Data and Specimen Banking

10.1 Data Storage

All data will be entered into a password-protected RedCap database, with hard copies

stored in locked file cabinets. We will not bank data for future use after study completion. This study does not involve specimen banking.

10.2 NA

10.3 NA

11.0 Data Management and Confidentiality

11.1 Data Analysis Plan

Feasibility
Feasibility will be characterized by calculating (1) the proportion of enrolled patients out of all patients approached, and (2) the proportion of patients who completed both the pre- and post-transfusion QUALMS surveys out of all enrolled patients. A convenience sample of 60 evaluable patients will be enrolled to the study. To reach this goal, we will enroll 90 participants total, with the expectation that some patients will not be able to complete the study protocol, despite being eligible at the time of consent (e.g., do not end up requiring future transfusions). If the observed survey completion rate is 50% (i.e. 30/60), then this observed rate is consistent, with 95% confidence, with the true survey completion rate being as low as 38% or as high as 62%.

Clinical and Utilization Outcomes
To be assessed for clinical and utilization outcomes, participants must have completed a pre-transfusion QUALMS, received an index transfusion, and completed a post-transfusion QUALMS. Each of the 60 enrolled evaluable patients will be matched 1:1 to historical controls seen between 2015 and 2017, for a matched sample size of 120 patients total. Subjects will be matched for transfusion group, IPSS-R, pre-transfusion Hb, and institution). Comparative analyses will be conducted separately by transfusion group. For the transfusion-naive, the primary outcome will be receipt of second transfusion (yes/no) within two months following the first transfusion. For the transfusion-dependent, the primary outcome will be defined as number of units pRBCs received within two months following the next transfusion.

For both groups, we will also compare the number of hospitalizations and clinic visits two months after index transfusion (Table).

PTQA Utilization and Patient-Reported Outcomes
We may find that patients and hematologists do not use the information in their PTQA reports to truly affect decision-making, as both may be anxious to forgo transfusions despite the fact that QOL did not improve. We plan to assess this parameter at two months post-transfusion by asking participants whether they discussed the PTQA report with their physician (see Appendix B). To help prevent the PTQA going unused, we will make sure that providers at each site have access to the consensus Hb data from our previous qualitative study (Protocol 18-064). These results will be disseminated to providers prior to study initiation. In addition, we will work closely with the DFCI Adult Patient and Family Advisory Council (PFAC) to vet the routine language in our PTQA patient reports so that is optimally educational and anxiety-reducing.

Exploratory analyses (e.g. descriptive statistics such as means and standard deviations) using the results from the follow-up survey (see Appendix B) will characterize decisional regret, perceptions of care, and perceived stress by the associated scales at two months post-transfusion (Table).

11.2 Power Analysis

Transfusion-naive patients: With a type I error of 5% and a sample size of 60 transfusion-naive patients total (30 PTQA versus 30 historical controls), we will have 85% power to detect changes in the proportion of transfusion-naive patients receiving second transfusion from 100% to 70%.

Transfusion-dependent patients: With a type I error rate of 5% and a sample size of 60 transfusion-dependent patients total (30 PTQA versus 30 historical controls), we will have 83% power to detect a decrease in mean number of units received from 8.0 to 6.5 if the standard deviation is 2.0 units.

11.3 Securing of Data

As mentioned above, data will be stored in a password-protected RedCap database. Participants will be linked to a deidentified study ID to ensure confidentiality. Please see the Data Safety Monitoring Plan (Appendix E) for further detail.

11.4 Quality Control of Data

We will make every effort to collect all QUALMS data from study participants. RAs will call participants to remind them to complete the questionnaire and to either bring it with them to clinic (pre-transfusion) or mail it back to the site (post-transfusion). We have piloted this technique with 3 patients with MDS at DFCI; all complied. If a QUALMS survey is not complete, the site PI will personally contact each participant. Participants that do not complete the pre-transfusion QUALMS despite personal contact by the PI will be regarded as not having enrolled. We will record all reasons for non-enrollment, and account for all approached participants in the reports.

There may be participants who enroll and complete the pre-transfusion QUALMS, but do not complete the post-transfusion QUALMS. In this case, a PTQA report will not be generated. We will attempt to replace participants who do not complete the post-transfusion questionnaire, although this may prove unfeasible during the two-year timeframe of the study. Whether these participants are replaced or not, we will evaluate the outcomes of these participants, as we may find that there is a change in future transfusion decisions simply from drawing attention to QOL through the pre-transfusion QUALMS. If appropriate, sensitivity analyses will be performed among the subset of patients for whom a PTQA report was generated.

It is possible, although rare, for a patient to die within the two-month follow up period; such patients will be included in analyses based on their clinical and utilization outcomes observed before death.

We will record the number of patients who do not complete the two-month follow up surveys (PTQA utilization, decisional regret, perceptions of care, and perceived stress), and compare patient characteristics between those who do and do not complete the two-month follow up surveys.

11.5 Handling of Data

All study three sites will enter study data into a password protected, secure RedCap database that will be managed by the DFCI study team. Data will be stored for the duration of the study enrollment and analysis period and will be deleted once study analysis/write-up is complete. Hard copies of the questionnaires will be kept in a locked filing cabinet and destroyed upon study completion.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

12.1 NA

13.0 Withdrawal of Subjects

13.1 Subjects may be withdrawn without consent if their treating provider feels they should no longer participate in the study.

13.2 In the event of orderly termination, subjects will be notified that they will no longer be enrolled in the study. Study PIs will be made available to discuss any of the subjects' questions or concerns.

13.3 If a subject wishes to withdraw fully from the study, the study team will cease all data collection relating to the withdrawn subject, including review of primary outcomes. If a subject wishes to forgo the completion of the post-transfusion QUALMS or two=month follow-up questionnaire, the study team will confirm with the participant whether it is permissible to continue collecting data regarding the patient's health outcomes/healthcare utilization, as relevant to the study.

14.0 Risks to Subjects

14.1 As this is a survey study, we do not anticipate any risks due to study participation. The only foreseeable risk is potential emotional distress due to the nature of the questionnaires. If a participant becomes upset at any point, he/she will be referred to appropriate resources (e.g., social work, counseling). In the unlikely event that a patient is made upset or uncomfortable by the QUALMS survey, the study investigators will contact the treating physician to inform him or her of the patient's concerns.

14.2 *NA*

14.3 *NA*

14.4 *NA*

15.0 Potential Benefits to Subjects

15.1 Potential Benefits

It is possible that this research study may benefit participants directly if subjects and/or their physician take the results of the PTQA report into consideration when making transfusion decisions. It is our goal that providing patients/providers with an accurate assessment of pre- and post-transfusion QOL will facilitate a better-informed discussion regarding transfusion.

15.2 Other

If participants and/or providers elect not to use the results of the PTQA report to guide transfusion decisions, then this study will not benefit participants directly.

16.0 Vulnerable Populations

16.1 NA

17.0 Community-Based Participatory Research

17.1 NA

18.0 Sharing of Results with Subjects

18.1 Study participants and their providers will receive the results of the PTQA. Once the participant has completed the post-transfusion QOL assessment, the RA will generate a report that compares the participant's pre- and post-transfusion QOL scores. This information will be compiled in a PTQA report and shared with the provider and patient via email.

19.0 Setting

19.1 Once a potentially eligible subject is identified and upon provider approval, the RA will meet the patient in clinic to initiate the consent discussion. After a patient consents to the study, he/she will be given a copy of the QUALMS and instructed to complete the survey at home on the day before the upcoming transfusion. The RA will meet the participant in clinic when he/she comes in for a scheduled transfusion. At this appointment, the RA will collect the completed pre-transfusion survey and will give the participant a second copy of the QUALMS to take home. The participant will be instructed to complete the survey at home one week post transfusion and return it by mail. Study participants will also receive the follow-up questionnaire by mail to be completed at home.

20.0 Resources Available

20.1 Study Team

Dr. Gregory Abel (DFCI) will serve as Principal Investigator, and Drs. Amer Zeidan (YCC) and Heidi Klepin (WFB) will be Co-Investigators. In addition to all having MDS clinical expertise, Dr. Abel has QOL expertise, Dr. Zeidan has MDS clinical trial expertise, and Dr. Klepin has geriatrics expertise. The research team also includes Dr. Michael Hassett, Medical Director for Clinical Information Systems at DFCI.

20.2 Other Resources

The three study sites—DFCI, YCC, and WFB—all have large MDS populations and demonstrated track records in high-impact research in MDS, QOL, geriatrics and hematologic malignancies.

21.0 Prior Approvals

21.1 We have obtained multi-center approval. No other approval is necessary for this study.

22.0 Recruitment Methods

22.1 Recruitment Procedure

Once the RA has identified potential study participants and confirmed eligibility with the patients' provider, potential study participants will be informed of the study at the appointment prior to their first/next transfusion.

- Patients that are nearing first transfusion will be approached at the appointment prior to their first transfusion.
- Patients that are transfusion-dependent will be approached at an upcoming appointment or transfusion.

Study consent will take place during these visits. Potential participants will be given the opportunity to ask questions, opt out of consideration, and take a consent form home to discuss further with their family and/or other clinicians. We will be clear that enrollment does not mean patients are required to forgo future transfusion if the resulting PTQA report indicates an unimproved or worsened QOL post-transfusion.

Once consented, all DF/HCC study participants will be registered in the DFCI OnCore Clinical Trial Management System by the RA as required by DF/HCC SOP REGIST-101.

22.2 The source population for this study is patients with MDS that are presenting to clinic for treatment with blood transfusion.

22.3 Eligible subjects will be identified using our study-specific Epic Workbench Report (as described above).

22.4 NA

22.5 NA

23.0 Local Number of Subjects

23.1 The target accrual at DFCI will be dependent upon accrual at external sites. subjects.

23.2 We will approach 90 participants across all three sites with a goal of enrolling 60 total evaluable participants study-wide. In addition to these 60 evaluable participants, we will have 60 historical controls that will be matched based on transfusion group.

24.0 Provisions to Protect the Privacy Interests of Subjects

24.1 During the consent process, the consenting member of the study team will communicate clearly that participants should feel no obligation to share more information than they are comfortable with. It will be made clear that participants can opt out of any question(s) on the questionnaire that may cause uneasiness.

24.2 The study team will be trained to respond to participant questions and inquiries with compassion and professionalism. Again, participants will be informed that they can skip any questions that cause discomfort.

24.3 The research team will only have access to information that is relevant to the study, including in participants' medical records. The team will follow HIPAA guidelines regarding patient information.

25.0 Compensation for Research-Related Injury

25.1 NA

25.2 NA

26.0 Economic Burden to Subjects

26.1 NA. There are no costs that subjects may be responsible for because of participation in the research.

27.0 Consent Process

27.1 We will be obtaining written consent for this study per SOP: Informed Consent Process (CON-100). Once a potentially eligible subject is identified, the RA will approach the subject at an upcoming appointment. The RA will book a consult room on the clinic floor to discuss the study with the subject either before or after an appointment with a provider. If the subject is interested, but not prepared to sign consent on the day of discussion, he/she can opt to sign up for the study at a later date.

28.0 Process to Document Consent in Writing

28.1 To obtain written consent, we will follow the DFCI SOP for the Informed Consent Process (CON-100).

28.2 NA. We will not be requesting a waiver of the requirement to obtain written documentation of consent.

28.3 We have submitted an Informed Consent Form for review alongside this protocol.

29.0 Drugs or Devices

29.1 NA

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A New Paradigm of Transfusion Decision Support for Patients with MDS

Pre-Transfusion Questionnaire

Instructions:
Please complete this survey at home on the day before your next transfusion and bring it with you to your appointment.

Initials: _____

Study ID: _____

Date survey complete: _____

How would you like to receive your quality of life report? ☐ Mail ☐ Email
☐ In person

If by email, what is your email address? _____

Initials: ____
Study ID: ____
Date: ____
Pre or Post Transfusion: ____

The QUALMS

The Quality of Life in Myelodysplasia Scale

Patients often have different experiences over the course of their illness; however, please limit your responses to your experience **over the past week only**. The information you provide will remain strictly confidential.

	During the past week, how often…	Never	Rarely	Sometimes	Often	Always
1	…did you feel as though there was a lack of clear information about your disease?	☐	☐	☐	☐	☐
2	…have you felt there was limited emotional support available for patients with MDS beyond their families?	☐	☐	☐	☐	☐
3	…did you feel as though you couldn't do anything about your disease?	☐	☐	☐	☐	☐
4	…did you feel the course of your disease was unpredictable?	☐	☐	☐	☐	☐
5	…did you have difficulty explaining MDS to your friends or family?	☐	☐	☐	☐	☐
6	…did you have trouble concentrating?	☐	☐	☐	☐	☐
7	…have you considered changing long-term plans due to health concerns?	☐	☐	☐	☐	☐
8	…have you experienced shortness of breath?	☐	☐	☐	☐	☐
9	…did low energy levels cause you to change your schedule?	☐	☐	☐	☐	☐
10	…did you feel as though your life was organized around medical appointments?	☐	☐	☐	☐	☐
11	…have you felt a sense of hopelessness?	☐	☐	☐	☐	☐
12	…have you been worried about getting an infection?	☐	☐	☐	☐	☐
13	…have you had sufficient energy for routine tasks?	☐	☐	☐	☐	☐
14	…were you afraid of dying?	☐	☐	☐	☐	☐
15	…did you feel angry about your diagnosis?	☐	☐	☐	☐	☐

16	…were you worried about bleeding?	☐	☐	☐	☐	☐
17	…did you feel a sense of gratitude for a part of life that you took for granted before?	☐	☐	☐	☐	☐
18	…did you feel nauseated?	☐	☐	☐	☐	☐
19	…did you worry about your MDS progressing or developing into leukemia?	☐	☐	☐	☐	☐
20	…did you take into account that you might be fatigued when planning your activities?	☐	☐	☐	☐	☐

For the following questions, please again mark the answer choice that best represents your experiences and feelings **over the past week**. The information you provide will remain strictly confidential.

	During the past week, how often…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
21	…were you concerned that your MDS caused a financial burden for you or your family?	☐	☐	☐	☐	☐
22	…did you feel your family relationships were strained by your disease?	☐	☐	☐	☐	☐
23	…have you felt weak?	☐	☐	☐	☐	☐
24	…have you been too tired to take on the responsibilities you used to have?	☐	☐	☐	☐	☐
25	…did you worry about becoming a burden to your friends or family?	☐	☐	☐	☐	☐
26	…were you unable to participate in activities you are used to doing?	☐	☐	☐	☐	☐
27	…have you felt anxious about test or lab results?	☐	☐	☐	☐	☐
28	…did you avoid crowds because of fear of getting an infection?	☐	☐	☐	☐	☐
29	…did you find yourself grateful for tomorrow?	☐	☐	☐	☐	☐
30	…did you feel you were able to find quality information about MDS treatments?	☐	☐	☐	☐	☐
31	…were you concerned about bruising?	☐	☐	☐	☐	☐
32	…did you feel as though there were a lack of concrete answers about what will happen with your MDS?	☐	☐	☐	☐	☐
33	…did you experience a change in bowel habits?	☐	☐	☐	☐	☐

Please continue on to the next page →

For the following questions, **you may select "not applicable"** if the question does not apply to you.

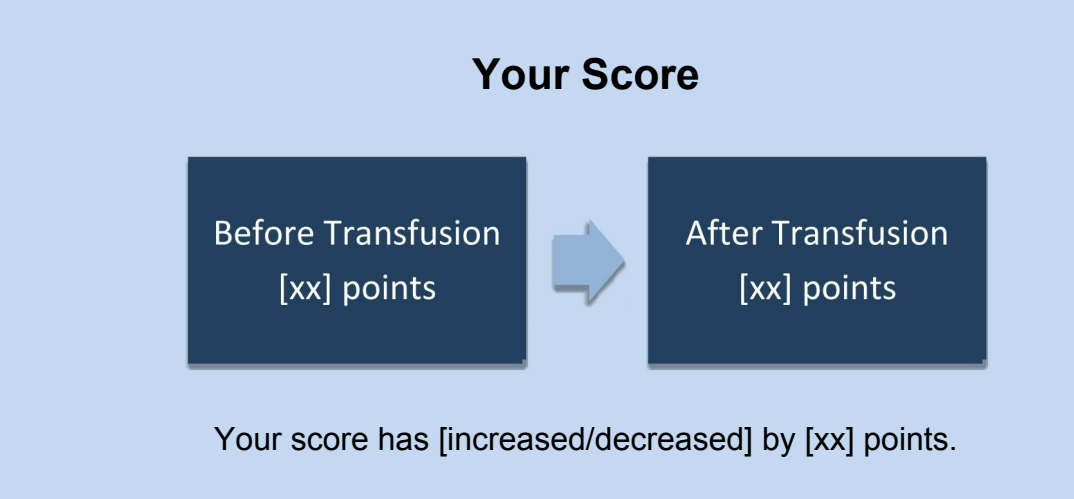
	During the past week, how often…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
34	…were you afraid of losing your job? (**check here** if not applicable because you are unemployed/retired)	☐	☐	☐	☐	☐
35	…did you feel too tired to drive? (**check here** if not applicable because you do not drive)	☐	☐	☐	☐	☐
36	…were you afraid to have sex due to your blood counts? (**check here** if not applicable because you are not currently sexually active)	☐	☐	☐	☐	☐
37	…were you afraid that your MDS treatment would stop working? (**check here** if not applicable because you are not currently being treated)	☐	☐	☐	☐	☐
38	…have you been too tired to take care of a family member or loved one? (**check here** if not applicable because you are not providing such care)	☐	☐	☐	☐	☐

Thank you for completing the QUALMS.

APPENDIX C: PTQA Reports

PTQA Score Report (UNCHANGED SCORE)

Thank you for participating in the Peri-Transfusion Quality of Life Assessment (PTQA) study. The goal of this study is to determine whether the use of a quality of life questionnaire can help patients with MDS and their providers make better informed transfusion decisions. We hope that you will use the information in this PTQA score report to discuss future transfusion options with [Provider name].



What does your score mean?

Since your first and second scores are within 5 points of each other, your quality of life has **remained stable** after transfusion.

How should you use the score?

Given that your quality of life did not improve after your transfusion, we recommend that you discuss the benefits and risks of transfusion with your doctor.

Based on a focus group we conducted as part of our research, experts on myelodysplastic syndromes (MDS) agree that it is safe for patients with MDS to increase the time between transfusions or stop them altogether, as long as they are otherwise healthy, experience no significant benefit in their quality of life, and their hemoglobin level stays above 7.5 g/dL.

Your PTQA score suggests that you might consider limiting the number of transfusions you receive. However, there may be other explanations for your quality of life score. We encourage you to use this report to discuss future transfusion decisions with your doctor.

What are the next steps in the study?

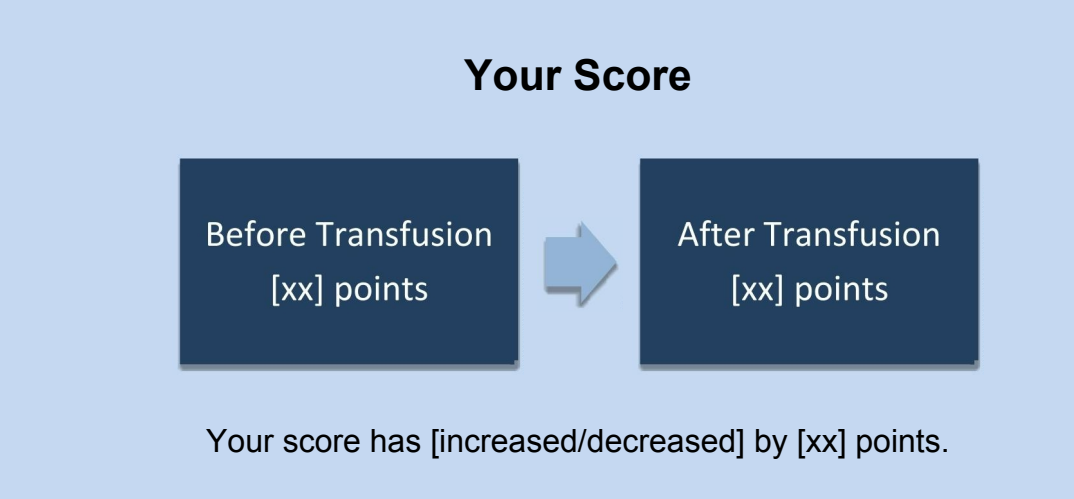
The study team will contact you to complete your follow-up survey during the week of [date].

Questions or comments?

Please contact the [study team - provide site-specific study contact].

PTQA Score Report (DECREASE)

Thank you for participating in the Peri-Transfusion Quality of Life Assessment (PTQA) study. The goal of this study is to determine whether the use of quality of life assessments can help patients with MDS and their providers make better informed transfusion decisions. We hope that you will use the information in this PTQA score report to discuss future transfusion options with [Provider name].



What does your score mean?

Since your second score is more than 5 points lower than your first, you have experienced a clinically significant **decrease** in your quality of life after transfusion.

How should you use the score?

Given that your quality of life did not improve after your transfusion, we recommend that you discuss the benefits and risks of transfusion with your doctor.

Based on a focus group we conducted as part of our research, experts on myelodysplastic syndromes (MDS) agree that it is safe for patients with MDS to increase the time between transfusions or stop them altogether, as long as they are otherwise healthy, experience no significant benefit in their quality of life, and their hemoglobin level stays above 7.5 g/dL.

Your PTQA score suggests that you should consider limiting the number of transfusions you receive. However, there may be other explanations for this change in your quality of life score. We encourage you to use this report to discuss future transfusion decisions with your doctor.

What are the next steps in the study?

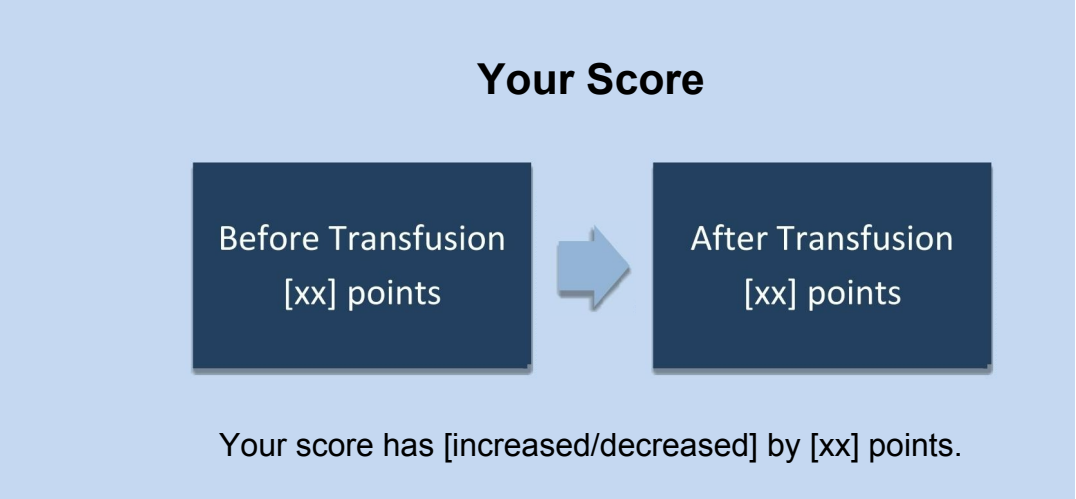
The study team will contact you to complete your follow-up survey during the week of [date].

Questions or comments?

Please contact the [study team - provide site-specific study contact].

PTQA Score Report (INCREASE SCORE)

Thank you for participating in the Peri-Transfusion Quality of Life Assessment (PTQA) study. The goal of this study is to determine whether the use of quality of life assessments can help patients with MDS and their providers make better informed transfusion decisions. We hope that you will use the information in this PTQA score report to discuss future transfusion options with [Provider name].



What does your score mean?

Since your second score is more than 5 points higher than your first, you have experienced a clinically significant **increase** in your quality of life after transfusion.

How should you use the score?

Given that your score indicates a clinically significant increase in your quality of life, we do not recommend that you change your transfusion plan at this time. We encourage you and your provider to take changes in your quality of life into consideration when making transfusion decisions in the future.

What are the next steps in the study?

The study team will contact you to complete your follow-up survey during the week of [date].

Questions or comments?

Please contact the [study team - provide site-specific study contact].

APPENDIX D: PTQA Email Example

Dear Dr. [Provider name],

Please see the attached reports for QOL changes pre/post transfusion for the patients below. I'll also send the patients these reports.

[Pt Initials] (MRN) – Index transfusion on [Date]

- This participant's score increased from 80 to 90 points, indicating a clinically significant increase in QOL.
- Per the study, we do not recommend any change in transfusion plan at this time.

[Pt Initials] (MRN) – Index transfusion on [Date]

- This participant's score remained stable at 39 points, indicating no clinically significant changes in QOL.
- Per the study, we suggest that she may consider limiting the number of transfusions she receives, given no end-organ effects of anemia and if her Hb stays above 7.5 g/dL

APPENDIX E: TWO-MONTH FOLLOW UP SURVEY

Initials: ____
Study ID: ____
Date: ____

PTQA UTILIZATION

Please think back to the PTQA results report you received after your post-transfusion questionnaire.

1. Did you and your doctor discuss the results of your PTQA report?
    a. Yes
    b. No

If yes…

2. Who initiated the PTQA/quality of life discussion?
    a. I did
    b. My doctor did

3. Did the results of the report affect your or your doctor's decision to pursue future transfusions?
    a. Yes
    b. No

DECISION REGRET SCALE

Please think about the decision you made about future blood transfusions after talking to your doctor. Please show how you feel about these statements by circling a number from 1 (strongly agree) to 5 (strongly disagree).

4. It was the right decision	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
5. I regret the choice that was made	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
6. I would go for the same choice if I had to do it over again	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
7. The choice did me a lot of harm	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
8. The decision was a wise one	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree

ABOUT YOUR CANCER CARE

These questions ask about your outpatient cancer care during the past twelve months; remember that you can leave any questions blank if you are not comfortable answering. When answering, please do not include care you got when you stayed overnight in a hospital.

9. Using any number from 0 to 10, where 0 is the worst possible and 10 is the best possible, what number would you use to rate your cancer care overall?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Worst care possible										Best care possible

10. In the last 12 months, when you needed care right away from your cancer doctor for a new symptom or condition, how often was your concern addressed as soon as you wanted?

1 Never
2 Sometimes
3 Usually
4 Always
5 Not applicable, never needed care right away

11. Using any number from 0 to 10, where 0 is the worst possible and 10 is the best possible, what number would you use to rate the doctor who prescribes your chemotherapy or hormonal therapy?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Worst cancer doctor possible										Best cancer doctor possible

12. In the last 12 months, how often did your cancer doctors, nurses or other cancer providers spend enough time with you?

1 Never
2 Sometimes
3 Usually
4 Always

13. In the last 12 months, how often did your cancer doctors, nurses or other cancer providers explain things in a way you could understand?

1 Never
2 Sometimes
3 Usually
4 Always

14. The role patients would like to play in making treatment decisions about their cancer may sometimes differ from how decisions actually get made. Which statement best describes the role you would prefer to play when decisions about treatment for your cancer are made?

1 I prefer to make decisions about my treatment with little/no input from my doctors
2 I prefer to make the decisions after considering my doctor's opinion
3 I prefer that my doctors and I make the decisions together
4 I prefer that my doctors make the decisions after considering my opinion
5 I prefer my doctors make the decisions with little or no input from me

PERCEIVED STRESS

15. The following questions ask you about your feelings and thoughts during the last month. In the last month, how often have you felt …

	Never				Often
...that you were unable to control the important things in your life?	1	2	3	4	5
...confident about your ability to handle your personal problems?	1	2	3	4	5
...that things were going your way?	1	2	3	4	5
...difficulties were piling up so high that you could not overcome them?	1	2	3	4	5

APPENDIX F: STUDY SCHEMA

Identify, Screen, & Recruit Participants

- RA uses study-specific Epic Workbench report to identify potentially eligible patients that are either (1) approaching first transfusion or (2) transfusion-dependent
- RA approaches 75 potentially eligible patients over the course of 15 months (23 at YCC and WFB, 29 at DFCI; goal is to reach 60 completed peri-transfusion quality of life assessments [PTQAs])
- Patients approached for consent discussion at appointment prior to first/next transfusion
- Willing participants consented to study and given study packet, including the QUALMS survey

Peri-Transfusion Quality of Life Assessment (PTQA)

Pre-Transfusion QOL Survey Administration

- RA calls participants with reminder to complete survey on the day prior to transfusion
- Participants fill out QUALMS survey at home on day prior to first/next pRBC transfusion

Post-Transfusion QOL Survey Administration

- On the day of transfusion, consenting participants given a second paper copy of the QUALMS survey with a stamped envelope addressed to appropriate site
- RA calls participants with reminder to complete survey exactly one week post-transfusion
- Participants fill out survey at home exactly one week post-transfusion; asked to mail survey back

Dissemination of PTQA Report

- Once received, second QUALMS survey scored and compared with the first
  - Stable QOL = post-transfusion score within 5 points of pre-transfusion score
  - Improved QOL = post-transfusion score 5 or more points higher than pre-transfusion score
  - Worsened QOL = post-transfusion score 5 or more points lower than pre-transfusion score
- Both patient and provider sent a report with PTQA results
  - Report will include language encouraging patients/providers to use results to inform next transfusion decision
  - Report will specifically suggest future transfusions be halted or decreased in frequency if QOL did not improve

Data Analysis

- Participants compared with historical controls (matched for transfusion group; pre-transfusion Hb; IPSS-R; and institution) seen between 2015 and 2017
  - For newly transfused, primary outcome is receipt of second transfusion (yes/no) within two months after index transfusion
  - For transfusion-dependent, primary outcome is number of units pRBCs received within two months after index transfusion
  - At two months post-transfusion, we will compare number of hospitalizations and clinic visits with number before index transfusion
- At two months post-transfusion, we will also send participants a follow-up survey to assess secondary outcomes, including PTQA utilization, decisional regret, perceptions of care, and perceived stress

APPENDIX G: QUESTIONNAIRE REMINDER CALL

PRE-TRANSFUSION

Hello - may I please speak to [PATIENT NAME]?

My name is [RESEARCH ASSISTANT], and I am calling from Dr. [NAME OF PROVIDER] office regarding the quality of life study you signed up for at your last appointment. This is a reminder to fill out your pre-transfusion study survey today. Please bring it with you to your upcoming transfusion appointment. I will meet you during your appointment to collect your completed survey and give you a second questionnaire for you to fill out one week after your appointment. Do you have any questions for me today?

Great! I'm looking forward to seeing you at your appointment. Thank you!

POST-TRANSFUSION

Hello - may I please speak to [PATIENT NAME]?

My name is [RESEARCH ASSISTANT], and I am calling from Dr. [NAME OF PROVIDER] office regarding the quality of life study. This is a reminder to fill out your post-transfusion study survey today. Once you've completed it, please send it back to us using the pre-stamped, pre-addressed envelope I gave you at your last appointment. Once we receive the completed survey, we will compare the results from your pre- and post-transfusion surveys and send you and your doctor a report with the results. Do you have any questions for me today?

30.0 **Great! I'm looking forward to seeing you at your appointment. Thank you!**

APPENDIX H: DSMP

INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified

in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions (Yale Cancer Center and Wake Forest Baptist) are expected to adhere to the following general responsibilities:

DF/HCC Sponsor

The DF/HCC Sponsor, Gregory Abel, MD, MPH, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC, and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting pPolicy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the

conclusion of a visit to review findings.

- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the members of the study team (Research Assistant and Project Manager) who will be obtaining consent and signing the consent form. Participating institutions must follow the DF/HCC requirements for consent. As this study does not involve an investigational drug, biologic, or device, non-physicians (Research Assistants and Project Managers) are able to obtain consent and sign the consent forms.

IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used

for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

DF/HCC Multi-Center Protocol Registration Policy

Participant Registration and Randomization

Each site will be responsible for registering study participants according to their own institutional policies and procedures. The Coordinating Center will only register patients that are consented and enrolled at DFCI in the DF/HCC CTMS.

Although we will not register participants from Participating Institutions in the DF/HCC OnCore system, Participating Institutions will still be required to complete:

- Signed informed consent document
- Completed Eligibility Checklist

Participating Institutions will notify the Coordinating Center about registrations via monthly phone call.

Protocol-specific interventions may begin once the Participating Institution has registered the participant at their specific site.

Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement.

DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number.

Case numbers will be assigned consecutively by DFCI as participants are enrolled. Participating Institutions will be responsible for tracking the appropriate case number as participants are enrolled.

Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

Safety Assessments and Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants. As this is a survey study, we do not anticipate any issues with regards to patient safety.

Data Management

All sites, including the Coordinating Center and Participating Sites, will enter data into a RedCap database that will be managed by the study team. We will not use case report forms developed by DF/HCC CTRIO for this study.

MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The study team at the Coordinating Center will provide quality control oversight for the protocol.

Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, response assessments, and data management.

The Coordinating Center will monitor the progress of the study during monthly calls with Participating Institutions. During these call, the Coordinating Center will assess whether Participating Institutions are enrolling patients in a timely manner. In preparation for these calls, the Coordinating Center will prepare a data report to ensure timely completion of data entry tasks in RedCap.

Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Each site will be expected to accrue 20 patients over the course of 18-months, with a minimum accrual requirement of 1-2 patients per month at each site.

AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.