PROTOCOL TITLE:

Randomized Trial of a Positive Psychology Intervention for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

PRINCIPAL INVESTIGATOR:

Hermioni L. Amonoo, MD, MPP
Department: Psychosocial Oncology and Palliative Care
NCT: 05147311

VERSION NUMBER: 1.3

DATE: 11/12/2021

Date of IRB Submission: 11/12/2021

Date of IRB Approval: 11/17/2021

Section 1: Protocol Schema

Screening:

Patients ≥ 18 with hematologic malignancy who have undergone allogeneic HSCT

Patient Enrollment

Complete registration and baseline data collection

Table of Contents

1.0 Objectives* 4
2.0 Background* 5
2.3 Relevant Preliminary Studies. 6
3.0 Inclusion and Exclusion Criteria* 7
4.0 Study-Wide Number of Subjects* 8
5.0 Study-Wide Recruitment Methods* 8
6.0 Multi-Site Research* 9
7.0 Study Timelines* 9
8.0 Study Endpoints* 10
9.0 Procedures Involved* 10
10.0 Data and Specimen Banking* 18
11.0 Data Management* and Confidentiality 21
12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects* 17
13.0 Withdrawal of Subjects* 25
14.0 Risks to Subjects* 26
15.0 Potential Benefits to Subjects* 27
16.0 Vulnerable Populations* 21
17.0 Community-Based Participatory Research* 21
18.0 Sharing of Results with Subjects* 28
19.0 Setting 28
20.0 Resources Available 29
21.0 Prior Approvals 29
22.0 Recruitment Methods 29
23.0 Local Number of Subjects 30
24.0 Provisions to Protect the Privacy Interests of Subjects 30
25.0 Compensation for Research-Related Injury 31
26.0 Economic Burden to Subjects 31
27.0 Consent Process 31
28.0 Process to Document Consent in Writing 32
29.0 Drugs or Devices 30

1.0 Objectives*

1.1 Overview

Allogeneic hematopoietic stem cell transplantation (HSCT) is an intensive treatment that offers a potential cure for some hematologic malignancies. The prolonged hospitalization and extended recovery is an intense experience associated with many physical symptoms and high rates of medical complications.[1] Accordingly, many allogeneic transplant recipients have substantial psychological distress[2] and experience diminished positive psychological well-being (PPWB; e.g., optimism, positive affect, or gratitude).[3] PPWB is prospectively associated with improved quality of life (QOL), physical functioning, and survival in allogeneic recipients, independent of medical or socio-demographic variables, and above and beyond the adverse effects of depression.[4,5,6] This suggests that there may be substantial benefit from cultivating PPWB in this population. Positive psychology interventions (PPIs) are interventions that encourage patients to perform simple, enjoyable activities (e.g., writing a gratitude letter,[7] performing acts of kindness[8]) that consistently and durably improve PPWB in a wide variety of populations.[9,10,11] PPIs have led to reduced depression, improved medication adherence, and more physical activity in studies of patients with a variety of medical illnesses.[7, 10-13,9, 14]

Although PPIs have been successfully used in other medical populations,[12, 15] they have never been tested in allogeneic transplant recipients. Informed by the Broaden and Build Theory of Positive Emotions,[16] an efficacious PPI that improved PPWB in cardiac patients,[17] and findings from our prior (17-154) work that explored PPWB in 25 allogeneic recipients via serial semi-structured interviews in which patients reported that positive emotional experiences resulted in increased motivation to engage in treatment and participate in health behaviors,[18] we developed the Positive psychology for Allogeneic Transplantation of Hematopoietic stem cell intervention (PATH), to fill this gap. PATH is a novel 9-week phone-delivered PPI comprised of activities based in gratitude, strengths, and life purpose. We have completed a one-arm proof-of-concept study (18-225) to assess the feasibility and acceptability of the PATH intervention.[19] The intervention was feasible, acceptable, and led to very small-to-medium effect size improvements in patient-reported outcomes such as optimism, positive affect, symptoms of depression and anxiety, quality of life, (QOL) and fatigue.[19] This was the first proof-of-concept study to establish feasibility of a positive psychology intervention in patients with hematologic malignancy undergoing HSCT. Enhancing PPWB via PPIs in allogeneic recipients could not only improve mood, QOL, and physical functioning, but could also increase long-term survival.[3]

We propose to conduct a single center randomized trial of the PATH intervention versus usual care in patients with hematologic malignancies undergoing HSCT. The primary goal of this study is to further test feasibility and preliminary efficacy of a positive psychology intervention in improving clinical outcomes for patients with hematologic malignancies undergoing HSCT with a larger and more diverse patient population than we had in our one arm open pilot trial. Data from this single center trial will lay the foundation for future, larger, multi-site randomized studies to examine the efficacy of positive psychology interventions for improving outcomes in patients with hematologic malignancies undergoing HSCT.

1.2 Specific Aims/Objectives

#1 (Feasibility; Primary Aim): To determine the feasibility and acceptability of the PATH intervention in patients with hematologic malignancy undergoing HSCT.

Hypothesis: *The PATH intervention will be deemed feasible with >75% of participants randomized to the intervention arm completing ≥ 6/9 positive psychology exercises. The PATH intervention will be deemed acceptable with mean ease and utility scores of each exercise being ≥ 7/10.*

#2 (Effects on Patient-Reported Outcomes): To assess the preliminary efficacy of the PATH intervention on psychological (e.g., depression, anxiety, optimism, positive affect), QOL, and functional outcomes compared to the usual care condition.

Hypothesis: Patients randomized to the PATH intervention will have improved PPWB (e.g., optimism, positive affect, gratitude), mood (e.g., depression and anxiety), and QOL compared to those in the usual care condition.

#3 (Effects on Health Behaviors): To examine the impact of the PATH intervention on behavioral outcomes (e.g., medication adherence, physical activity) compared to those in the usual care condition.

Hypothesis: Patients randomized to the PATH intervention will have improved behavioral outcomes (e.g., medication adherence, physical activity) compared to those in the usual care condition.

2.0 Background*

Hematopoietic stem cell transplantation offers a potential cure for some hematologic malignancies. Fifteen thousand allogeneic stem cell transplantations are performed in the United States annually, and this number is projected to increase five-fold by 2030.[20] Notwithstanding the great promise for remission and survival, the experience of allogenic transplantation is intense and prolonged, and it is accompanied by high rates of physical symptoms and a substantial risk of life-threatening complications and mortality due to chemotherapy-induced toxicities and early post-transplant complications.[21,22-27] For example, 50-70% of patients undergoing HSCT experience moderate to severe nausea, diarrhea, pain, insomnia, and fatigue.[24, 26] These symptoms, accompanied by the physical isolation during the prolonged HSCT hospitalization, often result in a rapid deterioration in psychological well-being and QOL throughout the early recovery post-HSCT.[26-28]

Psychological distress is common in hematopoietic stem cell transplant recipients.[29,30,31] The prolonged hospitalization, social isolation, quarantine status, painful side effects, infections, and frequent outpatient follow-up visits can cause significant psychological distress even in the absence of formal psychiatric diagnoses.[32,33,34] For example, 40% of patients report clinically significant depression and anxiety symptoms during HSCT.[23, 24, 26] Further, several studies have consistently shown that symptoms of psychological distress (e.g., depression, anxiety) is prospectively associated with worse health outcomes, including decreased QOL, higher risk of graft vs. host disease (GVHD), and increased mortality.[2, 35-37] Hence, patients with hematologic malignancies undergoing HSCT have significant physical and psychological needs, and interventions that reduce distress and its associated negative outcomes are needed for allogeneic transplant recipients.

Low levels of positive psychological well-being (PPWB) are also common in hematopoietic stem cell transplant recipients and have been independently associated with poorer health outcomes. Low levels of PPWB (e.g., optimism, positive affect) in allogeneic transplant recipients have also been associated with decreased QOL,[38] poorer immune response,[39] and increased mortality.[40] These poor health outcomes are likely mediated through deficits in health behaviors (e.g., medication adherence, physical activity),[41] and indeed low PPWB has been prospectively associated with poorer adherence to diet, medication, and physical activity in other

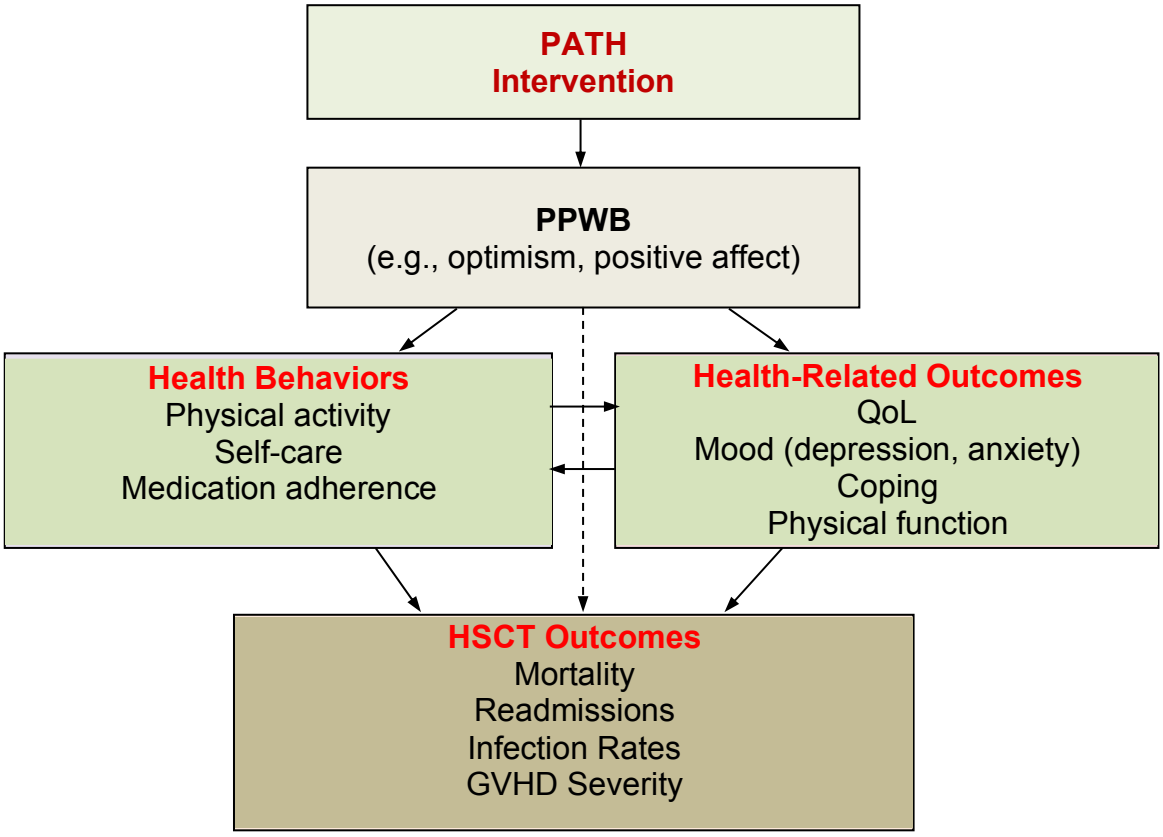
medical populations, independent of sociodemographic, medical comorbidity, and the ill effects of depression and anxiety.[42, 43] In HSCT recipients, low PPWB and its associated effects on health behaviors are not only important in the short-term (e.g., for adherence to immunosuppressants), but also in the long term, as poor adherence to health behaviors can lead to secondary health problems (e.g., cardiovascular disease), low QOL, and increased mortality in cancer survivors.[44,45] This suggests that enhancing PPWB in this population may have important behavioral and medical effects, and indeed such well-being in HSCT recipients is linked with improved QOL,[46] reduced fatigue and pain,[47] faster day to neutrophil engraftment,[39] and lower mortality.[40]

Positive psychological interventions (PPIs) could be used to promote PPWB in the allogeneic transplant population. PPIs are interventions that encourage patients to systematically perform simple, enjoyable structured tasks and activities (e.g., writing a letter of gratitude, leveraging previous successes) that increase the intensity of positive thoughts and emotions.[17, 48] A meta-analysis of 51 PPIs in >4000 participants found that PPIs enhance well-being and improve depressive symptoms, with effects persisting for up to 6 months.[7, 49] Randomized trials of PPIs in medical populations (e.g., patients with coronary artery disease,[11] hypertension,[10] or an acute coronary syndrome[9]) have found PPIs to be associated with greater PPWB, improved depression, improved QOL, greater medication adherence, and more physical activity.[42, 50-53] PPIs are simple to administer and have been well-accepted by patients with a wide variety of illnesses.[12, 54]

Scientific Premise of the Proposed Project: Despite the successful and effective use of PPIs in medical populations to reduce distress,[9, 54] increase QOL, and promote health behaviors,[51] they have never been tested in allogeneic recipients. Accordingly, informed by the Broaden and Build Theory of Positive Emotions,[16] our team's efficacious PPI for cardiac patients,[17] findings from prior work that explored PPWB in allogeneic recipients,[18] we have developed the Positive psychology for Allogenic Transplantation of Hematopoietic stem cell intervention (PATH), a novel 9-week phone-administered PPI. We have also completed a one-arm proof-of-concept study (18-225) to assess the feasibility and acceptability of the PATH intervention.[19] We demonstrated that the PATH intervention was feasible and acceptable in patients undergoing HSCT and led to very small-to-medium effect size improvements in patient-reported outcomes such as optimism, positive affect, symptoms of depression and anxiety, QOL, and fatigue.[19] This study established that a positive psychology intervention can be feasible in patients undergoing HSCT. Our findings from the proof-of concept trial (18-225) suggest that the next step in this intervention development line of research is to conduct a randomized feasibility and preliminary efficacy trial to demonstrate feasibility and preliminary efficacy of the intervention in improving clinical outcomes. Findings from this single center randomized trial will lay the important groundwork for larger, multi-site randomized trails to establish efficacy.

Conceptual Model: Our conceptual model in Figure 2, adapted from the Broaden and Build Theory of Positive Emotions, proposes that PPWB increases patients' emotional and cognitive resources for problem-solving strategies and coping.[16] Using this framework, we anticipate that our patient-centered, and low-burden PPI, the PATH intervention, will promote PPWB in patients with hematologic malignancies undergoing HSCT and could lead to improved HSCT outcomes (e.g., survival and GVHD severity)[3] via decreased depression and anxiety,[55] and improved coping, QOL,[42, 48] physical function,[9, 56] and health behavior adherence.[48] (Figure 2)

Figure 2. Conceptual Model



3.0 Inclusion and Exclusion Criteria*

We propose a single center randomized controlled trial of the PATH intervention versus usual care in 70 patients (age ≥18) with hematologic malignancies who have undergone HSCT. Participants will be recruited from the Dana Farber Cancer Institute (DFCI) HSCT Program. Participants will be randomized equally to the two arms using randomized permuted blocks of sizes two and four, with randomization stratified by presence/absence of graft versus host disease (GVHD). As allogeneic transplant recipients with GVHD have significantly different courses of recovery, QOL, and function post-transplant, we will stratify by GVHD status to ensure adequate and balanced representation between the two study groups.

3.1 Screening Procedures:

Eligible study participants will be identified using the DFCI HSCT clinic database. The clinical research coordinator (CRC) will review the database to screen for eligible patients. We have utilized this study procedure in our proof-of-concept trial (18-225) and enrolled 56% of potentially eligible participants.

Patients who have been approved for the study by their HSCT oncologist will be contacted twice via telephone or in person at a routine clinic visit by a member of the study team after inclusion/exclusion criteria is assessed. Eligible patients will be screened and provided (in-person at clinic, mailed or e-mailed) an information sheet (Appendix A) of the study to review prior to their completing consent procedures.

The DFCI 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.

3.2 Eligibility Criteria

Inclusion Criteria

1. Adult patients (≥ 18 years) with hematologic malignancies who have received allogeneic HSCT at the DFCI who are approaching 100-day post-transplant milestone.
2. Ability to speak, read and write English.
3. Access to a telephone.

Exclusion Criteria

1. Cognitive deficits impeding a study participant's ability to provide informed consent or participate adequately in the study procedures assessed via a commonly used 6-item cognitive assessment with the Brief Interview for Mental Status (BIMS).[57] (Appendix B)
2. Medical conditions precluding interviews.
3. Patients undergoing HSCT for benign hematologic conditions.
4. Patients undergoing outpatient HSCT.
5. Patients with psychiatric or cognitive conditions which the treating clinicians believes prohibits compliance with study procedures.
6. Patients who are unable to consent or are not yet adults (including infants, children, teenagers), pregnant women, or prisoners.

4.0 Study-Wide Number of Subjects*

We propose to recruit 70 patients with hematologic malignancies who have undergone HSCT from one site – DFCI. This is not a multi-site study.

5.0 Study-Wide Recruitment Methods

5.1 Recruitment and Enrollment Procedures:

Prior to study start, the PI will present at the DFCI HSCT protocol meeting to inform the HSCT clinicians about the study and to alert them to the screening, recruitment, and enrollment procedures. The CRC will screen the DFCI HSCT clinic database to recruit, screen, and identify potentially eligble patients. The CRC will then email the transplant oncology clinician to notify them that the patient is potentially eligible for study participation and to inquire about any concerns regarding their study participation (Appendix C). If the treating transplant clinician has any concerns regarding a patient's study participation, then the CRC will document the reason and not approach that individual. If there is no concern regarding study participation, the CRC will approach patients for study participation as they approach their 70-80-day post transplant recovery milestone over the phone or in clinic and ask if they are interested in participating (Appendix D). Patients will only be contacted twice over the phone and will be provided with a call back number to either opt-in or opt-out of the study. Interested participants will be screened with the BIMS and provided (in-person at clinic, mailed or e-mailed) an information sheet of the study to review prior to their completing consent procedures. Patients will have the option of enrolling in the study in-person at the patient's scheduled clinic visit or over the telephone with a

verbal consent (Appendix E) seven days after receiving the study information sheet. Consented participants will then receive an *Actigraph GT3X+* and MEMS Cap for baseline (Day 85-90 post-HSCT) physical activity and medication adherence assessment, respectively. Additionally, consented participants will complete baseline assessments around Day 85-90 post-HSCT.

Participants who provide verbal consent will be asked to sign HIPAA Authorization to review their medical records for the purposes of research. HIPAA authorization maybe provided at a clinic visit or remotely over e-mail or via mail in the setting of the COVID-19 stipulations. Participants who complete written informed consents will sign a HIPAA authorization as part of the written informed consent.

Participants will be registered with the Clinical Trials Management System after they have consented, provided baseline *Actigraph GT3X+* data, and completed baseline assessments. If participants provide consent but do not complete baseline Actigraph data collection and assessments, they will not count towards accrual numbers. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards accrual numbers.

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur after the initiation of protocol-specific procedures or assessments.

For registration of participants from the DF/HCC institutions, study staff will complete the DF/HCC protocol-specific eligibility checklist. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol. Study staff will then register study participants through OnCore. Study staff will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol.

Once the patient has been registered, a member from the MGH Cardiac Psychiatry Research Program (CPRP) team or the Cancer Outcomes Research and Education Program (CoRE) (independent from the study staff) will perform randomization procedures using a computer-generated randomization schema, stratified by GVHD status.

6.0 Multi-Site Research

Not Applicable. This research is located at one site – the DFCI main campus

7.0 Study Timelines*: Table 1 depicts the expected study timeline.

Time Point	Table 1: Study Procedure
Months 0-2	Finalize protocol development and submit to Institutional Review Board for approval
Months 3-4	**Staff Training** ❖ Hire CRC and train them in study procedures, recruitment, and data collection.
Months 5-29	**Randomized Controlled Trial:** ❖ Enroll and randomly assign 70 patients (35 per study group) to receive either the PATH intervention vs. usual care control.
Months 30-35	**Data Collection:** ❖ Complete longitudinal data collection with a minimum of 1 year follow-up on all study participants.
Months 36-40	**Data Analysis:** ❖ Complete data analysis and submit primary manuscripts. ❖ Prepare and submit grant proposal for large scale multi-site randomized controlled efficacy study.

Each participant will be enrolled for approximately one year to collect patient-reported outcomes. We estimate that we will complete the primary manuscripts in months 57-60 from the study start period.

8.0 Study Endpoints*

Primary Endpoint:

- Establish feasibility and acceptability of the PATH intervention in the intervention group.

Secondary Endpoints:

- Compare patients' QOL (FACT-BMT) scores longitudinally between the study groups
- Compare patients' positive psychological wellbeing factors [e.g., optimism (LOT-R) and positive affect (PANAS)] between the study groups
- Compare patients' symptoms of anxiety and depression (HADS) between the study groups
- Compare patients' post-traumatic stress symptoms (PCL-C) between the study groups
- Compare patients' fatigue (PROMIS-fatigue) scores between the study groups
- Compare patients' physical activity (Actigraph GT3X+ data) and physical functioning (PROMIS-PF-20) between the study groups
- Compare patients' medication adherence (MEMS Cap data, SSEQ, MARS-5) between the study groups
- There are currently no anticipated primary or secondary safety endpoints.

Exploratory Endpoints:

- Compare patients' coping (Brief Cope) between the study groups
- Assess whether group differences in patient reported QOL are mediated by improved mood (mediator: HADS) or coping (mediator: Brief Cope)

9.0 Procedures Involved*

9.1 Study Design

We propose a single center randomized trial of a positive psychology intervention (PATH) versus usual care in 70 patients with hematologic malignancies undergoing HSCT. Participants will be randomized equally to the two arms using randomized permuted blocks of sizes two and four, with randomization stratified by presence/absence of GVHD. As allogeneic transplant recipients with GVHD have significantly different courses of recovery, QOL, and function post-transplant, we will stratify by GVHD status to ensure adequate and balanced representation between the two study groups.

The goals of this study are to assess the feasibility, acceptability and preliminary efficacy of this novel 9-session, weekly PP-based intervention for HSCT patients.

Patients will be contacted via telephone or in person at a routine clinic visit close to their routine 70-80-day post-transplant visit for eligibility determination. Interested patients will be screened based on the inclusion/exclusion criteria and provided a study information sheet via mail, e-mail or in-person at a routine clinic visit. Consent procedures would be completed in-person at a routine clinic visit or verbally over the phone approximately seven days after study information is provided.

Upon consent to participate in the study, participants will be given an electronic pill bottle (MEMS Cap) [to be used from the time of baseline assessment completion through the entire duration of the intervention], and an accelerometer to be worn for 7 days prior to the initiation of the intervention. Between the 85-95-day point, all participants will also complete baseline questionnaires either in person, over phone or via a REDCap survey link to participants. Additionally, participants randomized to the intervention group will be given an intervention manual with 9 weekly PP exercises.

Participants randomized to the intervention group will be asked to complete 9 weekly PP exercises and to speak with the study interventionist, weekly. Immediately after the completion of each exercise, participants will rate the ease of exercise completion, overall utility of the exercise, and their current levels of positive affect. Prior to the last week of the intervention, all participants (regardless of whether they are in the intervention group or usual care group) will be mailed (or given in person at a routine follow-up clinic visit) an accelerometer to be worn for 7 days prior to the follow-up survey. After the Week 9 intervention phone session, all participants (regardless of whether they are in the intervention group or usual care group) will repeat self-assessment questionnaires completed at baseline either over the phone, in-person at a routine clinic visit or via a REDCap survey link emailed to participants. Additionally, participants randomized to the intervention group will be asked to complete a recorded exit interview (Appendix F) over the phone. At study completion, we will inquire about participants' potential interest in being contacted about our future studies. We will adhere to any and all participant requests regarding contact. Participants will also return the accelerometer and MEMS Caps at the end of the study via mail or in person during a routine follow-up clinic visit. All participants will receive a $50 check after the 9-week follow-up assessments. Participants who complete the 18-week follow-up assessments will receive an additional $50 check.

9.2 The PATH Intervention

Participants randomized to the PATH intervention will meet (via phone) with the interventionist around approximately day 100 post-HSCT. After the initial phone visit to introduce positive psychology and the PATH intervention, participants will be asked to complete 9 weekly positive psychology exercises. The interventionist will then meet weekly with patients via phone to review each positive psychology exercise.

Table 2. PP intervention component: modules and exercises. Intervention content will be customized to HSCT context.

Module 1: Gratitude/positive affect-based exercises		
Week 1	Gratitude for positive events[7]	Participants identify three positive events that have occurred in the past week and reflect on their feelings as they recall and describe these events.
2	Gratitude letter[7]	Participants write a letter of gratitude thanking a person for their support or kindness.
3	Gratitude skills application	Participants select a useful activity from the prior two weeks, consider how to adapt the activity to daily life, and develop a plan to utilize this skill regularly.
Module 2: Strengths-based exercises		
Week 4	Recalling past success[58]	Participants recall an event in which they experienced success, then write about the event, their contribution to the success, and positive feelings elicited by recalling it.
5	Using personal strengths[7]	Participants undergo a brief assessment of personal strengths, then find a specific new way to use one of their 'signature strengths' in the next 7 days.
6	Strength-based skills application	Participants select a useful activity from the prior two weeks, consider how to adapt the activity to daily life, and develop a plan to utilize this skill regularly.
Module 3: Optimism and meaning-based exercises		
Week 7	Enjoyable and meaningful activities[59]	Participants complete three activities: an enjoyable activity alone, an enjoyable activity with another person, and a meaningful activity completed alone or with others.
8	The good life[60]	Participants imagine and write in detail about a best possible (realistic) future one year from now and consider small short-term steps to take toward such a future.
9	Skills application + future planning	Participants select an activity from this module and develop a plan to utilize this skill—and additional skills from the program—this week and beyond

As shown in Table 2 above, the PATH intervention will focus on three main modules: 1) gratitude/positive affect-based exercises; 2) strengths-based exercises; and 3) optimism and meaning-based exercises.

- **Training:** The PP exercises for this trial have been identified via published literature, or directly from researchers, and modified appropriately for this population based on results from our prior work (17-154 and 18-225). Additional text outlining the rationale and instructions for each exercise are in the written packets for each exercise that are provided to participants. Dr. Amonoo, study interventionists (Dr. Amonoo will be the primary study interventionist and will be covered by psychologists (Drs. Feig and Milstein) who have extensive training and expertise in delivering positive psychology interventions), and CRCs will engage in several training exercises prior to study initiation. Dr. Amonoo and Dr. Hufffman (research mentor) have had substantial experience in delivering PP exercises from prior work which will inform training of other study team members. Together with Dr. Huffman, Dr. Amonoo will also review the treatment manual and the team's prior training manuals related to these exercises.
- **Ensuring Fidelity of the PATH Intervention**: We will take several measures to ensure the fidelity of our study design and intervention delivery. (Table 3) For the study design, we will use a well-established intervention guide utilized in prior studies by our group and pilot-tested in this population (18-225), and monitor the number of participants in our control group. Also, we will use rigorous training procedures for our CRCs. To ensure fidelity of the intervention delivery, the PI will meet weekly with Dr. Huffman, her primary research mentor for the study and a world leader in PPI development for patients with serious illnesses. Dr. Huffman will provide ongoing training on effective and consistent delivery of positive psychological exercises to participants and will help to problem-solve issues as they come up during the intervention delivery. We will audio-record all sessions and use a fidelity structure developed from prior work[17, 54] to measure the extent to which domains of each session are addressed. On a monthly basis, Drs. Huffman and El-Jawahri (research mentor) will independently review (and rate for

fidelity, using an adapted scale) a random sample of 10% of the audio-recorded sessions to ensure intervention fidelity.

Table 3: Fidelity	Steps Taken to Ensure Fidelity	Fidelity Assessment
Study Design	- Intervention based on extensive literature review, prior work in several medical populations and pilot trial in this study population - Standard intervention dose with clear feasibility data based on prior work	- Utilize evidence-based positive psychology intervention guide based on prior trials - Measure number of intervention visits
Intervention Delivery	- Utilization of prior tested positive psychology intervention guide with standardized content areas - Audio-record all intervention calls and sessions	- Study PI and interventionist will meet with primary mentor for this project and positive psychology intervention expert Dr. Huffman weekly for ongoing training of consistent intervention delivery - Dr. Huffman will help problem-solve issues as they come up during the intervention delivery - On a monthly basis, Drs. Huffman and El-Jawahri will independently review (and rate for fidelity, using an adapted scale) a random sample of 10% of the audio-recorded sessions to ensure intervention fidelity

9.3 Usual Care Control

Positive psychological interventions are not part of the routine psychosocial support for patients undergoing HSCT. Hence, due to the focus of feasibility for this trial, we will use a usual care control condition which entails regular social work assessments as part of the HSCT recovery. Routinely, allogeneic transplant recipients are evaluated by a social worker prior to their transplant and the social worker is available to meet regularly during their recovery; typically, social workers see patients once every 2-3 months, and their work does not focus on PPWB skill building or cognitive strategies. Participants in both conditions can see the social worker and receive any other treatments for mental or physical health, as desired. We will track social work visits and other supportive care measures (including any visits with mental health clinicians) in both groups. Data collected on social work consultations will be considered as covariates in our analyses.

9.4 Selection of Instruments

We have selected self-assessment measures based on our prior work and the conceptual framework of our intervention which seeks to improve psychological outcomes, QOL, fatigue, coping strategies, and health behaviors in patients recovering from an allogeneic stem cell transplant.

1.1.1. **Demographics:** Patients will complete a demographic questionnaire at baseline detailing their age, sex, race, ethnicity, religion, relationship status, educational level, annual household income, and living situation. (Appendix G)

1.1.2. **QOL:** We will use the 47-item Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) to assess QOL, which has been validated for use in patients undergoing HCT.[61] The FACT-BMT consists of five subscales assessing well-being across four domains (physical, functional, emotional, social, and bone marrow

transplant symptoms). These self-reported measures possess strong psychometric properties and have been validated for patients undergoing HSCT. (Appendix H)

1.1.3. **Fatigue:** We will use the Patient Reported Outcome Measurement Information System-Fatigue-8a (PROMIS-Fatigue-8a) questionnaire to assess fatigue. The PROMIS-Fatigue-8a is a 7-item well-validated fatigue scale for patients undergoing HSCT. Higher scores indicate greater fatigue.[62] (Appendix I)

1.1.4. **Overall Function:** We will use the 20-item Patient-Reported Outcomes Measurement Information System-Physical Function-20 (PROMIS-PF-20); higher scores indicate better physical function.[63] (Appendix J)

1.1.5. **Mood:** We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety in all study participants. The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week (Appendix K).[64] Used extensively in samples of patients with cancer, the questionnaire consists of a four-point item response form that quantifies the degree to which participants experience mood symptoms. Scores on each subscale range from 0 to 21, with a cutoff of 8 or greater denoting clinically significant anxiety or depression.

1.1.6. **PTSD symptoms:** We will use the Post-Traumatic Stress Disorder Checklist (PCL) to assess symptoms of post-traumatic stress in patients. The PCL is a 17 item self-reported measure that evaluates symptoms of post-traumatic stress disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV.[65](Appendix L)

1.1.7. **Optimism:** We will use the 10-item Life Orientation Test-Revised (LOT-R) to measure dispositional (trait) optimism. Higher scores indicate greater optimism.[66] (Appendix M)

1.1.8. **Positive Affect:** We will use the 10-item Positive and Negative Affect Schedule (PANAS) to measure positive affect; higher scores indicate greater positive and negative affect.[67] (Appendix N)

1.1.9. **Social Support**: We will assess social support using the 26-item Social Support Effectiveness Questionnaire (SSEQ), a validated instrument used in oncological population to assess patients' perception of social support.[68, 69] (Appendix O)

1.1.10. **Coping strategies:** We will use the Brief Cope, a 28-item questionnaire that assess 14 methods of coping (e.g., self-distraction, humor, denial) using a 4-point Likert scale.[70] (Appendix P)

1.1.11. **Satisfaction:** We will use the 5-item Satisfaction with Life Scale (SWLS) to measure satisfaction with life; higher scores indicate greater satisfaction with life.[71] [Appendix Q]

1.1.12. **Gratitude:** We will use the 6-item Gratitude Questionnaire to measure dispositional gratitude; higher scores indicate greater proneness to experience gratitude in daily life.[72] [Appendix R]

1.1.13. **Purpose and Flourishing:** We will use the 8-item Flourishing Scale to assesses a person's self-perceived success in critical areas such as engagement, relationships, self-esteem, meaning & purpose, and optimism; higher scores indicate many psychological resources and strengths.[73] [Appendix S]

1.1.14. **Health Behaviors**: Physical activity and medication adherence will be the target behavioral outcome measures. We will use the well-validated Actigraph GT3X+ accelerometer,[74] at baseline, Week 9, and Week 18, for 7 days of wear; minimum acceptable use is 4+ days with 10+ hours of recorded data as in prior guidelines[75-77] to measure minutes/day of light activity (100-1951 counts/min[78]) as our primary activity measure, along with sedentary leisure time (SLT),[74, 79] given their links to health outcomes. Medication (specifically immunosuppressant, tacrolimus or sirolimus) adherence will be measured via the widely used electronic pill monitoring system, MEMS Caps,[80] to electronically monitor immunosuppressant adherence over the duration of the study. From the EHR and confirmed by patients, we will determine immunosuppressant medication and dosing, and we will calculate changes in adherence over time (% of medication correctly taken, by week and month), based on MEMS data. Additionally, we will assess self-reported adherence to Tacrolimus (an immunosuppressant medication which all allogeneic HSCT patients must take) with the Medication Adherence Scale-5 (MARS-5).[81, 82] (Appendix T)

9.5 Data from the Electronic Health Record:

Study staff will collect clinical, disease, and transplant characteristics at baseline including: ECOG Performance Status at the time of HSCT, clinical comorbidities as measured by the HCT-Comorbidity Index,[83] underlying diagnosis, date of diagnosis, disease status at the time of HSCT, disease risk based on the Disease Risk Index,[84] conditioning regimen, donor type, donor source, date of HSCT, and hospital length-of-stay. We will also collect data on the incidence and severity of acute and chronic GVHD and the incidence of relapse at one year post-HSCT as these outcomes are associated with QOL.

9.6 Data Collection

We will collect and enter all patient-reported data electronically using Research Electronic Data Capture (REDCap). The REDCap Survey is a tool for building and managing online surveys. Vanderbilt University, in collaboration with a consortium of institutional partners, has developed this software and workflow methodology for electronic collection and management of research and clinical trial data. Our research team has extensive experience using REDCap and will create and design the surveys in a web browser, with institutional information technology support. The REDCap Survey system offers secure, HIPAA compliant, web-based applications that provide an intuitive interface for participants to enter data, with real-time validation rules at the time of entry.

Participants will be e-mailed (Appendix U) a remote access to the REDCap system containing questionnaires for them to complete or they can complete questionnaires during in-person clinic visits. If

any participants refuse or are unable to complete the questionnaires on the computer, they will be permitted to use hard-copy paper versions of the questionnaires. Participants will also be provided the option to complete questionnaires over the phone. The CRC will contact participants (in person or via telephone) daily for two days to remind them to complete and return the surveys. If study participants fail to complete the surveys within seven days of the expected time point, we will report the data as missing and document the reason for incompletion. Table 4 details the schedule for administering the self-report measures. At enrollment all participants will be mailed the *Actigraph GT3X+* (together with instructions (Appendix V) on how to use the *Actigraph*) for 7 days of wear; minimum acceptable use is 4+ days with 10+ hours of recorded data around day 85-95 post-transplant and prior to the intervention initiation around day-100 post-transplant. After baseline physical activity data collection, participants will mail back the *Actigraph* in prepaid envelopes we will provide. In addition to the *Actigraph*, participants will also be mailed the MEMS Cap (together with the instructions (Appendix W) on how to use the MEMS Cap) for medication (immunosuppressant) adherence assessment over the entire duration of the intervention starting at the time of baseline surveys around day 85-95 post-transplant. All participants will complete baseline assessments approximately 85-95 day post-transplant. All participants will then complete follow-up assessments at Week-9 (with a 1 week window) and at Week-18 (+/- 1 week window) of intervention initiation.

Table 4: Administration of Self-Report Measures

Participant	**Baseline**	**Week-9 (+ 1 week window)**	**Week-18 (+/- 1 week window)**
Patient Measures:			
Demographics	X		
FACT-BMT	X	X	X
PROMIS-Fatigue 8a	X	X	X
PROMIS-PF-20	X	X	X
HADS	X	X	X
PCL (PTSD)	X	X	X
LOT-R	X	X	X
PANAS	X	X	X
GQ-6	X	X	X
SWLS	X	X	X
Flourishing Scale	X	X	X
Brief Cope	X	X	X
MARS-5	X	X	X
SSEQ	X	X	X
Accelerometer	X	X	
MEMS-Cap	Longitudinal from baseline through week 9		

9.7 Overview of Research Procedures

Initial/Enrollment phone call: During this initial approach at a routine outpatient follow-up clinic or phone call, the study procedures will be explained to potential participants. Those who are interested will be screened for eligibility and, mailed or e-mailed a copy of the study information

sheet. We will then call patients upon receipt of the information sheet approximately seven days from receipt of the information sheet for enrollment and written consent procedures during a routine clinic visit or verbal consent procedures over the phone. Consented participants will then be randomized to usual care or the intervention group. All participants will be mailed (or given in person at a routine follow-up visit) the electronic pill bottle (MEMS Caps), and the accelerometer (Actigraph GT3X+, small half-dollar sized device that clip on to a belt with no visible readout thus preventing independent subject access to data) to wear for 7 days prior to the intervention initiation in the control group. Participants in the intervention group will also be mailed the study intervention manual together with their accelerometer and electronic pill bottle. At the time of the baseline survey and prior to the start of the intervention, adequate accelerometer wear (at least 4 days with 10+ hours per day worn) will be confirmed. Participants in the intervention group will also be mailed the study intervention manual. Those who have not completed sufficient wear of the device will be asked to re-wear the device until there is sufficient baseline data available.

Baseline Assessments: Around the time of each participant's routine 85-95-day post-transplant routine clinic visit, participants will be asked to complete baseline assessment questionnaires either in person during a routine follow-up visit in clinic, over phone, or via a REDCap survey link that will be e-mailed to participants.

After completion of the baseline survey and a returned accelerometer with adequate data, the interventionist will review the mailed treatment manual with weekly PP exercises to those in the intervention group. Participants in the intervention group will be assigned the first exercise (gratitude for positive events) in preparation for their first phone session.

Weekly phone sessions for positive psychology intervention: Participants in the intervention group will be asked to complete the 9 weekly PP exercises and to speak with the interventionist weekly. Weekly phone sessions will last approximately 15-20 minutes. Prior to completing each phone session, participants will be asked to rate their current level of happiness and optimism, using a 10-point Likert scale. Immediately after completing the exercise and phone session, participants will rate the ease of exercise/session completion, overall utility of the exercise/phone session, and their current levels of happiness and optimism, all using 10-point Likert scales. These calls will be recorded using the SONY IC Recorder ICD-PX370 so that a percentage (10%) of these recordings can be reviewed by Dr. Huffman, to ensure that the PP intervention is being delivered as described in the protocol. Given the results of our prior PP studies in medical populations yielding a 64-85% completion rate of the exercises, our recent proof-of-concept trial (18-225) yielding 100% completion rate in this population, and given that this is a feasibility study (i.e., we want to assess participants' willingness to complete the phone sessions), we will expect participants to complete at least 6 PP exercises. In other words, if a participant completes at least 6 sessions, missed sessions will not be considered a deviation from the protocol.

All participants will receive a $50 check after completion of the intervention. Participants in the usual care group will also receive a $50 at the same timepoint. All participants (in either the usual care group or intervention group) who complete 18-week follow-up assessments will receive an additional $50 check.

Follow-up assessments: During Week 8 of the intervention, all participants (those in the intervention group and the usual care group will be mailed (or given in-person during a routine follow-up clinic visit) an accelerometer to wear for 7 days in order to assess physical activity at follow-up. Then, at Week 9, participants will return the accelerometer and MEMS Cap, and will repeat self-assessment questionnaires obtained at the beginning of the study either in-person during a routine follow-up clinic visit, over the phone, or via a REDCap survey link e-mailed to them, depending on participant's preference. Furthermore, participants in the intervention group will be asked to provide feedback about the program via a recorded exit interview over the phone.

Positive Psychology Program Content: All phone sessions will include (a) a review of the ease and utility of the week's PP exercise, (b) a discussion of the rationale of the next week's PP exercise through a guided review of the PP manual, and (c) assignment of the next week's PP exercise. During the calls, the interventionist and participant will also review the next section of the treatment manual and prepare for the upcoming week's exercise.

9.8 Procedures performed to lesson the probability or magnitude of risks

We will ensure that contact with participants is confidential by using only the phone numbers and other contact information that are specifically allowed by the participants. We will not leave study-related messages for participants unless expressly allowed by participants. Upon enrollment, we will ask all participants for the preferred times for calls and if it is acceptable to leave voice messages on their phones. We will adhere to any and all patient requests regarding contact.

Digital recordings of the sessions and exit interviews will be completed using portable recorders. If a study participant were to refuse audio recordings, they can either remove themselves from the study or work with the study staff to choose an alternative to audio recording such as transcription. All recordings will be downloaded immediately from the recorders and the electronic files will be kept within the firewalled, password-protected file on a Partners/Mass General Brigham/DFCI server. Recordings will contain minimal personally identifiable information as the recordings will include the participant's voice but their names or other identifying information on the recordings will not be used and will be erased following review.

All data regarding the objective adherence devices will be encoded only with the study participant number that is linked to personal identifying information in the study database. The devices will not be marked with any personal identifiable information, and the database that will be used to monitor medication adherence and accelerometer data will only contain participant numbers. Data that is uploaded from each participant's accelerometer will be coded without identifying information and will be accessed from a locked computer in a research team office.

10.0 Data and Specimen Banking: Not Applicable

10.1. Data analysis

Specific Aim 1 (Feasibility; Primary Aim): To demonstrate the feasibility of the PATH intervention in patients with hematologic malignancy undergoing HSCT: Based on prior work, we define feasibility as >75% of enrolled participants who start the intervention completing at least 6 of the

9 PP sessions, consistent with metrics used in prior positive psychology feasibility trials[17, 54] and other behavioral intervention studies.[85-87] We will estimate the feasibility using the proportion who meet the criteria, and we will place an exact 95% binomial confidence interval around the proportion. We will assess acceptability using weekly ratings of ease and utility of each exercise (0=very difficult/not helpful; 10=very easy/very helpful). The mean ease and utility of each exercise and overall will be calculated, and and will use a threshold of a mean combined score of 7.0/10 for acceptability that was used in prior studies.[19,57]

Specific Aim 2 (Effects on Patient-Reported Outcomes): To assess the preliminary efficacy of the PATH intervention on psychological (e.g., depression, anxiety, optimism, positive affect), QOL, and functional outcomes compared to the usual care condition: Analyses will begin with descriptive and graphical summaries of the endpoints and evaluation of whether a normality assumption is reasonable for the endpoint or whether transformation is necessary. We will use a Bonferroni correction to address multiple measures and testing. All statistical tests will be two-sided with a liberal alpha level of 0.2 to detect a signal on the impact of the intervention on patient- reported outcomes. We will summarize participants' baseline characteristics using descriptive statistics (e.g., mean) for continuous variables and proportions for categorical variables.

To examine the immediate impact of the intervention on happiness and optimism, we will use generalized estimating equations (GEE) to determine the immediate impact of a PP session on optimism and happiness. The GEE model will allow us to account for the repeated observations on subjects from the different exercises.

We will compare between-group differences in change over time in all patient-reported outcome measures (i.e., psychological, functional, and QOL outcomes) at the 9 and 18-week time points using random effects regression models with a random intercept for each patient. Longitudinal analyses will include all time points. The model will include a categorical effect of time (baseline, week 9 and week 18), a group effect and a time by group interaction. The time by group interaction will estimate the difference in the change from baseline to each time point, and these regression coefficients will be the focus of the analysis.

Given that this pilot is not powered to detect statistically significant group differences, we will examine difference in the change with time and sample variance components on the secondary outcomes. Effect sizes (Cohen's d) will be calculated for changes in outcomes from baseline to 9 and 18 weeks, where 0.3 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect.[88] Effect sizes will be used in a power analysis to estimate the necessary sample size to conduct a full-scale efficacy trial with power >80%. We will also verify the needed sample size based on ability to detect a clinically meaningful difference and references to existing literature.[89]

Finally, we will explore (1) possible mediators of the intervention (e.g., coping strategies) by examining the bootstrapped confidence intervals of the indirect effects and (2) possible moderators (e.g., social support) of intervention effects by probing interactions between the moderator and group assignment that reach or approach significance ($p<0.15$) when predicting patient-reported outcomes.

Specific Aim 3 (Effects on Health Behaviors): To examine the impact of the PATH intervention on behavioral outcomes (e.g., medication adherence, physical activity) compared to those in the usual care condition: We will initially compare physical activity (# of steps/day) at 9- and 18-weeks between the intervention and control groups using a Wilcoxon rank sum test, given that the distribution of the number of steps will likely be skewed. We will also use random effects regression models with a random intercept for each participant to compare between-group differences in change over time in physical activity and medication adherence. All statistical tests will be two tailed, with $p<0.05$ considered significant.

Missing Data: We will also use the intention-to-treat principle with all randomized participants and conducting sensitivity analyses to explore various assumptions about missing data. If source of the missing data appear to be missing at random, the linear mixed effects models described above provide an unbiased estimate of the regression coefficients. However, if we find that participants do not complete the study because of disease worsening, suggesting missing data are not random, we will employ pattern mixture modeling or joint modeling approaches[90] to handle incomplete data, and perform sensitivity analysis[91] to assess the impact of missing data. In addition to the intention-to-treat analysis, we will also estimate the group differences in the completers to estimate the per protocol group difference.

10.2. Sample Size Calculation & Power Analysis:

Based on prior trials in this population,[92] we anticipate 15% of enrolled participants will be unable to complete the intervention due to medical complications and mortality. Hence, we will enroll 70 participants (35 in the [PATH] PP arm) to target having at least 30 PP participants who complete the intervention. For our primary aim (feasibility), in prior trials, approximately 80% of participants have completed 6 of 9 PP exercises.[9] Using the same rate, with 30 PATH participants, we will have 95% power (two-sided α=.05, binomial proportion test) to demonstrate that the proportion who complete >6 of 9 PP sessions is larger than 50% (i.e., a majority). For acceptability, using this sample size, we will have 95% power to detect a true mean score of >7.0 based on prior work (in which mean utility scores were 7.8 +/- 1.8).[12] This pilot RCT is not designed to definitively detect significant ($p<.05$) group differences in psychological, QOL, or behavioral outcomes (and we would need between-group effect size differences of d=.74 to be powered at 80% to detect significant differences). However, this sample of 30 completers in each group will allow us to preliminarily explore the impact of PATH on clinical outcomes and make tentative estimations of effect sizes.

10.3. Data security

Participant data will be collected using REDCap. We will maintain a separate list of participant names and study IDs, which will be saved in password-protected files. Participants will be identified on study forms by case number only to protect confidentiality. Identifiers such as names will only be used during the initial data retrieval process and can be destroyed once all data records have been obtained and data analysis has been completed as discussed previously.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the research team. Under these circumstances, as clearly stated in the participant

consent form, the study CRC will inform the PI who will determine the need to involve social work, psychiatry and/or take further action as deemed necessary.

We will ensure that contact with participants is confidential by using only the phone numbers and other contact information that are specifically allowed by the participants and not leaving study-related messages for participants unless expressly allowed by participants. Upon enrollment, we ask all participants if it is acceptable to leave voice messages on their phones, as well as the appropriate times to call them. We will adhere to all participant requests regarding contact.

In addition, as stated previously, all study staff will undergo an extensive training on study procedures as well as data management to ensure data security and maintaining of confidentiality.

10.4. Quality control for collected data:

Our study staff will utilize double-data entry for approximately 10% of the data entered through REDCap to ensure high data quality. A research coordinator, blinded to the study intervention, will double enter 10% of the data through REDCap to check on data fidelity. If an error is found, the research coordinator will double enter an additional 5% of the data through REDCap. This process will continue until no errors are found. Also, the research coordinator will perform 'test downloads' of the data to ensure that it can be captured in the statistical package to be used in this study.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Purpose of Data and Safety Monitoring Plan:
The purpose of the data and safety monitoring plan is to establish standards that will ensure that this protocol complies with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable Dana Farber Harvard Cancer Center (DF/HCC) Standard Operating Procedures.

General Roles and Responsibilities:

The PI (Dr. Amonoo) will work closely with Drs. Huffman (mentor) and El-Jawahri (mentor), who have extensive expertise conducting randomized supportive care trials to ensure the successful implementation of the proposed project. Dr. Amonoo will be responsible for all aspects of conducting the protocol, which includes:

- Overseeing the development, submission, and approval of the protocol as well as subsequent amendments.
- Ensuring that the research team members are qualified and appropriately resourced to conduct the protocol.
- Following the procedures as outlined in this Data and Safety Monitoring Plan. Detail plan is also in (Appendix X).

- Training the clinical research coordinators prior to enrolling participants and throughout the trial's conduct as needed.
- Monitoring the progress and overall conduct of the study.
- Reviewing data collection and entry and maintaining timely submission of data for study analysis.
- Ensuring compliance with all requirements as set forth in the Code of Federal Regulations, Dana Farber Harvard Cancer Center requirements, HIPAA requirements, and the approved protocol.
- Committing to provisions that the protocol will not be rewritten or modified by anyone other than the overall PI.
- Monitoring accrual and address concerns if accrual goals are not met.

The Dana-Farber Cancer Center is expected to comply with all applicable federal regulations and requirements, the protocol and HIPAA requirements. Specifically, it will be responsible for:

- Reviewing registration materials for eligibility and registering participants with the DF/HCC Quality Assurance for Clinical Trials (QACT).
- Overseeing the data collection process.
- Maintaining documentation of Serious Adverse Events (SAE) reports and deviations/violations.
- Maintaining regulatory documents which include but not limited to the following: IRB approvals/notifications, confirmation of Federal wise Assurances (FWAs), all SAE submissions, screening logs, IRB approved consents.
- Conducting regular communications with overall PI and maintain documentation of all relevant communications.
- Documenting the delegation of research specific activities to study personnel.
- Maintaining regulatory files.
- Having office space, office equipment, and internet access that meet HIPAA standards.
- Participating in quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Providing follow-up and/or corrective action plans for any monitoring queries or audit findings.

Intervention Training and Supervision:

- Study Staff Training: We will conduct a full day training for the clinical research coordinator (CRC) to ensure consistent recruitment and enrollment procedures. We will train the CRC to: 1) identify potentially eligible patients via the transplant clinic schedule and/or database; 2) track potentially eligible patients; 3) communicate with the treating clinicians about patient eligibility; 4) obtain informed consent from patients; and 5) monitor participants longitudinally and administer study questionnaires. In addition, Dr. Amonoo will meet with the CRC weekly to address any study issues or concerns. Drs. Huffman and El-Jawahri will join these weekly meetings as needed.
- Assessment of Intervention Fidelity: To ensure the appropriate delivery of the intervention, 10% of all intervention calls will be recorded and reviewed with the research mentorship team (Drs. Huffman and El-Jawahri). The research mentorship team will review recorded intervention sessions for consistency with explanation and delivery of positive psychology exercises. These measures will also provide accurate data on intervention feasibility. The research mentorship team will also discuss any issues or concerns regarding the intervention fidelity.

Informed Consent Requirements:
The Dana Farber Harvard Cancer Center approved informed consent document will serve as a template for the informed consent.

Protocol Confidentiality: All documents, investigative reports, or information relating to study participants will be kept strictly confidential. We will ensure confidentiality is maintained by identifying participants on all study materials only by participant number, visit number, and date of visit. By recording study data in this manner, all information will be considered 'de-identified,' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996. We will keep participant data in a computer file that is password protected. Only Dr. Amonoo and research team will have access to the data. We will maintain a link between the participant name and study number in a separate password protected file.

Data Management Organizational Structure: Dr. Amonoo and the CRC will develop the study specific database to ensure all data is entered appropriately. The CRC will routinely evaluate the data and discuss any problems and questions with Dr. Amonoo at a weekly meeting. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated once a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available.

Attrition Safeguards/Protection of Loss of Data:
A notable methodological consideration pertaining to the proposed research is protection against attrition. Our research group has conducted numerous clinical intervention studies. In our previous work, we have learned that individuals are best retained in studies when there is 1) a familiarity with study personnel (e.g., ability to effectively establish rapport), 2) team-based persistence in conducting follow-up assessments, and 3) intervention sessions happening in tandem with ongoing medical appointments or inpatient hospitalizations. Yet, it is worth noting here a number of key issues that we have thoughtfully considered in the construction of the present proposal related to attrition. Attrition in clinical research studies overall occurs from three major sources: (a) disease worsening/mortality, (b) refusal to participate, and (c) loss of contact.

- Disease Worsening/Mortality: Given the burden of treatment for patients with hematologic malignancies undergoing HSCT, we do anticipate that a minority of participants will be unable to complete the study protocol due to deteriorating health or death. Our research team has given considerable thought to this concern and adequately powered the study to account for missing data. Based on prior work, we anticipate a 15% attrition rate. The study CRCs will maintain detailed records for patient attrition due to disease-related factors.
- Refusal to Participate: Participants who are successfully recruited into the study but later refuse to participate in subsequent intervention sessions pose a threat to the proposed study. In our previous trial, our refusal to participate rate after study enrollment was quite low and all participants who started the intervention actually completed the all the intervention sessions. Again, the CRCs will maintain detailed records for patient refusals.
- Loss of Contact: Another source of attrition involves those subjects who are successfully recruited into the study but who cannot be located for subsequent follow-up assessments. Like attrition due to subject refusal, attrition due to loss of contact poses a threat to the proposed study. We do not anticipate this to be a major

issue for the proposed study given the intensive and frequent outpatient follow-up visits for patients with hematologic malignancies during the first six months post-HSCT.

- Participant Adherence: To minimize attrition, we plan to use multiple strategies to reduce drop-out. Potential participants will be invited to participate in the baseline assessment during which time participants will receive a thorough explanation of the study treatments, requirements, and follow-up procedures. Study staff will emphasize the patient's responsibility as a research participant, reiterate confidentiality, and work to develop good rapport. We will make a concerted and systematic effort to facilitate adherence to the completion of follow-up assessments. This task will be accomplished by: (1) obtaining longitudinal participant-reported measures during regular follow-up appointments; (2) providing participants with remote access to complete the longitudinal study measures; and (3) making reminder phone calls and administering the study measures over the phone if necessary for participants who do not have appointments in the window for assessment completion.

Data Safety and Monitoring Plan

The following procedures will be followed, in compliance with NIH requirements, to ensure the safety of study participants and the validity and integrity of data.

- Range of Safety Reporting: Dr. Amonoo will review all data pertaining to safety during the weekly research team meeting. These include adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety such as treatment retention rates and reasons for dropout.
- Data Repository: Dr. Amonoo will oversee all aspects of data collection for the study and the CRCs will have the operational responsibility of data management. Specifically, the research team will develop a study specific data management protocol and standard operating procedures for the creation and testing of all study forms, data collection, quality control, and data extraction. These forms will be standardized. We will provide ongoing oversight of data management throughout the study, and will be responsible for generating reports and datasets for quality control and data analysis. All data management activities will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. REDCap provides secure, HIPAA compliant, web-based applications with an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry.
- Serious Adverse Events: Expedited review will occur for all events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. Given that this is a supportive care study in a population at risk for disease relapse and death due to transplant complications (unrelated to the study procedures), only SAEs that may potentially be related to the study will be reported to the IRB. All relevant information will be reported to the IRB for each SAE including information about the event and its outcome, study condition, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by secure e-mail of all related study forms shall be made to the IRB within 24 hours of the occurrence of any SAE that might be relevant to the study. Information

will be reviewed and a determination made of whether there was any possible relevance to the study interventions. Additional reporting to the NIH will be made according to their respective regulations governing SAE reporting.

- Non-Serious Adverse Events: The research team will review monthly summary reports of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase.
- Other Safety-Related Reports: The research team will review weekly summary reports of treatment retention and reasons for dropout, by treatment group.

Monitoring of Data Quality by the research team:
The research team will review the following items on weekly basis to ensure data quality and completeness:

- Total enrollment compared with anticipated enrollment
- Number of ineligible patients registered
- Proportion of missing participant-reported outcomes
- Proportion of other missing data
- Number of participants lost to follow-up
- Number of participants completing the study

Additionally, the research team will receive a report on safety and outcome data for the trial:

- Number of deaths, listed by cause
- Number and types of SAEs
- Number and types of reportable AEs
- Number of participants with primary outcomes
- Number of participants with secondary outcomes

ClinicalTrials.gov Requirements
As per Public Law 110-85, this is an applicable clinical trial and will be registered and results will be reported with ClinicalTrials.gov. The CRC will be responsible for handling ClinicalTrials.gov requirement for this project under Dr. Amonoo's (PI) oversight. She will work closely with the Partners Human Research Affairs QI Program to register the trial prior to enrolling the first subject. Once a record is established, she will confirm accuracy of record content; resolve problems; and maintain records including content update and modification. She will also be responsible for aggregate results reporting and AE reporting at the conclusion of the project. We will ensure that summary results will be reported to clinicaltrials.gov no later than one year after the primary completion date.

12.0 Withdrawal of Subjects*

We do not anticipate any circumstances under which the subjects will be withdrawn from the research without their consent. We do not anticipate any termination of participants. When informed consent is being obtained from patients, we will emphasize to patients that they can withdraw from the study at any time for any discomforts. Participants who withdraw from the study will still have their data potentially analyzed depending on when in the study they withdraw, and participants will be informed of this as well. We will ensure that contact with participants is confidential by using only the phone numbers and other contact information that are specifically allowed by the participants and not leaving study-related messages for participants unless expressly

allowed by participants. Upon enrollment, we ask all participants if it is acceptable to leave voice messages on their phones, as well as the appropriate times to call them. We adhere to any and all participant requests regarding contact. If a participant requests withdrawal from the study, we will ask them if they are comfortable sharing the reason for withdrawal to ensure that there are no adverse events to report to the IRB. We will ask the study participant if they are still willing to permit the study team to continue to monitor their health record, but withdraw from all other study procedures.

13.0 Risks to Subjects*

The risks to participating in this study should be relatively limited and is no more than minimal risk. Given this is a supportive oncology study, we do not anticipate any study-related events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This study population is comprised of individuals undergoing HSCT who frequently experience disease worsening, high rate of symptoms, and hospitalizations from the underlying disease and/or side effects of treatment. Therefore, regular fluctuations in cancer-related symptoms, disease worsening, hospitalizations, emergency department visits, and deaths are to be expected throughout the study, and we will not consider or report such events as SAEs in this trial.

We anticipate no physical risks to participating in this study. Study participants may experience discomfort from discussing psychological experiences and could experience the evaluation as intrusive. Study participants who do not find any benefit from participation may find this upsetting. Activities to obtain data through the baseline and follow-up assessment battery may provide some inconvenience to study participants.

Non-Serious Adverse Events: The IRB will be provided with unblinded summaries of study related non-serious adverse events by treatment group at the continuing reviews. These reports will include types of events, severity, and treatment phase. To date, we have had very few non-serious events in our supportive care studies.

As this is a behavioral study, there are no ingested medications, and no biomedical procedures. It is unlikely that participants will be at any risk for physical harm as a result of study participation.

Reaction Management: Informed consent will be provided by each participant following the explanations by the CRC. The consent will include all study procedures, information about potential risks and benefits of participation, and information regarding whom the participant can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their medical care. All study staff will complete the required human subjects training before working on any human subject aspects of the study.

Should a participant exhibit or express distress, they will be reassured by the study staff that they need not answer any questions they find upsetting. They will also be reminded that study participation is voluntary. If participants remain distressed, both the study PI and primary transplant clinician will be notified. Should several participants express distress over an individual item, the research team will review the questionnaire and contact the IRB to consider removing it from the study.

If a participant reports severe distress or suicidal ideation during the study conduct, the CRC will inform the PI. The PI will determine the need to involve psychiatry and take further action as deemed necessary. The research

team will review sensitive items regarding suicidal ideation within 120 hours (5 business days) of receipt of completed surveys and will report any suicidal ideation to the PI promptly. We will take all measures to ensure that participants are comfortable and we will postpone or end intervention sessions at study participants' requests. We will also ensure that the PI or other psychiatry study staff is available to intervene if needed (due to participant discomfort or to answer specific questions about the study), during intervention sessions, baseline and follow-up assessments. We have been thoughtful to use the briefest methods necessary to assess emotional states and other outcomes to reduce participant discomfort.

With regard to the devices to be used in this study, the medication adherence device, MEMSCap, carries minimal risk; it has no sharp edges, no shock risk, and no other known risks. The accelerometer (ActiGraph GT3X+) used to measure activity is small, light, and without sharp edges – it should pose minimal to no risk. Immersing the device in water for a prolonged period may render it unusable but does not pose a shock risk. Participants will mail the device back after 7 days in a pre-paid envelope provided by the study team. We will provide explicit instructions (in person, via zoom video session, or via mailed documents) regarding the use of the MEMS Cap and accelerometer to ensure safety and proper use, and to reduce inconvenience/distress associated with uncertainty about their safety or use. We will reduce technological failure by educating study participants and providing phone support if participants encounter any difficulties with the devices. Study staff will liaise with participants regarding any battery problems or technical advice for the MEMS Cap and/or Actigraph accelerometer. The participant will be instructed to contact study staff by phone should a problem develop with the MEMS Cap and/or accelerometer during the course of the study. If there is an irresolvable problem, the participant will send the device back to the CRC, and be provided a new one. Study staff will work directly with MEMS Cap and Actigraph technical support to resolve any device issues. A log of all technical difficulties will be maintained.

As with any study, there is the risk of a breach of confidentiality of data collected. To minimize the potential loss of confidentiality, we will employ multiple safeguards and measures. Study procedures will be executed by trained study staff. Intervention sessions will be administered by trained interventionist. Study participants will be assigned a unique study identification number which will be stored separately from personal identification information. All data, including telephone recordings and transcripts will be securely stored in locked file drawers. All project file cabinets and computer databases will be secured in locked offices. Devices will not be marked with any personally indentifiable information, and the database that will be used to monitor medication adherence and accelerometer data will only contain participant numbers. We will ensure to not provide any data to third particies. Data will be aggregated and summary reports will be generated without any personal identification information.

14.0 Potential Benefits to Subjects*

Positive psychology interventions are not a standard of care for patients with any form of malignancy. To our knowledge, this trial is the first of its kind testing a positive psychology intervention in patients with hematologic malignancies undergoing HSCT. Therefore, a potential benefit of the proposed research to human subjects is that participants may experience benefits from receiving the intervention as they reflect and share positive experiences in their lives. As part of the intervention, participants will be given the opportunity to identify positive emotions and consider ways to enhance their own positive emotions. Description of the PP exercises may enlighten them as to potential means of improving their own emotional states and well-being.

Furthermore, they will have the opportunity to consider possible barriers to adherence to health-related behaviors. Additionally, some participants may enjoy the opportunity to complete study measures and reflect on their illness experience. Some may also value the possibility that their contribution to the study may benefit other patients with hematologic malignancies. It is also possible that some participants may not derive these benefits. However, the risk from participation in the study is small (and will be minimized by the procedures outlined above), and overall risk to benefit ratio is favorable.

15.0 Vulnerable Populations

Not Applicable. This trial does not involve vulnerable populations including pregnant women, prisoners, adults who cannot consent, children or patients with cognitive difficulties.

16.0 Community-Based Participatory Research

Not Applicable. This trial does not involve community-based participatory research.

17.0 Sharing of Results with Subjects*

Given the nature of the population included in the study, it is not appropriate to proactively contact participants at the conclusion of this study. We anticipate that a proportion of our participants will die during or within months of completing the study. We do not wish to cause unnecessary distress to participants' family members by attempting to contact participants who have died. Therefore, we provide the research team contact information to each participant and encourage them to contact us if they would like to receive updates and information on the research findings.We hope to publish the results from the study in peer review journal articles but data will be de-identified – patients will be made aware of the fact that the results will be published.

18.0 Setting

18.1 Location

As stated previously in the recruitment and enrollment procedures (section 5.1), patients who are adult (age ≥18) English speaking patients with hematologic malignancies recruited from the Brigham and Women's Hospital (BWH) and Dana Farber Cancer Institute (DFCI) HSCT Program will be eligible for the study. Eligible study participants will be identified using the DFCI HSCT database. Patients will be contacted when they are approaching the time of their 70-80-day post-transplant visit for eligibility determination and to obtain either written consent during a routine clinic visit or verbal consent over the phone. Upon agreement to participate in the study, participants will be mailed (or given in person via a routine follow-up clinic visit) study information sheet, an electronic pill bottle (MEMS Cap), and an accelerometer to wear for 7 days. Additionally, participants randomized to the intervention group will be mailed a treatment manual (or given in person via a routine follow-up clinic visit). Around the time participants' 85-90-day oncology visit they will be emailed a REDCap link with self-assessment questionnaires. Participants will also be provided the option to complete baseline self-assessment questionnaires in person during a routine clinic visit, over the phone, or mailed paper copies of questionnaires. The intervention will be delivered via phone and participants in the intervention group will be called on a private phone they designate. Follow-up assessments will be completed over phone, via a REDCap survey link that study staff e-mails, during a routine clinic visit, or via

mailed paper copies. There will be no involvement from a community advisory board and no research will be conducted outside the DFCI or its affiliates.

19.0 Resources Available

19.1 Team Qualification and oversight

The PI of the project (Dr. Amonoo) is responsible for full oversight of the project. She will be meeting with the research coordinator on weekly basis (and more often as urgent issues arise) to ensure the study process is being followed accurately and to address potential challenges or issues as they may arise. Dr. Amonoo is a member of the MGH Cancer Outcomes Research Program (CORe). CORe has extensive experience conducting randomized clinical trials of supportive care interventions in oncology and has the necessary expertise to ensure the success of the proposed project. Dr. Amonoo is also a member of the MGH Cardiac Psychiatry Research Program (CPRP) which has extensive expertise in conducting positive psychology based intervention studies in patients with serious illnesses – resources from the CPRP will help to ensure the success of the project.

19.2 Other Resources

The DFCI HSCT program performs approximately 550 transplantations per year. We anticipate that 10% of patients would be ineligible for study participation. Therefore, we will have approximately 495 patients eligible for study participation per year. We have successfully enrolled >50% of potentially eligible patients in our prior studies. We therefore conservatively estimate enrolling at least 50% of eligible patients to meet our recruitment goal of approximately 70 subjects – enrolling 5-6 patients per month will help us reach our accrual goal of 70 participants in 12-15 months.

Dr. Amonoo currently has 75% of her time protected to conduct research activities. She will dedicate at least 50% of her time specifically for this project.

If participants exhibit distress due to study procedures, both the PI and the primary oncology clinician will be notified. If participants report acute medical symptoms, they will be directed to emergency medical care, and their primary medical and transplant oncologists may be contacted as needed. If the patient is at imminent risk to self-harm, the study PI, psychiatrist, will take all needed steps to ensure emergent psychiatric evaluation, which may include ensuring evaluation in the nearest emergency room. Participants will be informed of these measures to ensure confidentiality—and the limits of confidentiality, such as arranging for emergent medical or psychiatric care if safety is at imminent risk—as part of the informed consent process. However, given that this is a medical rather than a psychiatric population we anticipate the rate of suicidality in this population will be low.

20.0 Prior Approvals

This research does not involve any prior approvals for subjects.

21.0 Recruitment Methods

As previously outlined in section 5.1, we will use the same successful recruitment and enrollment procedures from our prior work. Prior to the study start, the principal investigator will

meet with the transplant oncology team to review recruitment and enrollment procedures. Specifically, the CRC will send an email to the transplant clinicians to notify them that their patient is eligible for study participation and inquire about any concerns regarding their participation. If the clinicians have objections to their patients' participating in the study, the CRC will document the reason and not approach those individuals. If the transplant clinicians have no objections, the CRC will approach patients for study participation.

Eligible study participants will be identified using the DFCI HSCT database. Patients who are approaching their routine 70-80-day post-transplant visit will be contacted for eligibility determination and to obtain verbal consent. Upon agreement to participate in the study, participants will be mailed study information sheet, an electronic pill bottle, MEMS Cap, and an accelerometer to wear for 7 days. Additionally, participants randomized to the intervention group will be mailed an intervention manual. Around the time of participants' 85-90-day oncology visit, a REDCap survey link with baseline self-assessment questionnaires will be sent to participants. Participants will also be given the option to complete self-assessment questionnaires via phone or mail or in-person during their routine follow-up visit in clinic. Patients who refuse study participation will be asked the reason for deferring.

Patients who complete informed consent and complete baseline questionnaires are then registered with the Clinical Trials Management System. If patients provide consent, but do not complete baseline questionnaire, they will not count towards accrual numbers.

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur prior to the initiation of protocol-specific procedures or assessments.

For registration of patients from DF/HCC institutions, study staff will complete the DF/HCC protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol and the criteria on the eligibility checklist.

Once a patient has been registered, a member from of the CPRP research team (independent from the study staff) will perform randomization procedures using a computer-generated randomization schema, stratified by GVHD status.

Patients will receive a $50 check for completing baseline and week 9 assessments. Participants will receive an additional $50 for completing week 18 follow-up assessments. In order to issue these checks, we will have to ask participants for their Social Security Number.

22.0 Local Number of Subjects

We anticipate that we will recruit approximately 70 patients locally during the study period.

23.0 Provisions to Protect the Privacy Interests of Subjects

We will use REDCap to collect patient data. Patient names and study IDs will be saved in password-protected files. Participants will be identified on study forms by case number only to protect confidentiality. Identifiers such as name will only be used during the initial data retrieval process and can be destroyed once all data records have been obtained and data analysis has been completed as discussed previously.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the research team. Under these circumstances, the study CRC will inform the PI. The PI will then determine the need to involve social work, psychiatry and/or take further action as deemed necessary.

During the informed consent process, it will be emphasized to the patient that at any time during the research, they are free to say they will not participate in the study. Their decision to participate in any part of the study will not in any way interfere with their care at the DFCI. We will also emphasize that only study staff will have access to the data.

It will be emphasized throughout the study that participants should not feel obligated to answer any questions that is asked of them that causes uneasiness.

24.0 Compensation for Research-Related Injury

We do not anticipate any research-related injury to participants due to involvement in this supportive care trial.

25.0 Economic Burden to Subjects

We do not anticipate any financial burden on study participants.

26.0 Consent Process

As this study has no more than minimal risk, the CRC will either obtain verbal consent from potential participants via phone or written consent during a routine clinic visit based on what is most convenient for participants and also considerations from the ongoing COVID-19 pandemic. A waiting period will be available between approaching the potential participant and obtaining verbal consent. The CRC will remind the potential participant that participation is completely voluntary, and that participation or refusal to participate will not impact the standard or quality of care received. The CRC will also clarify the potential minimal risks associated with the study: breach of confidentiality and feelings of distress from answering questions of a personal or sensitive nature, as well as possibly feeling inconvenienced/distressed when using the accelerometer. To ensure ongoing consent, the CRC will explain the participant's right to withdraw at any time and will explain the appropriate means of contacting the research team to initiate the withdrawal process.

***Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)*:** Verbal consent will be obtained, and participants' willingness to partake in the study will be indicative of consent. Although we have written consent procedures to offer participants, we advocate for a waiver of written informed consent because this study is no more than minimal risk and the goal is to prioritize patient safety and reduce their exposure to study staff in the setting of the ongoing COVID pandemic. For the nature of this study, remote consenting is not feasible for our cohort as it requires a level of technical knowledge and maybe burdensome for some patients. Electronic consenting may also result in a selection bias in participation procedures. Lastly, in the setting of the pandemic, patients (especially those who are immunocompromised like our cohort) are increasingly conducting virtual visits with their oncology

clinicians, limiting our ability to effectively conduct in-person consent procedures. As part of the verbal consent process, a study information sheet will mailed to all study participants in the study.

Participants who complete verbal consents will be asked to sign HIPAA Authorization to review their medical records for the purposes of research. HIPAA authorization maybe provided at a clinic visit or remotely over e-mail or via mail in the setting of the COVID-19 stipulations.

27.0 Process to Document Consent in Writing

As stated earlier, written informed consent will be obtained . Instead, verbal consent will be obtained, and participants' willingness to partake in the study will be indicative of consent. We will advocate for a waiver of written informed consent because this study is no more than minimal risk and the goal is to prioritize patient safety and reduce their exposure to study staff in the setting of the ongoing COVID pandemic. For the nature of this study, remote consenting is not feasible for our cohort as it requires a level of technical knowledge and maybe burdensome for some patients. Electronic consenting may also result in a selection bias in participation procedures. Lastly, in the setting of the pandemic, patients (especially those who are immunocompromised like our cohort) are increasingly conducting virtual visits with their oncology clinicians, limiting our ability to effectively conduct in-person consent procedures. As part of the verbal consent process, a study information sheet will mailed to all study participants in the study.

28.0 Drugs or Devices

The ActiGraph GT3X+ accelerometer will be used to measure physical activity. It is small, light, and without sharp edges. Immersing the device in water for a prolonged period may render it unusable but does not pose a shock risk.

The MEMSCap will be used to measure medication adherence. It carries minimal risk; it has no sharp edges, no shock risk, and no other known risks.

29.0 References

1. Kroemeke A, Sobczyk-Kruszelnicka M, Kwissa-Gajewska Z. Everyday life following hematopoietic stem cell transplantation: Decline in physical symptoms within the first month and change-related predictors. *Qual Life Res*. 2018;27(1):125-135. doi:10.1007/s11136-017-1705-3
2. El-Jawahri AR, Vandusen HB, Traeger LN, et al. Quality of life and mood predict posttraumatic stress disorder after hematopoietic stem cell transplantation. *Cancer*. 2016;122(5):806-812. doi:10.1002/cncr.29818
3. Amonoo HL, Barclay ME, El-Jawahri A, Traeger LN, Lee SJ, Huffman JC. Positive Psychological Constructs and Health Outcomes in Hematopoietic Stem Cell Transplantation Patients: A Systematic Review. *Biol Blood Marrow Transplant*. Jan 2019;25(1):e5-e16. doi:10.1016/j.bbmt.2018.09.030

4. Chida Y, Steptoe A. Positive psychological well-being and mortality: A quantitative review of prospective observational studies. *Psychosom Med*. Sep 2008;70(7):741-756.
5. Jim HS, Syrjala KL, Rizzo D. Supportive care of hematopoietic cell transplant patients. *Biol Blood Marrow Transplant*. Jan 2012;18(1 Suppl):S12-S16. doi:10.1016/j.bbmt.2011.10.029
6. Ehrlich KB, Miller GE, Scheide T, et al. Pre-transplant emotional support is associated with longer survival after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. Jul 18 2016;doi:10.1038/bmt.2016.191
7. Seligman ME, Steen TA, Park N, Peterson C. Positive psychology progress: Empirical validation of interventions. *Am Psychol*. 2005;60(5):410-421. doi:10.1037/0003-066X.60.5.410
8. Lyubomirsky S, Sheldon KM, Schkade D. Pursuing happiness: The architecture of sustainable change. 2005.
9. Huffman JC, Feig EH, Millstein RA, et al. Usefulness of a Positive Psychology-Motivational Interviewing Intervention to Promote Positive Affect and Physical Activity After an Acute Coronary Syndrome. *Am J Cardiol*. Jun 15 2019;123(12):1906-1914. doi:10.1016/j.amjcard.2019.03.023
10. Ogedegbe GO, Boutin-Foster C, Wells MT, et al. A randomized controlled trial of positive-affect intervention and medication adherence in hypertensive African Americans. *Archives of internal medicine*. Feb 27 2012;172(4):322-326. doi:10.1001/archinternmed.2011.1307
11. Peterson JC, Charlson ME, Hoffman Z, et al. A randomized controlled trial of positive-affect induction to promote physical activity after percutaneous coronary intervention. *Archives of internal medicine*. 2012;172(4):329-336. doi:10.1001/archinternmed.2011.1311
12. Huffman JC, Millstein RA, Mastromauro CA, et al. A positive psychology intervention for patients with an acute coronary syndrome: Treatment development and proof-of-concept trial. *J Happiness Stud*. 2016;17(5):1985-2006.
13. Robertson SM, Stanley MA, Cully JA, Naik AD. Positive emotional health and diabetes care: Concepts, measurement, and clinical implications. *Psychosomatics*. 2012;53(1):1-12. doi:10.1016/j.psym.2011.09.008
14. Celano CM, Gianangelo TA, Millstein RA, et al. A positive psychology-motivational interviewing intervention for patients with type 2 diabetes: Proof-of-concept trial. *Int J Psychiatry Med*. Aug 16 2018:91217418791448.
15. Moskowitz JT, Hult JR, Duncan LG, et al. A positive affect intervention for people experiencing health-related stress: development and non-randomized pilot test. *Journal of health psychology*. Jul 2012;17(5):676-692. doi:10.1177/1359105311425275
16. Fredrickson BL. The broaden-and-build theory of positive emotions. *Philos Trans R Soc Lond B Biol Sci*. 2004;359(1449):1367-1378. doi:10.1098/rstb.2004.1512
17. Huffman JC, Mastromauro CA, Boehm JK, et al. Development of a positive psychology intervention for patients with acute cardiovascular disease. *Heart Int*. 2011;6(2):e14. doi:10.4081/hi.2011.e14
18. Amonoo HL, Brown LA, Scheu CF, et al. Positive psychological experiences in allogeneic hematopoietic stem cell transplantation. *Psychooncology*. 2019;28(8):1633-1639. doi:10.1002/pon.5128
19. Amonoo HL, El-Jawahri A, Celano CM, et al. A positive psychology intervention to promote health outcomes in hematopoietic stem cell transplantation: the PATH proof-of-concept trial. *Bone Marrow Transplant*. Apr 20 2021;doi:10.1038/s41409-021-01296-9
20. Broder MS, Quock TP, Chang E, et al. The cost of hematopoietic stem-cell transplantation in the United States. *Am Health Drug Benefits*. 2017;10(7):366-374.
21. Wong FL, Francisco L, Togawa K, et al. Long-term recovery after hematopoietic cell transplantation: Predictors of quality-of-life concerns. *Blood*. 2010;115(12):2508-2519. doi:10.1182/blood-2009-06-225631

22. Pidala J, Anasetti C, Jim H. Health-related quality of life following haematopoietic cell transplantation: patient education, evaluation and intervention. *British journal of haematology*. Feb 2010;148(3):373-85. doi:BJH7992 [pii]
10.1111/j.1365-2141.2009.07992.x
23. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. *Blood*. Jul 2 2009;114(1):7-19. doi:blood-2008-10-182592 [pii]
10.1182/blood-2008-10-182592
24. McQuellon RP, Russell GB, Rambo TD, et al. Quality of life and psychological distress of bone marrow transplant recipients: the 'time trajectory' to recovery over the first year. *Bone marrow transplantation*. Mar 1998;21(5):477-86. doi:10.1038/sj.bmt.1701115
25. Bevans MF, Marden S, Leidy NK, et al. Health-related quality of life in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. *Bone marrow transplantation*. Jul 2006;38(2):101-9. doi:1705406 [pii]
10.1038/sj.bmt.1705406
26. El-Jawahri AR, Traeger LN, Kuzmuk K, et al. Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer*. Mar 15 2015;121(6):951-9. doi:10.1002/cncr.29149
27. Fife BL, Huster GA, Cornetta KG, Kennedy VN, Akard LP, Broun ER. Longitudinal study of adaptation to the stress of bone marrow transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 2000;18(7):1539-49.
28. Prieto JM, Atala J, Blanch J, et al. Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone marrow transplantation*. Feb 2005;35(3):307-14. doi:1704788 [pii]
10.1038/sj.bmt.1704788
29. Loberiza FR, Jr., Rizzo JD, Bredeson CN, et al. Association of depressive syndrome and early deaths among patients after stem-cell transplantation for malignant diseases. *J Clin Oncol*. Apr 15 2002;20(8):2118-2126. doi:10.1200/JCO.2002.08.757
30. Prieto JM, Atala J, Blanch J, et al. Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone Marrow Transplant*. 2005;35(3):307-314. doi:10.1038/sj.bmt.1704788
31. Bubalo J. Managing the mental distress of the hematopoietic stem cell transplant (HSCT) patient: A focus on delirium. *Curr Hematol Malig Rep*. Apr 2018;13(2):109-113. doi:10.1007/s11899-018-0441-2
32. Cooke L, Gemmill R, Kravits K, Grant M. Psychological issues of stem cell transplant. *Semin Oncol Nurs*. 2009;25(2):139-150. doi:10.1016/j.soncn.2009.03.008
33. Bevans MF, Mitchell SA, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). *Support Care Cancer*. 2008;16(11):1243-1254. doi:10.1007/s00520-008-0420-6
34. Gomez-Bernal F, Madva EN, Puckett J, Amonoo HL, Millstein RA, Huffman JC. Relationships between life stressors, health behaviors, and chronic medical conditions in mid-life adults: A narrative review. *Psychosomatics*. 2019;60(2):153-163. doi:10.1016/j.psym.2018.12.007
35. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: A review of the literature. *Psychooncology*. 2009;18(2):113-127. doi:10.1002/pon.1399

36. Kuba K, Esser P, Mehnert A, et al. Depression and anxiety following hematopoietic stem cell transplantation: A prospective population-based study in Germany. *Bone Marrow Transplant*. 2017;52(12):1651-1657. doi:10.1038/bmt.2017.190
37. Costanzo ES, Juckett MB, Coe CL. Biobehavioral influences on recovery following hematopoietic stem cell transplantation. *Brain Behav Immun*. Mar 2013;30 Suppl:S68-S74. doi:10.1016/j.bbi.2012.07.005
38. Kenzik K, Huang IC, Rizzo JD, Shenkman E, Wingard J. Relationships among symptoms, psychosocial factors, and health-related quality of life in hematopoietic stem cell transplant survivors. *Support Care Cancer*. Mar 2015;23(3):797-807. doi:10.1007/s00520-014-2420-z
39. Knight JM, Moynihan JA, Lyness JM, et al. Peri-transplant psychosocial factors and neutrophil recovery following hematopoietic stem cell transplantation. *PLoS One*. 2014;9(6):e99778. doi:10.1371/journal.pone.0099778
40. Lee SJ, Loberiza FR, Rizzo JD, Soiffer RJ, Antin JH, Weeks JC. Optimistic expectations and survival after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2003;9(6):389-396.
41. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol*. 2011;4(4):437-452. doi:10.1586/ehm.11.39
42. Huffman JC, Albanese AM, Campbell KA, et al. The Positive Emotions after Acute Coronary Events behavioral health intervention: Design, rationale, and preliminary feasibility of a factorial design study. *Clin Trials*. Apr 2017;14(2):128-139. doi:10.1177/1740774516673365
43. Huffman JC, Beale EE, Celano CM, et al. Effects of optimism and gratitude on physical activity, biomarkers, and readmissions after an acute coronary syndrome: The Gratitude Research in Acute Coronary Events study. *Circ Cardiovasc Qual Outcomes*. Jan 2016;9(1):55-63. doi:10.1161/CIRCOUTCOMES.115.002184
44. Blanchard CM, Courneya KS, Stein K, American Cancer Society's SCS, II. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: Results from the American Cancer Society's SCS-II. *J Clin Oncol*. 2008;26(13):2198-2204. doi:10.1200/JCO.2007.14.6217
45. Hoodin F, Uberti JP, Lynch TJ, Steele P, Ratanatharathorn V. Do negative or positive emotions differentially impact mortality after adult stem cell transplant? *Bone Marrow Transplant*. 2006;38(4):255-264. doi:10.1038/sj.bmt.1705419
46. Fromm K, Andrykowski MA, Hunt J. Positive and negative psychosocial sequelae of bone marrow transplantation: implications for quality of life assessment. *J Behav Med*. 1996;19(3):221-240.
47. Leeson LA, Nelson AM, Rathouz PJ, et al. Spirituality and the recovery of quality of life following hematopoietic stem cell transplantation. *Health Psychol*. 2015;34(9):920-928. doi:10.1037/hea0000196
48. Bolier L, Haverman M, Westerhof GJ, Riper H, Smit F, Bohlmeijer E. Positive psychology interventions: a meta-analysis of randomized controlled studies. *BMC Public Health*. Feb 8 2013;13:119. doi:10.1186/1471-2458-13-119
49. Sin NL, Lyubomirsky S. Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: A practice-friendly meta-analysis. *J Clin Psychol*. 2009;65(5):467-487. doi:10.1002/jclp.20593
50. Celano CM, Albanese AM, Millstein RA, et al. Optimizing a positive psychology intervention to promote health behaviors after an acute coronary syndrome: The Positive Emotions After Acute Coronary Events III (PEACE-III) randomized factorial trial. *Psychosom Med*. 2018;80(6):526-534xxx. doi:10.1097/PSY.0000000000000584
51. Celano CM, Gianangelo TA, Millstein RA, et al. A positive psychology-motivational interviewing intervention for patients with type 2 diabetes: Proof-of-concept trial. *Int J Psychiatry Med*. 2019;54(2):97-114nnn. doi:10.1177/0091217418791448

52. Labarthe DR, Kubzansky LD, Boehm JK, Lloyd-Jones DM, Berry JD, Seligman ME. Positive cardiovascular health: A timely convergence. *J Am Coll Cardiol*. Aug 23 2016;68(8):860-867. doi:10.1016/j.jacc.2016.03.608
53. Van Cappellen P, Rice EL, Catalino LI, Fredrickson BL. Positive affective processes underlie positive health behaviour change. *Psychol Health*. Jan 2018;33(1):77-97. doi:10.1080/08870446.2017.1320798
54. Huffman JC, DuBois CM, Millstein RA, Celano CM, Wexler D. Positive Psychological Interventions for Patients with Type 2 Diabetes: Rationale, Theoretical Model, and Intervention Development. *J Diabetes Res*. 2015;2015:428349. doi:10.1155/2015/428349
55. Chakhssi F, Kraiss JT, Sommers-Spijkerman M, Bohlmeijer ET. The effect of positive psychology interventions on well-being and distress in clinical samples with psychiatric or somatic disorders: a systematic review and meta-analysis. *BMC Psychiatry*. Jun 27 2018;18(1):211. doi:10.1186/s12888-018-1739-2
56. Park N, Peterson C, Szvarca D, Vander Molen RJ, Kim ES, Collon K. Positive psychology and physical health: Research and applications. *Am J Lifestyle Med*. May-Jun 2016;10(3):200-206. doi:10.1177/1559827614550277
57. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Med Care*. Sep 2002;40(9):771-81. doi:10.1097/00005650-200209000-00007
58. Selimbegovic L, Régner I, Sanitioso RB, Huguet P. Influence of general and specific autobiographical recall on subsequent behavior: The case of cognitive performance. *J Exp Soc Psychol*. 2011;47(1):72-78. doi:10.1016/j.jesp.2010.08.011
59. Peterson C, Park N, Seligman MEP. Orientations to happiness and life satisfaction: The full life versus the empty life. journal article. *J Happiness Stud*. 2005;6(1):25-41. doi:10.1007/s10902-004-1278-z
60. Sheldon KM, Lyubomirsky S. How to increase and sustain positive emotion: The effects of expressing gratitude and visualizing best possible selves. *J Posit Psychol*. 2006/04/01 2006;1(2):73-82. doi:10.1080/17439760500510676
61. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant*. Feb 1997;19(4):357-68. doi:10.1038/sj.bmt.1700672
62. Cella D, Lai JS, Jensen SE, et al. PROMIS Fatigue Item Bank had Clinical Validity across Diverse Chronic Conditions. *J Clin Epidemiol*. May 2016;73:128-34. doi:10.1016/j.jclinepi.2015.08.037
63. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. Nov 2010;63(11):1179-94. doi:10.1016/j.jclinepi.2010.04.011
64. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica*. Jun 1983;67(6):361-70.
65. Smith MY, Redd W, DuHamel K, Vickberg SJ, Ricketts P. Validation of the PTSD Checklist-Civilian Version in survivors of bone marrow transplantation. Research Support, Non-U.S. Gov't. *Journal of traumatic stress*. Jul 1999;12(3):485-99. doi:10.1023/A:1024719104351
66. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. *J Pers Soc Psychol*. 1994;67(6):1063-1078. doi:10.1037/0022-3514.67.6.1063
67. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070.

68. Rini C, Redd WH, Austin J, et al. Effectiveness of partner social support predicts enduring psychological distress after hematopoietic stem cell transplantation. *J Consult Clin Psychol*. Feb 2011;79(1):64-74. doi:10.1037/a0022199
69. Stapleton LR, Schetter CD, Westling E, et al. Perceived partner support in pregnancy predicts lower maternal and infant distress. *J Fam Psychol*. Jun 2012;26(3):453-63. doi:10.1037/a0028332
70. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med*. 1997;4(1):92-100. doi:10.1207/s15327558ijbm0401_6
71. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess*. Feb 1985;49(1):71-5. doi:10.1207/s15327752jpa4901_13
72. McCullough ME, Emmons RA, Tsang JA. The grateful disposition: a conceptual and empirical topography. *J Pers Soc Psychol*. Jan 2002;82(1):112-27. doi:10.1037//0022-3514.82.1.112
73. Diener E, Wirtz D, Tov W, et al. New Well-being Measures: Short Scales to Assess Flourishing and Positive and Negative Feelings. *Social Indicators Research*. 2010;97:143-156.
74. Copeland JL, Esliger DW. Accelerometer assessment of physical activity in active, healthy older adults. *J Aging Phys Act*. Jan 2009;17(1):17-30.
75. Sylvester BD, Ahmed R, Amireault S, Sabiston CM. Changes in light-, moderate-, and vigorous-intensity physical activity and changes in depressive symptoms in breast cancer survivors: A prospective observational study. *Support Care Cancer*. Nov 2017;25(11):3305-3312. doi:10.1007/s00520-017-3745-1
76. Helgadottir B, Forsell Y, Ekblom O. Physical activity patterns of people affected by depressive and anxiety disorders as measured by accelerometers: A cross-sectional study. *PLoS One*. 2015;10(1):e0115894. doi:10.1371/journal.pone.0115894
77. Garriguet D, Colley RC. A comparison of self-reported leisure-time physical activity and measured moderate-to-vigorous physical activity in adolescents and adults. *Health Rep*. Jul 2014;25(7):3-11.
78. KL C, CM G. Accelerometer Data Collection and Scoring Manual for Adult & Senior Studies. Accessed June 16, 2019. http://sallis.ucsd.edu/Documents/Measures_documents/Accelerometer_Data_Collection_and_Scoring_Manual_Updated_June2012.pdf
79. Choi L, Ward SC, Schnelle JF, Buchowski MS. Assessment of wear/nonwear time classification algorithms for triaxial accelerometer. *Med Sci Sports Exerc*. Oct 2012;44(10):2009-2016. doi:10.1249/MSS.0b013e318258cb36
80. Partridge AH, Archer L, Kornblith AB, et al. Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: Adherence companion study 60104. *J Clin Oncol*. May 10 2010;28(14):2418-2422. doi:10.1200/JCO.2009.26.4671
81. Leino AD, King EC, Jiang W, et al. Assessment of tacrolimus intrapatient variability in stable adherent transplant recipients: Establishing baseline values. *Am J Transplant*. May 2019;19(5):1410-1420. doi:10.1111/ajt.15199
82. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. *Br J Clin Pharmacol*. Jul 2020;86(7):1281-1288. doi:10.1111/bcp.14193
83. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S. *Blood*. Oct 15 2005;106(8):2912-9. doi:10.1182/blood-2005-05-2004
84. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. Jun 5 2014;123(23):3664-71. doi:10.1182/blood-2014-01-552984

85. Siddiqi AE, Sikorskii A, Given CW, Given B. Early participant attrition from clinical trials: Role of trial design and logistics. *Clin Trials*. 2008;5(4):328-335. doi:10.1177/1740774508094406
86. Steinhauser KE, Clipp EC, Hays JC, et al. Identifying, recruiting, and retaining seriously-ill patients and their caregivers in longitudinal research. *Palliat Med*. 2006;20(8):745-754. doi:10.1177/0269216306073112
87. Bowen DJ, Kreuter M, Spring B, et al. How we design feasibility studies. *Am J Prev Med*. 2009;36(5):452-457. doi:10.1016/j.amepre.2009.02.002
88. Cohen J. A power primer. *Psychol Bull*. Jul 1992;112(1):155-9. doi:10.1037//0033-2909.112.1.155
89. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. *Arch Gen Psychiatry*. May 2006;63(5):484-9. doi:10.1001/archpsyc.63.5.484
90. Hogan JW, Laird NM. Model-based approaches to analysing incomplete longitudinal and failure time data. *Stat Med*. Jan 15-Feb 15 1997;16(1-3):259-72.
91. Daniels MJ, Hogan JW. *Missing Data in Longitudinal Studies Strategies for Bayesian Modeling and Sensitivity Analysis*. Taylor and Francis,; 2008:1 online resource (324 p.). http://gallaudet.eblib.com/patron/FullRecord.aspx?p=332401
92. El-Jawahri A, Traeger L, Greer JA, et al. Effect of Inpatient Palliative Care During Hematopoietic Stem-Cell Transplant on Psychological Distress 6 Months After Transplant: Results of a Randomized Clinical Trial. *J Clin Oncol*. Nov 10 2017;35(32):3714-3721. doi:10.1200/JCO.2017.73.2800