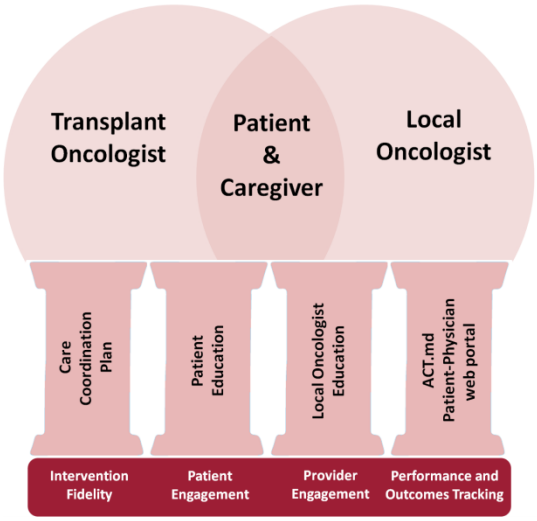
Version 8 11/16/2020

Shared Care: Patient-Centered Management after Hematopoietic Cell Transplantation



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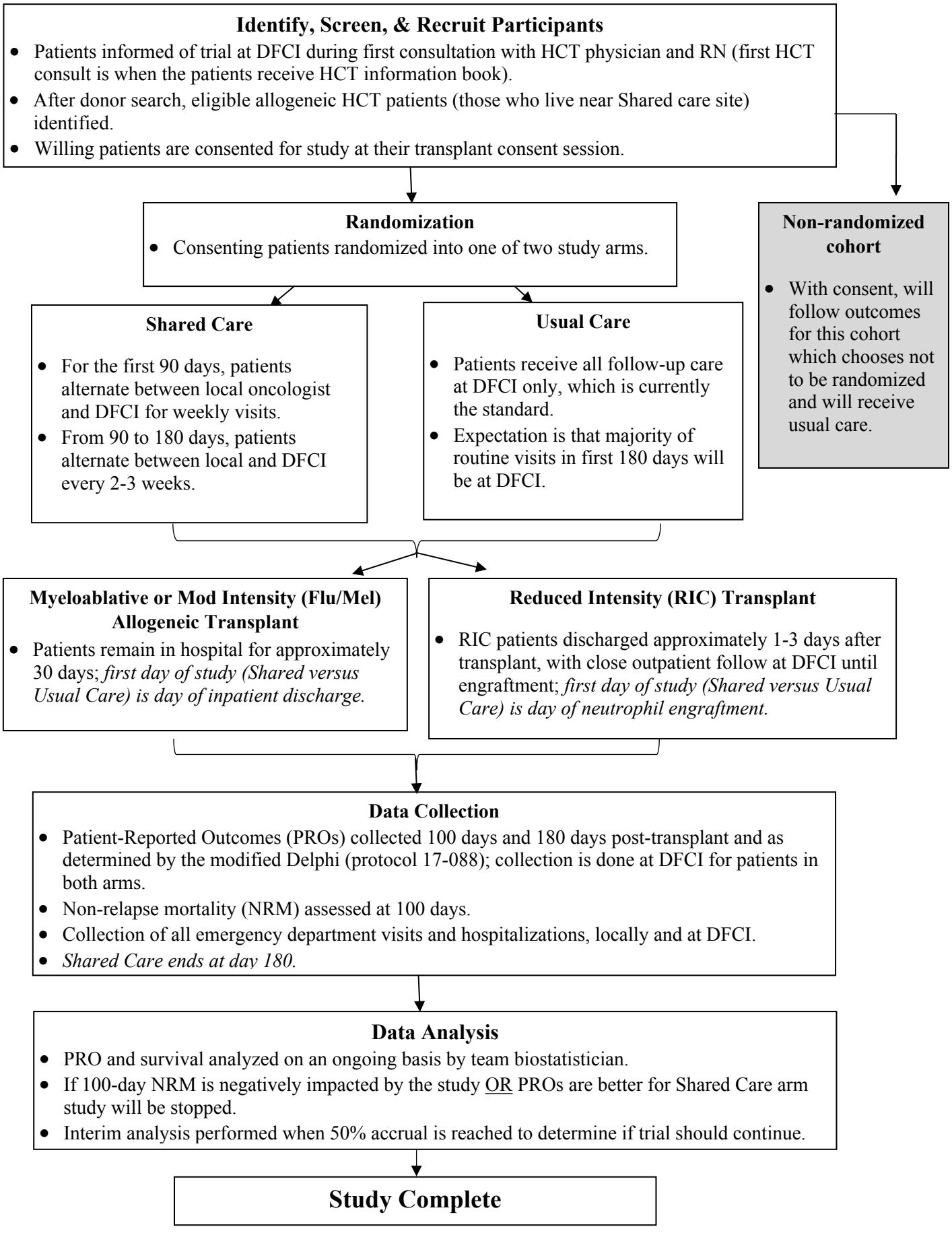
Protocol Schema



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1.0INTRODUCTION

1.1 OVERVIEW

Hematopoietic cell transplantation (HCT), commonly known as bone marrow transplantation, is the only potentially curative treatment for many advanced hematologic malignancies.[1-3] It is a

highly technical inpatient procedure that is only available at select centers in the United States: those that have the capacity for collecting and storing hematopoietic stem cells, as well as caring for patients before the new immune cells take hold. For this reason, many patients who undergo HCT live at great distances from their HCT center. Moreover, after hospital discharge, the first 180 days post-HCT are critical. Patients must be watched closely for infections and/or the development of graft-versus-host disease (GVHD) and specialized anti-rejection medications must be tightly managed. For those who live far away, the need for close follow-up for such a long period can cause a great burden in terms of familial finances, impact on caregivers, and compromised quality of life.[4-6]

One way of potentially ameliorating these effects is to allow some of the post-HCT care to be provided by non-HCT oncologists who practice closer to where patients live. Such a model could reduce patient-centered burdens post-HCT; however, it is not known if, given its complexity, post-HCT care can truly be "shared" between HCT specialists and local oncologists without compromising HCT-related outcomes. We aim to assess the effectiveness of a Shared Care program which allows patients to receive half of their post-HCT care at the HCT center, and the other half with their local oncologist.

1.2 BACKGROUND AND RATIONALE

HCT has become a standard treatment option for many advanced blood cancers. According to the Center for International Blood and Marrow Transplantation Research (CIBMTR), the overall number of allogeneic HCTs in adults in the US surpassed 8,000 per year in 2013, with 8,351 in 2015.[7] In addition, likely due to advances in approaches to infectious disease and other HCT complications, outcomes have significantly improved. Such good news about the increasing availability of HCT has contributed to improvement in the length of life of those transplanted.[8]

Although many HCT survivors eventually return to baseline health, those who undergo an allogeneic procedure (receiving cells from another person) are at particular risk of experiencing short- and long-term effects of the procedure itself. These include rare and common infections, GVHD (acute or chronic), and many other issues that, in addition to the ever-present concern for disease relapse, require diligent monitoring by the HCT team after discharge from the initial inpatient procedure. Usual care for patients after HCT at most centers consists of returning to the HCT center weekly for the first three months and bi-weekly for the next three months (except for emergency care). This intense visit schedule for the first 180 days can be very difficult for patients who live far away in terms of their quality of life (QOL) and personal financial well-being, and distance from transplant center may even impact survival. For example, it has been shown that long driving time (≥160 min) to the HCT center is associated with a decreased likelihood of being disease-free one year after the procedure.[8]

Until recently it was not known if living far away from the HCT center was associated with compromised post-HCT familial finances and/or QOL. A pilot study assessing patient and caregiver costs in the first three months after HCT (n=30)[9] revealed that the median out-of-

pocket cost was over $2,000 (range: $199 to $13,769), and that patients/caregivers who required temporary lodging had higher expenses compared with those who did not. Another study of allogeneic HCT survivors (assessed a median of 2.3 years after the procedure) found that 47% reported ongoing financial burden after HCT – defined as household income decreased by >50%, selling/mortgaging home, or withdrawing money from retirement accounts.[10] With 268 respondents (56% response rate), 73% reported that having had an HCT "hurt them financially." These analyses show **familial financial hardship to be prevalent shortly after HCT, but do not reveal if it is associated with worse patient-reported outcomes such as QOL during this period.**

We recently completed a multi-site survey of adult patients approximately 180 days after HCT (DFCI protocol 14-144; n=325; 72% response rate) to assess the familial financial hardship they might experience after HCT, its sources, and its effect on patient QOL. Income decline was reported by 46% of patients from DFCI center as well as two others (Mayo Clinic in Phoenix, AZ and Roswell Park in Buffalo, NY); 57% reported financial hardship after HCT (defined as dissatisfaction with present finances, difficulty meeting monthly bill payments, or not having enough money at the end of the month), and 16% reported extreme hardship (all three).[4,11,12] In multivariable models controlling for income, **those reporting HCT-related costs such as travel to the HCT center were more likely to report post-HCT income decline and extreme financial hardship**. Moreover, reporting financial hardship was in turn associated with reporting QOL below the median (OR 3.0 [1.8, 5.0]), health status below the median (OR 2.2 [1.4, 3.6]), and stress above the median (OR 2.1 [1.3, 3.5]) as assessed by the PSS-4, a validated measure of perceived stress.[13-15]

At most HCT centers, patients are required to return to the center itself for the bulk of their follow-up even if it is very far away from their home. Another care delivery model used by some centers is to discharge patients completely to local providers (primary care or oncology) shortly after the procedure. Unfortunately, primary care physicians and local non-HCT oncologists often lack sufficient education to manage complex HCT issues, and such models can also leave patients feeling unsupported after having been in the hospital for almost a month after their initial procedure.[16,17] In contrast, we have created a new post-HCT delivery model in which both local oncologists and transplant oncologists work together to care for patients after HCT. We call this model "Shared Care," and plan a randomized controlled trial to test its effectiveness in improving patient-reported outcomes (PROs).

2.0 OBJECTIVES

This study will assess the effectiveness of a shared approach to post-HCT care to Usual Care (all care at DFCI) with respect to highly-relevant PROs and traditional HCT outcomes**.** We aim to:

1. Compare highly-relevant PROs for Shared versus Usual Care at 180 days post-HCT.
2. Compare 100-day non-relapse mortality (NRM) for patients in Shared Care versus Usual Care.

3.0 RESEARCH SUBJECT SELECTION

Overall, 324 patients will be recruited and consented on-site at DFCI to participate in this randomized controlled trial. Annually, approximately twenty participants will be recruited to share care with each site. Post-HCT visits for the 162 patients randomized to Shared Care will occur about 50% at Dana-Farber and 50% at the local site, supported through an innovative web-based provider communication portal (ACT.md). The local sites are:

1. Lifespan Cancer Institute (Providence, RI; 21 participants per year)
   PI: John Reagan (jreagan@lifespan.org)mailto:
   IRB Manager: Andrew Schumacher (ASchumacher@Lifespan.org)
2. Dartmouth-Hitchcock (Lebanon, NH; 20 participants per year)
   PI: Kenneth Meehan (Kenneth.R.Meehan@hitchcock.org)
   IRB Manager: Dianne Ferris (Dianne.M.Ferris@dartmouth.edu)
3. New York Oncology Hematology (Albany, NY; 20 participants per year)
   PI: Ira Zackon (ira.zackon@usoncology.com)
   IRB Manager: Chris Kritzman (chris.kritzman@usoncology.com)
4. New England Cancer Specialists (Brunswick, Maine; 14 participants per year)
   PI: John Winters (wintej@newecs.org)
   Covered by Dana-Farber IRB
5. Eastern Maine Medical Center (Brewer, Maine, 14 participants per year)
   PI: Rodrigo Maegawa (rmaegawa@emhs.org)
   IRB Manager: Laurie Lewis (llewis@emhs.org)
6. DFCI Community Cancer Care and Satellites (Weymouth and Milford, MA; 20 participants per year)
   PI: Michael Anderson (MichaelJ_Anderson@dfci.harvard.edu)
   Covered by Dana-Farber IRB

Inclusion criteria include:

1. Age >= 18 years of age
2. Scheduled to receive an allogeneic HCT at the Dana-Farber Inpatient Hospital or BWH under the care of a DFCI physician.
3. Residence in New York, Maine, New Hampshire, Vermont, Connecticut, Rhode Island, or Massachusetts.
4. Referred from one of the above six centers, or chooses to receive care at one of the six centers.
5. Ability to read English (to fill out standard QOL forms)

Exclusion criteria include:

1. Age <18 years of age
2. Scheduled to receive an autologous HCT

3. Has received an allogeneic transplant in the past; scheduled to receive a second allogeneic transplant
4. Did not receive an allogeneic HCT at Dana-Farber
5. Does not live in New York, Maine, New Hampshire, Vermont, Connecticut, Rhode Island, or Massachusetts.

4.0 RESEARCH SUBJECT ENTRY

Potential study participants will be informed of the study during their first consultation with an HCT physician and/or nurse at DFCI (an information sheet [Appendix A] will be added to the *Guide to Transplant* binder). Study consent will take place at the same time patients consent to HCT, which is always on a subsequent visit. 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 also be clear that enrollment does not guarantee assignment to **Shared Care**, and that there will be a 50% chance they will assigned to **Usual Care**, which means outpatient routine follow-up exclusively at Dana-Farber in Boston.

Once recruited, all study participants will be registered in the DFCI OnCore Clinical Trial Management System by the Research Assistant. Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.

Registration requires a signed informed consent document and a completed eligibility checklist according to DF/HCC SOP REGIST-104.

Patient enrollment happens after stem cell infusion. Patients will not be enrolled if the transplant is canceled prior to Day 0.

5.0 STUDY DESIGNS AND METHODS

5.1 DESIGN/ STUDY TYPE

We propose a randomized control trial with two arms. Participants will be randomized 1:1 to the intervention arm (Shared Care) or to the conventional arm (Usual Care). Randomization will be stratified by site and conditioning intensity (Full vs Reduced intensity).

5.2 SELECTION OF INSTRUMENTS

Data will be collected via medical record reviews and four PRO surveys: (Short Form [SF] Post-HCT Financial Assessment (Appendix B), Caregiver Quality of Life – Adapted Patient Survey (Appendix C), EORTC QLQ-C30 (Appendix D), and FACT-BMT (Appendix E). Medical record review will include sociodemographic information, diagnoses, recurrence, surgical procedures, cardiac events, and mortality. Patient survey data will include measures of the chosen PROs. All data will be entered into a password-protected RedCap database, with hard copies stored in locked file cabinets.

5.3 DESCRIPTION OF INTERVENTION

Shared Care involves four specific strategies to allow patients to be followed locally after HCT, where clinic and laboratory visits are equally shared between the local oncologist and primary HCT team. The challenges of delivering complex care will be met by addressing communication and knowledge gaps within each stakeholder group (transplant physician, local oncologist and patients/caregivers). As such, we have broken down the Shared Care intervention into four targeted components:

1. Formal Care Coordination Plan (CCP): A comprehensive online document created pre-HCT that will clearly define responsibilities of patients and their two teams of providers. This will freely available for review by all three groups (Appendix F).

2. Patient Engagement and Education: The DFCI HCT program has numerous resources for patient education, covering nutrition, medication, and infection prevention. This includes the *Stem Cell Education: An Information Guide for Patients and Caregivers*, access to an online portal (sctpatiented.dana-farber.org – password *dfci*), and a transplant-specific CancerConnect community. Both Shared Care patients and Usual Care patients will receive all of these materials; Shared Care patients will also have specific pieces of education "pushed" to them through the ACT.md portal (Appendix G).

3. Local Oncologist Engagement and Education: Shared Care local oncologists will attend a three-day conference at DFCI's HCT center before patient enrollment starts, aimed to address knowledge gaps and to educate them in management of HCT complications. For draft curriculum see Appendix H. There will also be yearly follow-up education at Dana-Farber which will feature review of post-HCT clinical scenarios and clear protocols for reaching out to the primary HCT team. Additionally, Dr. Abel and Dr. Ho will visit each of the local sites annually to discuss the study and answer any transplant-related questions.

4. Patient/Local Oncologist/Transplant Oncologist Web Portal: A patient-facing centralized web platform (ACT.md) will ensure timely communication with the two teams of providers, patients, and their families. The web portal will also be available for patients to share with emergency providers that they see locally (Appendix I).

5.4 DATA COLLECTION

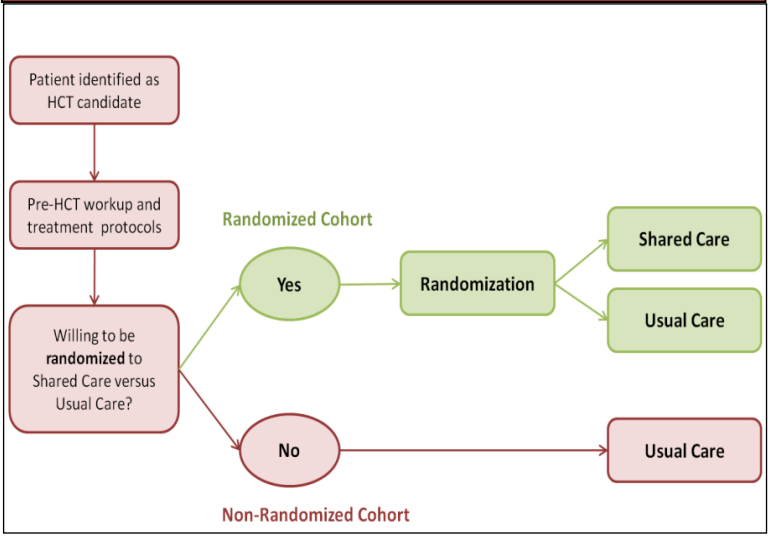
A detailed Multi-Center Data and Safety Monitoring Plan Template (DSMP) is available in the Appendices (Appendix G).

Patient-Reported Outcomes: In a recent study (17-088) a modified Delphi technique was used to determine the optimal PROs and collection methods to measure patient quality of life after

transplant. Per the results of the study, patients will be asked to fill out the (SF) Post-HCT Financial Assessment (Appendix B), Caregiver Quality of Life – Adapted Patient Survey (Appendix C), EORTC QLQ-C30 (Appendix D), and FACT-BMT (Appendix E). The participants deemed that four surveys in one sitting is appropriate, since each of the surveys takes approximately 5 minutes to complete (for a total of 20 minutes to take all four surveys). All patients will be asked to complete PROs at DFCI visits close to 100 days and 180 days post-transplant. These surveys will be administered and collected by the research assistant.

HCT-Related Outcomes: We have chosen 100-day non-relapse mortality (NRM), as this is a standard measure for much of the clinical trial literature surrounding upfront interventions in HCT. We will also measure overall survival (OS) and GVHD symptoms. However, 100-day NRM is more directly applicable because it will be assessed during the critical time of the Shared Care intervention, which lasts 180 days. Transplant data management is unique in that all U.S. transplant centers are required to submit outcomes data for each allogeneic transplant they perform to the national Stem Cell Therapeutic Outcomes Database. To ensure all data are entered in a timely manner, the DFCI team will perform data quality review quarterly, and follow up on any delayed data entry for each patient enrolled.

Figure 1. The Shared Care Study Process



5.5 DESCRIPTION OF STUDY PROCESS

This study of the effectiveness of the Shared Care method will be conducted with a randomized control trial comparing Shared Care and Usual Care. There will be 324 participants. Please see the protocol schema for the study time line. To review:

Pre-Transplant:

1. Recruit participants. Patient sign informed consent on day of overall HCT consent.
2. Patients randomized to one of two arms of the study.

Transplant:

Month 1: Patients admitted to DFCI or BWH for transplant. Receive stem cells.

1. Patients receiving full intensity allogeneic HCT will remain at the hospital for approximately 30 days.

2. Patients receiving a reduced intensity chemotherapy (RIC) HCT will be discharged approximately 1-2 days post-transplant. However, they will remain in Boston to attend frequent clinic visits until engraftment (10-12 days post-transplant).

Post-HCT: Full Intensity

Start of Shared Care: Patients will be discharged from hospital. Usual Care patients return to DFCI for all scheduled appointments through 180 days. Shared Care patients adhere to the following schedule:

1. For the first 90 days post-transplant, patients will alternate between local oncologist and DFCI for weekly visits.
2. From 90 to 180 days post-transplant, patients will alternate between local and DFCI every 2-3 weeks.

Post-HCT: Reduced-Intensity

Start of Shared Care: After evidence of engraftment at follow-up DFCI patient visits (ANC >500). Usual Care patients return to DFCI for all scheduled appointments through 180 days. Shared Care patients adhere to the following schedule:

1. For the first 90 days post-transplant, patients will alternate between local oncologist and DFCI for weekly visits.
2. From 90 to 180 days post-transplant, patients will alternate between local and DFCI every 2-3 weeks.

For patients who have not already established care with their designated local oncology team, a visit will be scheduled with that provider before HCT admission. An example of a Full Allo Shared Care patient's potential schedule is provided in Appendix K.

Premature termination of Shared Care:

Patients who relapse or require a second transplant will remain on protocol for QOL assessment but will no longer share care as part of the protocol.

5.51 Instrument Administration

In addition to the standard data collection that is required for all patients who undergo HCT in the United States (CIBMTR)—including NRM and overall survival (OS)—all patients will be asked to complete PROs at 100 days and 180 days post-transplant, including any patients that prematurely terminate Shared Care for any reason. This was determined based on recommendations made by the modified Delphi panel of patients from a previous study (17-088). PROs will focus on assessing physical, social, and emotional wellbeing.

To understand the care that is received by individuals who choose not to be randomized, for those who consent, the study will track in parallel fashion their HCT-related outcomes and PROs. This will provide a non-randomized observational cohort which will be a second source of analysis and will also allow us to determine if there is a participation bias for those randomized. Given exuberant non-randomized (NR) enrollment and since NR participants are not included in our main analysis, we will cap the number of participants enrolled in the non-randomized arm at 1 patient per month. This will further lessen the burden of data collection with our limited resources and will allow us to better utilize the time of our research assistant involved in data collection. Patients declining randomization will receive usual care following HCT at Dana-Farber.

5.52 Intervention Administration

Along with care at DFCI, patients randomized to Shared Care will receive half of their care at one of six community practice sites (Stamford Hospital, Dartmouth-Hitchcock, New York Oncology Hematology, New England Cancer Specialists, Eastern Maine Medical Center, and DFCI Community Cancer Care/Dana-Farber Satellites).

Each local site will be responsible for obtaining local IRB approval after OHRS approval at DFCI (except for DFCI Community Cancer Care/Dana-Farber Satellites), and all Shared Care Investigator Group (SCIG) members (DFCI and local) will require receipt of education in the protection of human research participants (CITI training). Site investigators and clinicians will also receive HCT training in post-HCT care in Boston, and training in the use of the selected HIPAA-compliant web app, ACT.md. ACT.md will be used as a communication platform for patients, local oncologists, and transplant oncologists during Shared Care. Clinical outcomes will be collected in government-mandated systems already in place for HCT patients at DFCI and maintained by the Dana-Farber Department of Research Computing. PROs during the first 180 days will be collected by the Research Assistant when patients are at Dana-Farber.

GVHD is a potential outcome of an allogeneic HCT transplant. It is a condition where the new cells attack the recipient's tissues, such as the skin and gastrointestinal tract, and specialized anti-rejection medications must be managed closely. The GVHD-related tasks segment of ACT.md will be very detailed because local oncologists will be most unfamiliar with looking for and treating GVHD. There will be a flowsheet integrated in the system that will document the level of GVHD if any.[18]

Shared Care will start on the first clinic visit after stem cell engraftment (reduced intensity transplant), or after hospital discharge (myeloablative transplant). Importantly, we will aim to have the first post-engraftment or post-discharge visit for patients randomized to Shared Care to occur locally even if patients are experiencing post-transplant complications. Transplant teams will provide a "warm pass-off" to the local team before this visit, send a discharge summary of the inpatient stay, and make sure that the online comprehensive care plan is reviewed by all parties.

ACT.md is a crucial component of Shared Care. To avoid gaps in communication between physicians, both local and DFCI oncologists will update each Shared Care patient's profile as they are meeting with the patient. Each provider will write a short visit summary that will be visible both to the other care team and the patient (Appendix I). The note will comprise salient information for the next visit without duplicating the medical record. Providers will be encouraged to call or page one another if an issue is urgent or needs to be discussed in more detail.

Patients will be able to post messages to their care teams in a limited capacity. However, there will be clear communication that messages sent through ACT.md will not be checked in real time, and any issues that require immediate attention would require going to the ER.

Two trained Shared Care physicians will be present at each participating site; however, there will be some physicians who are not part of Shared Care but who will find themselves covering these patients on nights, weekends and vacations. Some providers and patients may feel uncomfortable with a rapid transition of care, which could curb their overall enthusiasm to participate in Shared Care. To ease their concerns, we will ensure a dedicated "Shared Care" transplant attending at Dana-Farber will be available on page at all times for consultation. This call schedule and paging information will be available for each doctor at the Shared care local sites, and continuously updated.

During scheduled monthly calls and periodic on-site visit from the Dana-Farber PIs (Drs. Abel, Antin, and Ho), the local oncologists will have an opportunity to discuss any patients they want additional guidance from the transplant oncologists.

ACT.md will be available via smartphone, tablet or computer. If patients do not have access to one of these platforms, we will supply them with a tablet and/or a WiFi card.

5.53 Compensation

The patients will receive no compensation for their participation.

5.6 ADVERSE REACTION AND THEIR MANAGEMENT

A potential area of concern is that there may not be continuous communication among patients, DFCI transplant providers, and local providers. For this reason we have created the ACT.md web tool for providers to communicate with each other in real time and for patients to directly observe – and potentially add to – this communication (see section 5.52).

The non-randomized cohort of patients will receive Usual Care following their HCT procedure. They will be subject to the same medical record reviews and surveys in the Usual Care arm.

The consent forms outline the risks associated with participation. The risks to both the randomized and non randomized cohorts are expected to be minimal and all attempts will be made to minimize any anticipated issues with communication. If a patient declines

randomization and collection of outcomes, then the patient declines complete participation, s/he will not sign informed consent, will not be in this research study and no data will be collected.

The coordinating center (Dana-Farber) will take several steps to protect against and to minimize risks to privacy of individuals and confidentiality of data:

1. All data analyses will be conducted at Dana-Farber under the direct supervision of the PI.
2. Once the data are received, all study data will be stored on a password-protected RedCap database.

Data will be used for research purposes only. At no time will any patient be individually identified in the final analyses. We are confident that the steps outlined above will effectively protect against this risk.

Estimated study population characteristics are presented in Table 3, which are derived from our recent survey of patients at 180 days after HCT (in the table, autologous patients are excluded).[4,11,12] The response rate we achieved (72%) provides insight into the high level of engagement of HCT patients and caregivers, even when concerning difficult topics such as personal finances.

Finally, to address study risk of missed tasks and miscommunication, we have planned interim analyses to determine if there are worse HCT-related outcomes for Shared Care patients; if so, the study will be stopped immediately and patients returned to usual care.

5.61 Reporting Adverse or Unanticipated Events

Any unanticipated event will be reported to the IRB and the DSMB. Interim analyses will help determine if there are worse HCT-related outcomes for Shared Care patients; if so, the study will be stopped immediately and patients returned to usual care

6.0 STATISTICAL ANALYSIS

In September and October of 2015, we undertook 32 in-depth qualitative interviews with patients in both care models (Table 1). 8 patients had experienced Shared Care, and 24 patients had received all their post-HCT care in Boston (Usual Care). Of the latter, 20 (83%) specifically stated they would have been willing to receive some of their post-HCT care locally. Perhaps

most impressive was this comment by a patient who had been cured of acute myeloid leukemia by a HCT at our center: *"I live an hour north of Portland [Maine] so Dana-Farber was the closest place for my transplant. I was in the hospital in Boston for about a month for the transplant, and discharged on a Saturday. I was very weak, had low blood counts, and was still taking oral antibiotics for an infection I had contracted in the hospital. After a three-hour ride home, on Monday I had to turn around and go back to Dana-Farber. Honestly, my husband and I almost couldn't face it—and we had to do this trip every week for several months.*" Additional patient comments from our interviews are detailed in Table 1.

Table 1. Sample of Shared Care and Usual Care Patient Feedback

"It's always very inconvenient [to come to Boston]...I'd be happy to see Dr. X occasionally and see my local oncologist more often, as long as there is 100% communication between the two. I would want to be able to confirm that they are talking."—**L.B., Usual Care**
"I got great care with my doctors at NYOH, and they really did their best to fight for me. I am glad I still saw the team at Dana-Farber as well."—**J.I., Shared Care**
"If it's something routine like blood counts, seeing a local oncologist would be OK. But what if I got really sick—how would Dana-Farber know? I am not sure that I would want my private information sent by email. Is it secure? "—**W.S., Usual Care**
"Every time [visiting Dana-Farber] is inconvenient. I have to drive over 3 hours each way and I can't do that in one day. Seeing my NYOH doctor is so much better since I don't have to spend money on hotels, gas or food."—**M.G., Shared Care**
"I would never want to get my post-HCT only in NH. I like my oncologist, but I would be scared that they wouldn't know what to do."—**A.G., Usual Care**
"We live in Caribou [Maine], but use the Internet every day. Why can't we use it to make communication between my old team and my new one better?"—**W.J., Shared Care**
"I live pretty close to Boston (about 35 minutes), but is still difficult to get in and see Dr. X; I would love to be able to see my local oncologist who is down the street."—**D.S., Usual Care**

In 2014-2015, an average of 136 patients per year was referred from the 6 participating potential Shared Care sites for allogeneic HCT. Assuming similar number of patients will continue to undergo allogeneic HCT referred from these sites, and considering our qualitative interviews (Table 1) in which 83% of patients stated they would have wanted to receive some post-HCT care locally, we project approximately 80% will agree to be randomized to Shared or Usual Care (108 per year; Table 2). With 3 years of accrual, we anticipate a total of 324 randomized patients (162 in Shared Care and 162 in Usual Care), as well 108 non-randomized patients who will also receive usual care.

6.1 GENERAL DESCRIPTION AND CHARACTERISTICS OF DFCI HCT PATIENT POPULATION

Estimated study population characteristics are presented in Table 3, which are derived from our recent survey of patients at 180 days after HCT (in the table, autologous patients are excluded).[4,11,12] More detail about PROs, handling of missing data, and heterogeneity of effects are detailed below.

Table 2. Shared Care Participating Sites and Number of Allogeneic HCT Patients in 2014 and 2015; Estimates for Accrual Per Year

Proposed Shared Care Sites	State	Mean DFCI Allo HCT 2014 & 2015	If 80% agree to RCT/year
Stamford Hospital	CT	27	21
Dartmouth–Hitchcock	NH/VT	25	20
New York Oncology Hematology	NY	26	20
New England Cancer Specialists	S. ME	17	14
Eastern Maine Medical Center	N. ME	17	14
DFCI CCC/Satellites	MA	25	20
Total		**136**	**108**

6.2 PATIENT-REPORTED OUTCOMES (POWERED ON FACT-BMT)

Our primary hypothesis is that patients in the Shared Care group will have improved PROs compared to those in Usual Care due to a decreased burden of traveling and/or relocation to the HCT center. To investigate this hypothesis, the primary endpoint of this aim is powered by an expected improvement in FACT-BMT score between Shared Care to Usual Care 180 days post HCT. Of the total 324 patients who are randomized at study entry, we project that 80% will be alive at six months after allogeneic HCT and 70% will participate in the day 180 PRO assessment. These projections are based on survival data of DFCI HCT patients between 2012 and 2015, and the response rate from our prior survey regarding financial hardship experienced at 180 days after HCT described above (DFCI RR=72%; Table 5). This yields a sample size of 180. In a previous study of QOL for patients after allogeneic HCT, the mean FACT-BMT score at 100 days after HCT was 110 (±20).[19] Therefore, we believe a difference of 20 or more will be meaningful to show improved PROs at a similar time period (day 180). Extrapolating from this information, if the FACT-BMT score is 120 for Shared Care and 100 for Usual Care at 180 days post-HCT, there will be >99% power to detect this difference. If, however, the difference is 10, then there will be 90% power to detect this difference. This power calculation is based on asymptotic power of the Wilcoxon-Rank-Sum test against an alternative shift at the two sided significance level of 0.05, assuming the standard deviation of the difference is 20. An additional preliminary endpoint is expected difference in mean PSS-4, one of the potential quality of life surveys, score at day 180 post-HCT. In our financial hardship survey, the mean PSS-4 score for DFCI allogeneic patients (n=139) was 5.6 (±3.2). Extrapolating from these data, if the difference in PSS-4 between the Shared and Usual Care groups is 2 with standard deviation 3.2, there will be 98% power to detect this difference at the two-sided significance level of 0.05.

Table 3. Sample DFCI Allogenic HCT Patient Characteristics (n=139)

Patient Characteristics	%*
Diagnosis	
Acute Myeloid Leukemia	35
Myelodysplastic Syndromes (MDS)	20
Myeloproliferative Neoplasms	15
Acute Lymphoblastic Leukemia	15
Other	15
Sex	
Female	41
Male	59
Age	
60 or under	50
Over 60	50
Race	
White	96
Non-white	4
Insurance Type	
Employer sponsored	64
Government sponsored	29
Self-insured	7
Employment Status	
Employed	49
Unemployed	4
Not in the labor force (e.g., retired)	48
Marital Status	
Married	73
Not married	27
Education	
BA/Graduate Degree	49
No BA/Graduate Degree	51
Monthly Income	
Low income (< $3,000)	28
Middle income ($3,000 to $6,999)	45
High income (>$7,000)	27

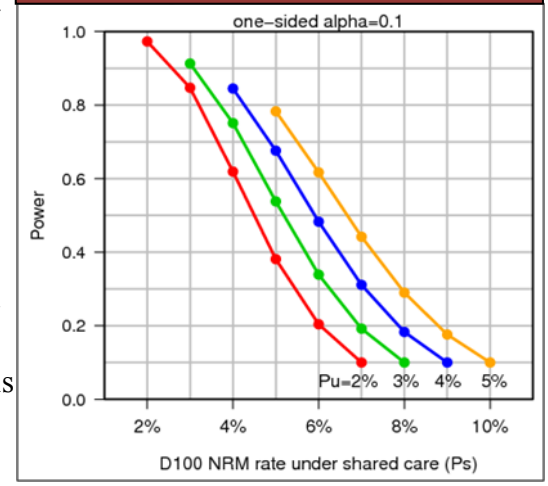
*All categories do not equal 100% due to rounding

6.3 HANDLING OF MISSING DATA

We will make every effort to collect all PRO data from study participants. We will collect these data in-person at the DFCI clinic visit closest to 180 Days (and additionally at earlier time points according to the results of 17-088) which, as compared to a mailed design, will help assure compliance. If a QOL survey is not completed, the PI or co-PI will personally contact each patient to ensure return at the next clinic visit. If patients do not complete the PROs despite personal contact by the PI, they will be regarded as non-responders (dropouts). We will record

all reasons for dropouts, and account for all patients in reports, whether or not they have dropped out. Of note, those who do not agree to participate (~30%) for the PRO assessment will not be regarded as missing.

Figure 2. Power for Non-Inferiority Test (NRM)



We will take a standard approach to handling individual missing items on PROs that are received. For example, if item(s) are unanswered in FACT-BMT, subscale scores will be prorated by multiplying the sum of the subscale by the number of items in the subscale and then dividing by the number of items actually answered. Multiple imputation is a well-known approach for handling missing data. While this approach is a valid method for imputing missing independent variables to preserve study power, imputing outcome variables is more difficult, as this may introduce bias into the study conclusions. We will thus take several approaches to handling missing data from dropouts. First, to assure PRO scores for non-responders are missing at random, we will perform a sensitivity analysis comparing the patient, HCT characteristics, and clinical outcomes between responders and non-responders. Second, we will perform multiple imputation on the outcome variable (including all independent variables) and compare the result without multiple imputation (i.e., inclusion of responding patients only). More importantly, with voluntary patient consent to participate in the study and proactive collection of survey data by the research team, we anticipate that the non-compliance rate will be minimal (<5%). Moreover, we anticipate that there will be no missing independent variables in all HCT patient-related data as this data must be reported to the CIBMTR database by the DFCI/BWH HCT center. Finally, to assure the robustness of our results, we will compare the FACT-BMT scores of the randomized Usual Care cohort with the non-randomized usual care cohort.

6.4 Non-relapse Mortality

The population for the analysis of NRM will be all participants who are randomly assigned to receive either Shared Care or Usual Care based on an intent-to-treat principle (n=324), meaning that the patients will be analyzed according to their randomly assigned treatment, regardless of how they may have actually been treated. The primary hypothesis of this aim is that HCT-related clinical outcomes will not be compromised in the Shared Care group (i.e., non-inferiority test). Causes of death after allogeneic HCT can be due to relapse of the primary diagnosis, but also due to causes other than the disease itself such as infection, GVHD, or organ failure which are termed “non-relapse mortality (NRM).” **100-day NRM** will be the primary outcome, as it is most sensitive to quality of post-HCT care. Other endpoints in this aim include overall survival, progression-free survival, relapse, emergency room admissions, infections, and GVHD. Between 2012 and 2015, the 100-day NRM rate at DFCI was 2-3%. Based on this information, the

hypothesis of testing non-inferiority of Shared Care is defined such that the difference in 100-day NRM rate is not greater than a non-inferiority margin of 5%, that is:

$$\mathbf{H_o: P_s\text{-}P_u \geq 0.05;\ H_a: P_s\text{-}P_u < 0.05}$$

where H_o and H_a denote the null and alternative hypothesis, respectively, P_s denotes the 100-day NRM rate in the Shared Care group and P_u denotes the rate in the Usual Care group. For example, if the 100-day NRM rate is 2% in the Usual Care group and 3% in the Shared Care group, there will be 85% power of rejecting the null hypothesis of inferiority at one-sided type I error rate of 0.1 (Figure 2). If, however, the 100-day NRM is 3% in the Usual Care and 3.7% in the Shared Care group, there will be 81% power of rejecting the null hypothesis of inferiority. This power calculation is based on a Pearson chi-square test for two proportions using PROC POWER in SAS v9.2. Finally, when the study reaches 50% of its accrual (n=162) and the last patient in this set is followed for 100 days, we will perform an analysis of 100-day NRM to ensure the difference in the 100-day NRM rate is within a 5% non-inferiority margin (an "interim look.") If the 100-day NRM rate in Shared Care is > 5% higher than that in Usual Care, accrual will be halted pending review by the Data Safety Monitoring Board. The DSMB may recommend permanent closure of enrollment or continuation of the study. Of note, there may be a small attrition in type I error rate due to the interim look, which is not incorporated in the above error rate of 0.1.

Table 4. Pre-specified Attributes to Examine Heterogeneity

Patient attribute	Age Patient sex CMV seropositive status
Donor attribute	Donor sex Donor type: related vs. unrelated HLA type: matched vs. mismatched CMV seropositive status
Disease attribute	Blood Cancer Diagnosis Disease status
Transplant attribute	Conditioning intensity GVHD prophylaxis Graft source

The data analysis will be based on the intent-to-treat principle. The 100-day NRM will be analyzed as a binary outcome as well as in the competing risks framework treating relapse as a competing event, with the latter being the primary analysis. In the competing risks data analysis, we will examine whether the competing event of relapse is similar between the two types of care. Other endpoints in this aim include overall survival, progression-free survival, NRM, relapse, and a/c GVHD. For overall and progression-free survival, standard survival analysis will be performed, including the Kaplan-Meier method for estimation of survival functions, log-rank test for comparison of KM curves, and Cox proportional hazards model for multivariable regression analysis. For NRM, relapse and a/c GVHD, competing risks data analysis will be performed. Since these endpoints are immunologically intertwined, it is critical to analyze them in a competing risks framework.[20,21] In addition, we will perform a sensitivity analysis comparing baseline characteristics and clinical outcomes between the Shared Care and the non-randomized usual care group, and between the randomized Usual Care group and the non-randomized usual care group. Again, we anticipate no missing data in HCT clinical outcomes since reporting of HCT-related outcomes data to the CIBMTR is mandatory

6.5 HETEROGENEITY IN TREATMENT (HTE) EFFECTS

Heterogeneity of the group effect (Shared Care vs. Usual Care) on outcomes will be examined for pre-specified patient, donor, disease and transplant related attributes (Table 4). The attributes

shown are known risk factors for allogeneic HCT. Since this is a randomized study, we anticipate that all these attributes will be well balanced between two groups. With respect to patient gender and ethnicity, we are aware of no data that would lead us to expect differential effects of treatments in allogeneic HCT by gender and ethnicity. However, when the proposed study is completed, we will perform a multivariable linear regression analysis on FACT-BMT and PSS-4 including attributes shown in Table 4 and type of care (Shared vs. Usual) to identify factors associated with a better outcome. In addition, we will test interactions between each group (Shared vs. Usual) and attributes. If any of these attributes perform better in one group over the other, we will report the results to facilitate further investigation in future studies.

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8.0 APPENDICES

A. Patient Enrollment Information Sheet

Research Study Brief Information Sheet:

Shared Care vs. Usual Care

There is an ongoing study at the Dana-Farber Cancer Institute (DFCI) investigating the effectiveness of a shared model of care following a hematopoietic cell transplantation (HCT) compared to the effectiveness of usual care. Patients in the Shared Care model receive half of their scheduled follow-up appointments at a local site and the other half at Dana-Farber. Usual Care patients receive all scheduled follow-up appointments at Dana-Farber. This study is being sponsored by the Patient-Centered Outcomes Research Institute (PCORI).

If you are eligible for this study you will be asked to consider participating at your tranplsant consent session. If you agree, you will be randomized into either Shared Care or Usual Care. You would have an equal chance of being placed into either model.

Shared Care:

- *You will receive half your care at DFCI and half at a local oncologist*. The local oncologist may or may not have been the physician who referred you to transplant. This oncologist will have received training at DFCI specifically in post-transplant care.
- For the first 90 days post-transplant, you will alternate between your local oncologist and DFCI for weekly visits.
- From 90-180 days, you will alternate between your local oncologist and DFCI every 2-3 weeks, depending on your specific case.
- Your physicians will coordinate your care using a web-based program called ACT.md. You may use this website to keep track of appointments and view your care plan.
- You will be asked to fill out quality of life surveys periodically throughout the 180 days.

OR

Usual Care:

- You will receive all follow-up care at *DFCI only*. This does not mean you must only come to Dana-Farber when you are sick; if you cannot travel to Boston, please seek care locally.
- You will be asked to fill out quality of life surveys periodically throughout the 180 days.

If you have any questions about this study, please contact Research Assistant Priya Marathe at 617-632-5766 or priya_marathe@dfci.harvard.edu.

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B. Short Form (SF) Post-HCT Financial Assessment

About You

1. Including yourself, how many adults 18 years or older currently live in your household?
Write in number of adult(s): _____

2. How many children under 18 years old currently live in your household?
Write in number of children: _____

3. What is the highest level grade or level of school that you have completed?

- ☐ 8th grade or less
- ☐ Some high school, but did not graduate
- ☐ High school graduate or GED
- ☐ Some college or Associate degree
- ☐ Bachelor degree
- ☐ Graduate degree

4. Do you consider yourself Hispanic or Latino?

- ☐ Yes, Hispanic or Latino
- ☐ No, not Hispanic or Latino

5. What is your race? Please mark one or more.

- ☐ White
- ☐ Black or African-American
- ☐ Asian
- ☐ Native Hawaiian or Pacific Islander
- ☐ American Indian or Alaskan Native
- ☐ More than one race

6. What is your current marital status?

- ☐ Married
- ☐ Widowed
- ☐ Divorced

☐ Separated

☐ Never married

7. What is your <u>current</u> employment status?

☐ Not employed (including retired, student or homemaker)
☐ Unemployed and looking for work
☐ Taking a leave of absence, but still have a job
☐ Working full or part-time (if self-employed, also check here ☐)

8. What is your current occupation, or if not currently working, what was your last job for pay?

Please specify occupation: _____

Employment

9. In the week of your transplant, what was your employment status?

☐ Not employed (including retired, student or homemaker)→ **If not employed, go to #17**
☐ Unemployed and looking for work → **If unemployed, go to #17**
☐ Taking a leave of absence or time off, but still had a job
☐ Working full or part-time (if self-employed, also check here ☐)

10. What was your job for pay during the week of your transplant?

Please specify occupation: _____

11. What was your <u>monthly income</u> from employment at that time?

☐ Less than $1,000

☐ $1,000 to $2,999

☐ $3,000 to $4,999

☐ $5,000 to $6,999

☐ $7,000 or more

12. Since your transplant, how supportive has your employer been about you returning to work? Please circle one.

Unsupportive				Completely Supportive	Not Applicable
1	2	3	4	5	NA

13. Since your transplant, were you able to use family and medical leave (FMLA) provided

through your employer?

- ☐ Yes
- ☐ No, not offered by employer
- ☐ No, did not need it
- ☐ No, self-employed or not employed

14. Since your transplant, have you used any of the following? Please mark yes or no for each.

Vacation time..... ☐ Yes ☐ No

Employer paid sick days or paid medical leave..... ☐ Yes ☐ No

Personally purchased or employer-sponsored disability insurance..... ☐ Yes ☐ No

Unpaid time off..... ☐ Yes ☐ No

15. Since your transplant, about how much total time have you taken off from work?

Write in number of weeks: _____

16. Since your transplant, how much of the time you took off was paid time off?

- ☐ None
- ☐ Less than half
- ☐ About half
- ☐ More than half
- ☐ All

Current Household Finances

17. In general, how satisfied are you with your family's present financial situation? Please circle one.

Not satisfied at all				Completely satisfied
1	2	3	4	5

18. How difficult is it for you/your family to meet monthly payments on your bills? Please circle one.

Not difficult at all				Extremely difficult
1	2	3	4	5

19. How do your family's finances usually work out at the end of the month?

☐ Some money left over

☐ Just enough money

☐ Not enough money

20. Compared to before your transplant, how has your monthly household income changed?

☐ It has decreased
☐ It is about the same
☐ It has increased

21. The following questions ask about things people do when money is tight. Since your transplant, how often did you or your family have to do any of the following? Please circle one.

	Never	Rarely	Sometimes	Often
Reduce spending on essential household expenses (food, clothing, rent/mortgage)?.....	1	2	3	4
Withdraw from retirement or savings accounts?...	1	2	3	4
Borrow money to help pay for bills?.....	1	2	3	4
Reduce leisure activities?.....	1	2	3	4
Cut back on prescribed medications?.....	1	2	3	4

22. Since your transplant, have you received any of the following resources to help cover expenses? Please check all that apply.

☐ Social Security Disability Insurance or Social Security Insurance
☐ Government assistance programs (food stamps, fuel or cash assistance)
☐ Dana-Farber financial assistance (discount hotel rooms, gas or food gift cards)
☐ Local or national charities (churches/synagogues, American Cancer Society)
☐ None of the above

23. What is your <u>current</u> monthly household income (include income from all household members)?

☐ Less than $1,000
☐ $1,000 to $2,999
☐ $3,000 to $4,999
☐ $5,000 to $6,999
☐ $7,000 or more

Health Insurance and Medical Costs

24. How satisfied are you with your current insurance coverage? Please circle one.

Not satisfied at All				Completely satisfied
1	2	3	4	5

25. About how much of your <u>own money</u> did you spend <u>last month</u> for your medical care (including prescriptions, co-payments, deductibles, and premiums)?

$_____dollars per month

26. The next questions are about costs associated with your transplant that are not direct medical costs. Since your transplant, how difficult has it been for you to pay for the following costs? Please circle one number or "N/A" if you did not have the type of cost after your transplant.

	Not at all difficult				Extremely difficult	Not Applicable
Paying to temporarily relocate closer to transplant center.....	1	2	3	4	5	N/A
Paying for transportation to and from your appointments (gas, parking).....	1	2	3	4	5	N/A
Paying for transplant-related changes at home (cleaning, special foods).....	1	2	3	4	5	N/A
Paying for care services for children or parents usually in my care.....	1	2	3	4	5	N/A

27. How difficult is it for you to pay your medical bills (including prescriptions, co-payments, premiums, and deductibles)? Please circle one.

Not difficult at all				Extremely difficult
1	2	3	4	5

28. The following questions ask about things that may make your life more difficult or stressful.

During the last month, how much have each of the following added stress in your life?

	Not at all			A lot
Worry about being a burden on your family…	1	2	3	4
Worry about not having money for necessities like food, utilities, and housing…….	1	2	3	4
Worry about losing or not having health insurance……...	1	2	3	4
Worry about cost of your health insurance.....	1	2	3	4
Worry about paying medical bills…….	1	2	3	4

29. Thinking back to before your transplant, how informed do you feel you were about post-transplant related costs?

☐ Not at all informed

☐ Somewhat informed

☐ Extremely informed

30. Who gave you information about post-transplant related costs? (Check all that apply)

☐ Doctor

☐ Nurse

☐ Social worker

☐ Resource specialist

☐ Someone else → Who? _____

☐ No one

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C. Caregiver Quality of Life – Adapted Patient Survey

100 days post transplant:

Which of the following statements best describes your relationship with your primary caregiver?

My caregiver is a family member.
My caregiver is a friend.
My caregiver is a paid professional.
My caregiver is other_____

Below is a list of statements that people caring for loved ones with cancer have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

0 = Not at all **1** = A little bit **2** = Somewhat **3** = Quite a bit **4** = Very much

<u>My caregiver seems…</u>						
1.	…supported by friends and neighbors	**0**	**1**	**2**	**3**	**4**
2.	…to have adequate information about my care	**0**	**1**	**2**	**3**	**4**
3.	…to have a new daily routine since my transplant	**0**	**1**	**2**	**3**	**4**
4.	…more tired than before my transplant	**0**	**1**	**2**	**3**	**4**
5.	…more stressed than before my transplant	**0**	**1**	**2**	**3**	**4**
<u>I feel that…</u>						
6.	…my caregiver is part of my decision-making team regarding my transplant	**0**	**1**	**2**	**3**	**4**
7.	…my caregiver and I have developed a closer relationship since transplant	**0**	**1**	**2**	**3**	**4**
8.	…the transplant process has negatively impacted my relationship with my caregiver	**0**	**1**	**2**	**3**	**4**
9.	…I am dependent on my caregiver for transportation	**0**	**1**	**2**	**3**	**4**
10.	…my caregiver takes primary responsibility for my diet	**0**	**1**	**2**	**3**	**4**

<u>Circle the answer below that bests describes the employment situation of your caregiver:</u>
My caregiver…

a. was not working before and is not working now
b. was not working before and is working now
c. was working before and is not working now
d. was working before and is working now

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180 days post transplant:

Has your primary caregiver changed since you last filled out this survey (at 100 days post-transplant)?

Yes, I have a different caregiver.
No, my caregiver has remained the same.
I do not remember.

Which of the following statements best describes your relationship with your primary caregiver?

My caregiver is a family member.
My caregiver is a friend.
My caregiver is a paid professional.
My caregiver is other_____

Below is a list of statements that people caring for loved ones with cancer have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

0 = Not at all **1** = A little bit **2** = Somewhat **3** = Quite a bit **4** = Very much

My caregiver seems…					
1….supported by friends and neighbors	**0**	**1**	**2**	**3**	**4**
2…to have adequate information about my care	**0**	**1**	**2**	**3**	**4**
3…to have a new daily routine since my transplant	**0**	**1**	**2**	**3**	**4**
4…more tired than before my transplant	**0**	**1**	**2**	**3**	**4**
5…more stressed than before my transplant	**0**	**1**	**2**	**3**	**4**
I feel that…					
6…my caregiver is part of my decision-making team regarding my transplant	**0**	**1**	**2**	**3**	**4**
7…my caregiver and I have developed a closer relationship since transplant	**0**	**1**	**2**	**3**	**4**
8…the transplant process has negatively impacted my relationship with my caregiver	**0**	**1**	**2**	**3**	**4**
9…I am dependent on my caregiver for transportation	**0**	**1**	**2**	**3**	**4**
10…my caregiver takes primary responsibility for my diet	**0**	**1**	**2**	**3**	**4**

Circle the answer below that bests describes the employment situation of your caregiver:
My caregiver…

a. was not working before and is not working now
b. was not working before and is working now
c. was working before and is not working now
d. was working before and is working now

D. European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year): 31

Not at A Quite Very **All (1) Little (2) a Bit (3) Much (4)**				
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week: Not at A Quite Very **All (1) Little (2) a Bit (3) Much (4)**				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week: Not at A Quite Very **All (1) Little (2) a Bit (3) Much (4)**				
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

Very poor 1 2 3 4 5 6 7 Excellent

30. How would you rate your overall quality of life during the past week?

Very poor 1 2 3 4 5 6 7 Excellent

E. FACT-BMT

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4

GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

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BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

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F. Sample Post-HCT Care Coordination Plan

DANA-FARBER CANCER INSTITUTE

NYOH New York Oncology Hematology

John Smith's Post-HCT Care Coordination Plan

Dana-Farber Cancer Institute and New York Oncology Hematology

DFCI HCT Team
Vincent Ho, MD.
Mobile: (617) 123-4567
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Ira Zackon, MD.
Mobile: (518) 123-4567
Office: (518) 123-7890

Jane Smith, NP.
Mobile: (518) 123-4567
Office: (518) 123-7890

Background

John is a patient at Dana Farber's Hematologic Oncology unit. He was diagnosed with Non-Hodgkin lymphoma in early 2013. He has undergone an HCT on November 1, 2016- post 10 wks of chemotherapy. He will be a part of the Shared Care program as he recovers from the transplant.

Post Transplant Information

Primary Malignancy: **Non-Hodgkin's Lymphoma**
Disease status at transplant: **Stable**
Remission status at transplant: **Stable**
Type of transplant: **URD**
Protocol/Treatment Plan: **924 - Flu/Bu**

Date of transplant (Day 0): **11/1/2016**

Blood Type		CMV Status	
Recipient	Donor	Recipient	Donor
O+	O-	NEGATIVE	NEGATIVE

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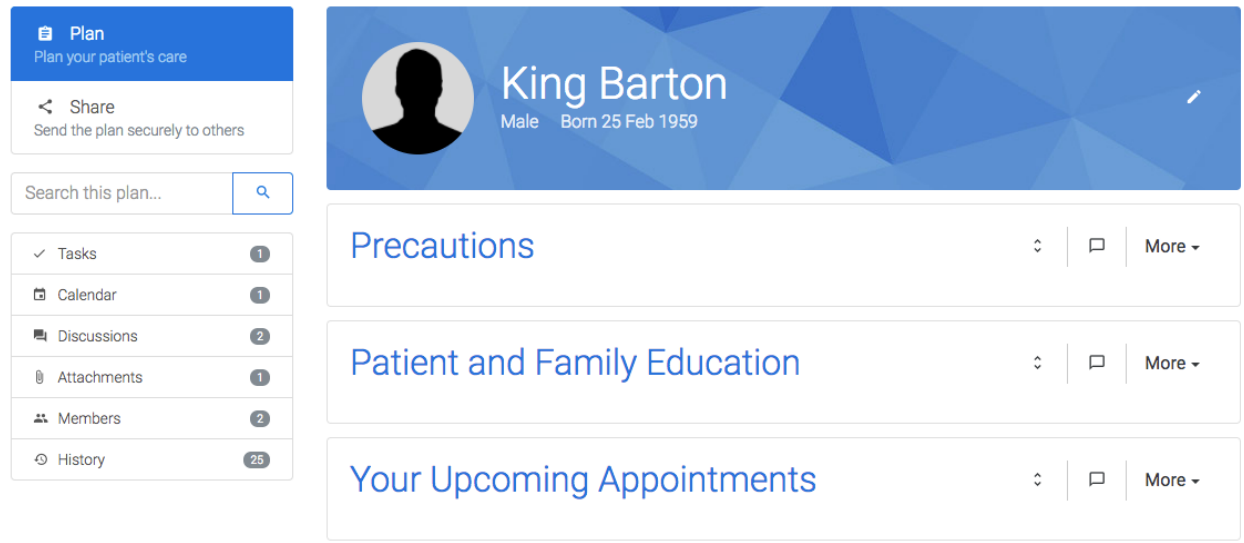
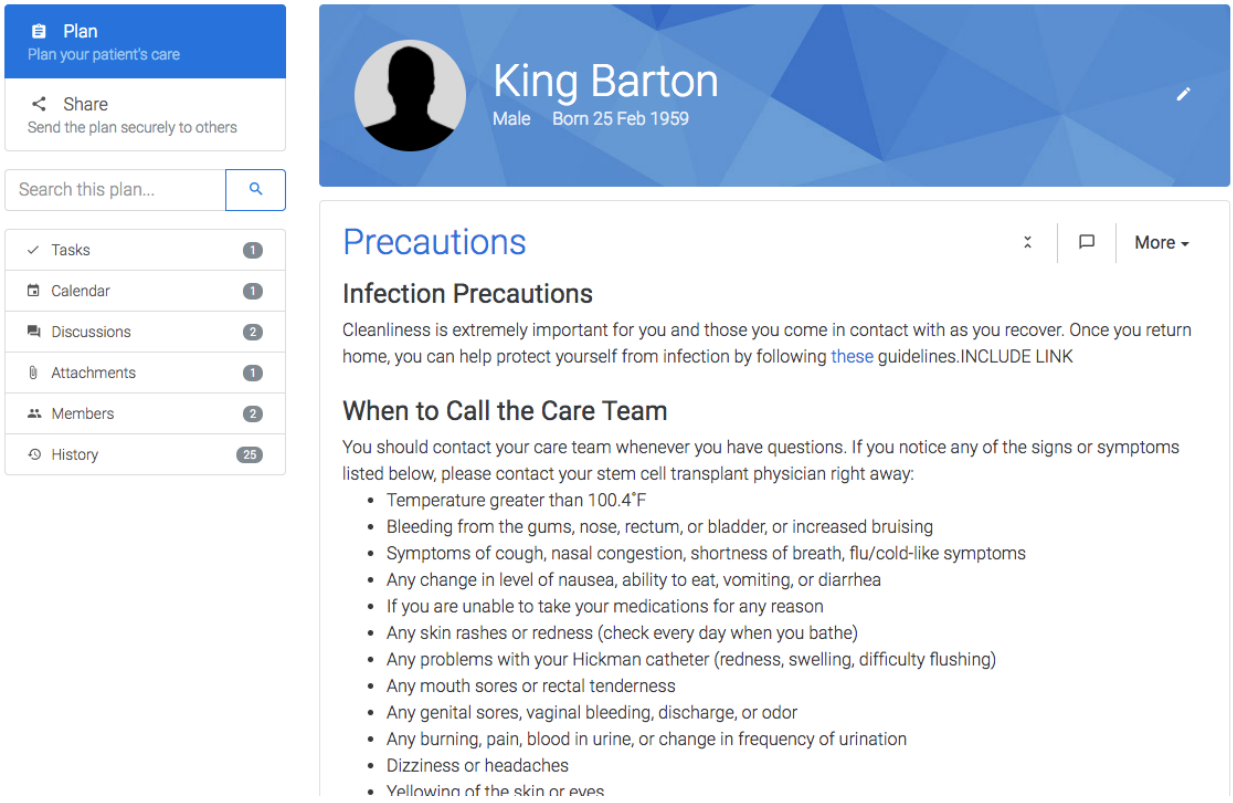
G. ACT.md Education Screenshot





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H. Draft of Local Provider Education Curriculum

Dana-Farber Cancer Institute Transplant Education Program for
PCORI Partners, Shared Care Partners, and all other payers and providers

Friday:		
Schedule		
7:30-8:00	Breakfast	
8:00-10:00	Rounding on BMT A, BMT B, HM PA	
8:00-10:00	Clinic shadowing	
10:00-10:30	Break	
10:30-11:00	Introduction	
11:00-11:30	Pre-transplant process and donor management	
11:30-12:00	Inpatient Care	
12:00-1:00	Lunch	
1:00-1:30	Graft-versus-host-disease	
1:30-2:30	Infectious disease	
2:30-3:00	Post-Auto HSCT Follow-up	
3:00-3:30	Post-Allo HSCT Follow-up	
3:30-3:45	Break	
3:45-4:15	Immuno Effector Cell Therapy	
4:15-4:45	Relapse and Survivorship	
Saturday morning:		
Schedule		
7:30-8:00	Breakfast	
8:00-10:00	Rounding on BMT A, BMT B, HM PA	
10:00-10:30	Break	
10:30-11:30	Shared Care Model	
11:30-12:30	Case studies and discussion	
12:30-1:30	Lunch	
Saturday afternoon:		
Schedule		
1:30-2:30	PCORI Overview	
2:30-4:30	Act.md	
Sunday:		
Schedule		
7:30-8:00	Breakfast	
8:00-10:00	Rounding on BMT A, BMT B, HM PA	PCORI Shared Care PIs only
9:30-10:00	DFCI tour	PCORI SC-PAP and Stakeholders
10:00-10:30	Break	
10:30-11:00	Welcome and introductions	
11:00-12:30	Integrating PCORI into your hospital	PCORI Shared Care PIs
11:00-12:30	Patient engagement	SC-PAP
11:00-12:30	Stakeholder engagement	PCORI Shared Care Stakeholders
12:30-1:30	Lunch	
1:30-2:30	Reporting for PCORI	PCORI Shared Care PIs
1:30-2:30	Future goals	SC-PAP and Stakeholders
2:30-3:30	Close of session	

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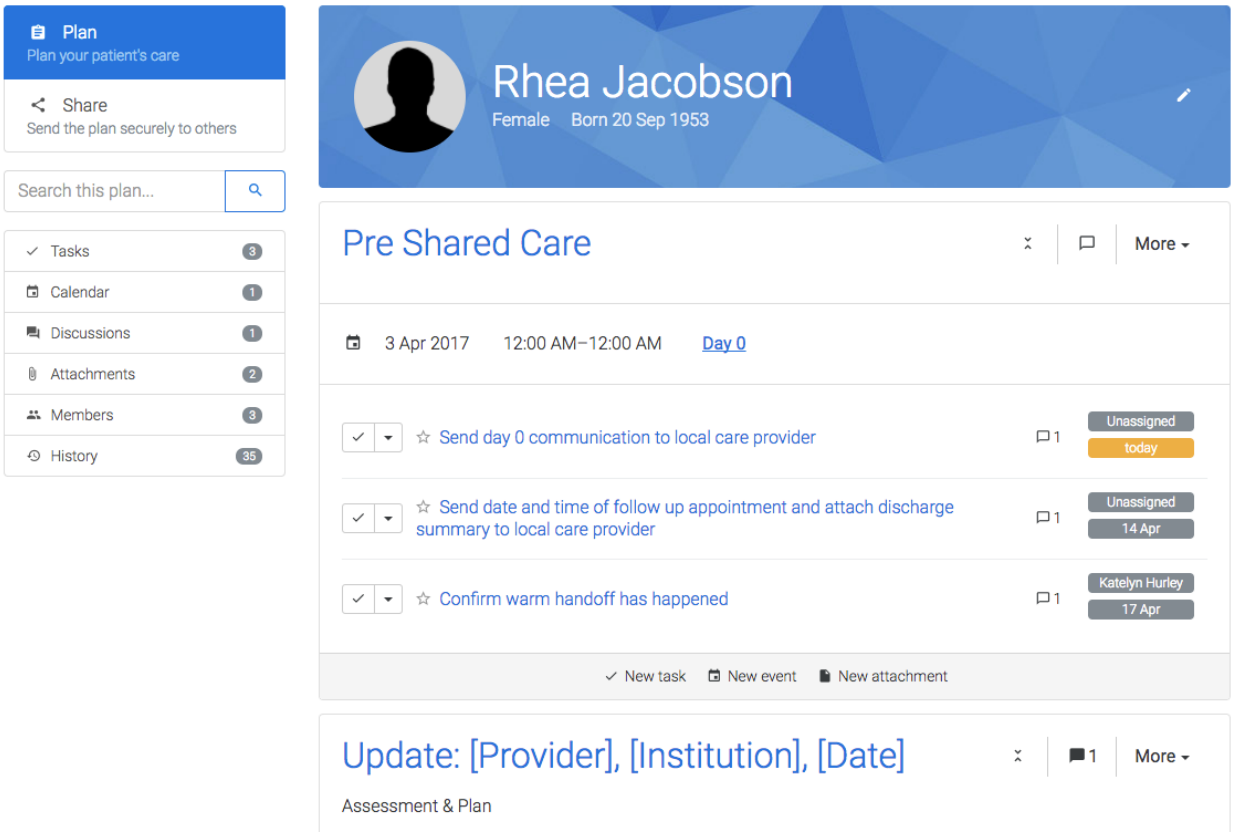
I. ACT.md Communication Screenshot



J. Multi-Center Data and Safety Monitoring Plan (DSMP)

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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 are expected to adhere to the following general responsibilities:

DF/HCC Sponsor

The DF/HCC Sponsor, **Patient-Centered Outcomes Research (PCORI)** 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 in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB) and DF/HCC 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, **DFCI**, 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 (OnCore).
- 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 Policy 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 (monthly conference calls web-based communication platform) 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.
- 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 (in-person training conference at DFCI).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- 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.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol 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 be the sole consent form for the entire study. Participants in this study are consenting to receive half their care at DFCI and half at a Participating Institution; therefore, all participants will be consented at DFCI. Though a Participating Institution may recommend potential participants, all recruitment will take place at DFCI, the Lead Institution. This consent form will follow the consent template and will adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

The DFCI research team will submit the consent forms to the IRB for approval.
Participating institutions must follow the DF/HCC requirement that all informed consent and re-consent for all research will take place at DFCI.

IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the DFCI Informed Consent Form
- 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. DFCI, will not register participants to receive half their care at a Participating Institution 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, PCORI, 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

All registration will take place at the Coordinating Center, DFCI.

Participant Registration and Randomization

To register a participant, the following documents should be completed by the Coordinating Center:

- Signed informed consent document
- Protocol Registration Form

To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (OnCore).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution, provide the study specific participant case number, and begin coordinating care per the protocol and study design.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

Initiation of Therapy

Participants must be registered with the DF/HCC OnCore before the initiation protocol-specific interventions. The protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. The process for requesting an eligibility exception is defined below.

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. This information will be recorded at the Coordinating Center.

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, PCORI, 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 Toxicity 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.

All participants receiving protocol mandated care plan will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 5.6.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements.

Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

Data Management

Guidelines for data collection and management are detailed in section 5.4 All patients will be registered in OnCore.

Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

Ongoing Monitoring of Protocol Compliance

Meetings will be held at least twice each year, which will mean at least eight reviews during the proposed Shared Care study period. Each protocol is discussed in both an open and a closed session. In the open session, members of the study team, including the study statistician Dr. Kim and the PI, Dr. Abel, may be present to review the conduct of the trial and to answer questions from members of the DSMB. The focus of this open session will

be on accrual, protocol compliance, and general toxicity issues. Outcomes will normally not be discussed during the open session. The closed session of the DSMB will include only the voting, non-voting, and ad hoc members, and will include discussion of the general conduct of the trial and outcomes, including non-relapsed mortality. The study statistician may be asked to present outcome data during the closed session.

The DSMB will review interim analyses of outcomes (prepared by the lead statistician) and make recommendations as to whether the study needs to be continued, changed or terminated. Site adverse event reports will be submitted to the Statistical Coordinating Center at Dana-Farber. If such an event occurs, three entities (SCIG; site IRB; SC-PAP and the DF/HCC DSMB) will convene to determine if it is safe for the subject to remain on study, if the study is safe to continue, if all subjects need to be notified, and if any changes to the protocol are warranted.

DSMB meetings close with an executive session to summarize and evaluate the overall meeting, finalize recommendations, and plan the next meeting. The Principal Investigator (Dr. Abel) and the Study Biostatistician (Dr. Kim) will be available as needed for each meeting of the DSMB and be responsible for disseminating and implementing any concerns to PCORI, the SCIG, the SC-PAP, and other Stakeholders.

The Participating Sites and the Lead Institution will maintain communication regarding a patient's care via email, telephone, pager, and a HIPAA-compliant web app, ACT.md. ACT.md will be used as a communication platform for patients, local oncologists, and transplant oncologists during Shared Care

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

All accrual will take place at the Lead Institution, DFCI. We anticipate a total of 324 randomized patients, as well as 84 non-randomized patients who will receive all their care at the Lead Institution. Though, no accrual will take place at any Participating Site, we anticipate the following number of patients per year to be referred from or live near each Participating Site:

Lifespan Cancer Institute: 21 participants

Dartmouth-Hitchcock: 20 participants

New York Oncology and Hematology: 20 participants

New England Cancer Specialists: 14 participants

Eastern Maine Medical Center: 14 participants

DFCI Community Cancer Care: 20 participants

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 Standard Operating Procedures (SOPs), 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 scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which 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 DFCI IRB is 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.

K. Shared Care Patient Schedule (Example)

Week 1-5 (Day 30 – 58): Patient will alternate between the local oncologist and DFCI for weekly visits.

- Week 1 (day 30): local
- Week 2 (day 37): DFCI
- Week 3 (day 44): local
- Week 4 (day 51): DFCI
- Week 5 (day 58): local

Week 6-11 (Day 59 – 100): Patient will alternate between the local oncologist and DFCI for bi-weekly visits.

- Week 6 (day 65): no visit
- Week 7 (day 72): DFCI
- Week 8 (day 79): no visit
- Week 9 (day 86): local
- Week 10 (day 93): no visit
- Week 11 (day 100): DFCI

Week 12-23 (Day 107-184): Patient will alternate between the local oncologist and DFCI for bi-weekly visits.

- Week 12 (day 107) no visit
- Week 13 (day 114): local
- Week 14 (day 121): no visit
- Week 15 (day 128): DFCI
- Week 16 (day 135): no visit
- Week 17 (day 142): local
- Week 18 (day 149): no visit
- Week 19 (day 156): DFCI
- Week 20 (day 163): no visit
- Week 21 (day 170): local
- Week 22 (day 177): no visit
- Week 23 (day 184): DFCI