PROTOCOL TITLE:

Proof-of-Concept Trial of a Positive Psychology Intervention for Caregivers of Patients Undergoing Hematopoietic Stem Cell Transplantation (PATH-C)

PRINCIPAL INVESTIGATOR:

Hermioni L. Amonoo, MD, MPP
Department: Psychosocial Oncology and Palliative Care
NCT: 05216978

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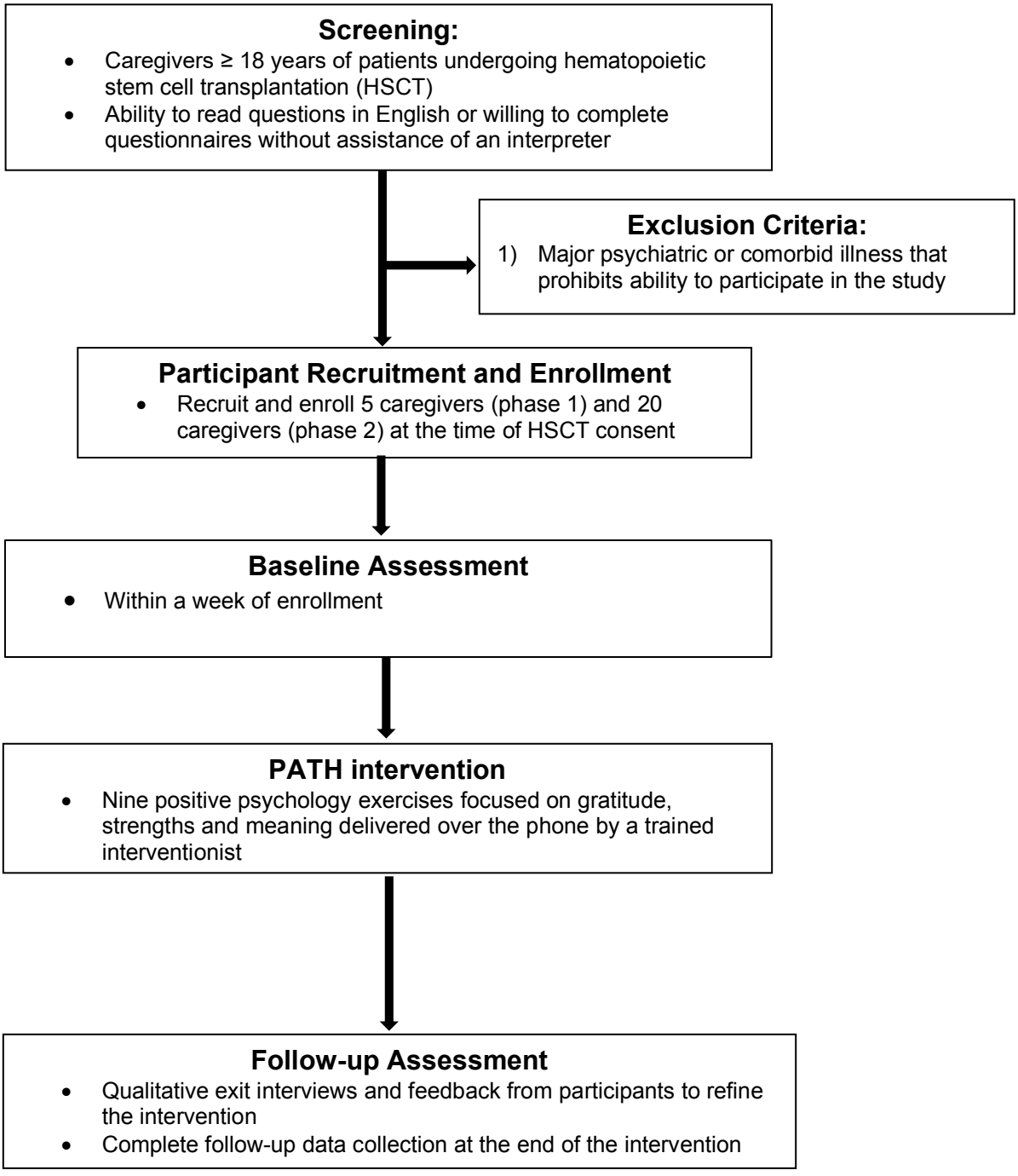
Figure 1: Protocol Schema



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1.0 Objectives*

1.1 Overview

Caregivers (i.e., family and friends) are essential care providers during cancer treatment. Caregivers of patients with serious illnesses, especially cancer, experience significant caregiving burden with the increased shift to home healthcare.[1] Growing evidence supports that caregiving burden is associated with increased psychological distress that results in poorer health outcomes (e.g., decreased quality of life [QOL], increased fatigue, depression, and sleep problems) for both the caregiver and patient being cared for.[2] In addition to distress, caregivers of patients with serious illnesses report diminished positive psychological wellbeing (PPWB: e.g., optimism, resilience, positive affect, gratitude).[3] Diminished PPWB in caregivers has also been associated with higher levels of caregiver burden and frailty, and worse QOL.[3-6]

Caregivers of patients undergoing hematopoietic stem cell transplantation (HSCT) experience tremendous burden and distress. HSCT is a potentially curative treatment for patients with hematologic malignancies. However, the treatment is intensive and accompanied by a protracted hospitalization as patients recover from chemotherapy-induced toxicities and early post-transplant complications.[7-12] The intensive nature of HSCT requires patients to designate a caregiver for support before, during, and after HSCT. As patients often grapple with elevated rates of physical symptoms (e.g., severe diarrhea), psychological distress, and prognostic uncertainty, their caregivers experience a decline in QOL and an increase in symptoms of depression during the prolonged hospitalization.[13] In the months following the HSCT hospitalization, the caregiver helps the patient manage ongoing physical symptoms, complex medication regimens and multiple outpatient follow-up visits. Additionally, the demands of the HSCT and its recovery could result in significant disruptions in caregivers' personal lives, especially concerning occupational and familial responsibilities.[14-16] Consequently, the burdens of HSCT and its acute and long-term recovery requirements significantly and negatively impact the patient and their caregiver.

Population-specific empirical interventions which address caregivers' needs over the cancer care and treatment cycle are especially limited among caregivers of HSCT recipients.[11, 17, 18] To our knowledge, existing supportive interventions for caregivers of patients undergoing HSCT have primarily focused on training in caregiving skills, stress management or cognitive-behavioral therapy skills.[19] However, interventions that specifically target PPWB in this population are lacking despite their potential to buffer against distress, boost QOL, and improve physical health.[3, 20, 21] Positive psychology interventions (PPIs) entail exercises (e.g., writing a gratitude letter) completed systematically and deliberately to cultivate PPWB.[22-26] PPIs are simple, well-accepted, cost-effective, and can be delivered via phone by bachelor-level clinicians. Although PPIs have been successfully used in other caregiver populations (e.g., caregivers of patients with dementia),[27, 28] they have never been tested in caregivers of HSCT recipients. Hence, a PPI tailored for HSCT recipient caregivers holds promise for improving caregiver wellbeing, reducing caregiver burden, and, ultimately, improving the quality of care for patients undergoing HSCT.

The primary goal of this study is to refine (phase 1) and test the feasibility (phase 2) of a positive-psychology based intervention in caregivers of HSCT recipients. Data from this study will lay the groundwork for randomized studies to examine efficacy of positive psychology interventions among caregivers of patients who have undergone HSCT.

1.2 Specific Aims/Objectives and Hypothesis

Specific Aim 1 (Phase 1: Intervention Refinement): To refine a positive psychology intervention (PATH) in caregivers of HSCT recipients based on findings from an open-pilot study (N=5).

Specific Aim 2 (Phase 2: Feasibility): To determine the feasibility and acceptability of the refined PATH intervention and our assessment battery in caregivers of patients who have undergone HSCT using a single-arm trial (N=20).

Hypothesis 1: The intervention will be deemed feasible if >60% of eligible participants enroll and >60% of enrolled participants complete ≥6/9 positive psychology (PP) exercises.

Hypothesis 2: The intervention will be deemed acceptable if weekly ratings of ease and utility of the PP exercises are >7/10 on a 10-point Likert Scale (0=very difficult/not helpful; 10=very easy/very helpful).

2.0 Background*

From diagnosis to recovery and survivorship, caregivers (i.e., family and friends) are essential care providers for the entire cancer care cycle. Caregivers of patients with cancer experience significant caregiving burden with increasing shift to home health care.[1] However, rising caregiving burden is associated with poorer health outcomes characterized by a myriad of physical and psychological distress symptoms, such as increased fatigue, depression, anxiety, sleep problems and decreased quality of life [QOL] for both the caregiver and patient being cared for.[2] Additionally, caregivers of patients with serious illnesses report reduced positive psychological wellbeing (PPWB: e.g., optimism, resilience, positive affect, gratitude).[3] Diminished PPWB in caregivers has also been associated with higher levels of caregiver burden, frailty, and worse QOL.[3-6]

Hematopoietic stem cell transplantation (HSCT) is potentially curative for some patients with hematologic malignancies. However, the treatment is demanding and accompanied by protracted hospitalizations. Due to chemotherapy-induced toxic side-effects and early post-transplant life-threatening complications, patients often grapple with elevated rates of physical symptoms (e.g., severe diarrhea, pain, nausea, fatigue), and mortality.[29,7-12] Hence, the prolonged HSCT hospitalization, required isolation after transplant for immune system reconstitution and extended recovery, threatens caregivers and their loved ones' the psychological wellbeing and quality of life (QOL).[23] Access to a reliable caregiver is a prerequisite for HSCT. The physical and psychological demands of the HSCT and recovery necessitate the crucial involvement of caregivers throughout the transplant trajectory, from the HSCT hospitalization through survivorship.[11, 18, 30] Consequently, both patients and their caregivers are significantly impacted by the HSCT and its demands during the acute and long-term recovery.

Patients undergoing HSCT and their caregivers must cope with the uncertainty of patients' prognosis, attend regular outpatient follow-up visits, and manage complex medication regimens.[18, 30] Additionally, the demands of the HSCT could significantly disrupt caregivers in their personal lives, especially concerning work-related and family responsibilities.[14-16] The substantial caregiving burden among caregivers of patients undergoing HSCT is associated with increased symptoms of depression, anxiety, fatigue, and sleep disturbance, especially during the HSCT hospitalization.[15, 16, 31-33] Additionally, decreased PPWB in caregivers have been associated with higher levels of caregiver burden and worse QOL.[3-5] Inevitably, caregiver and patient psychological and physical outcomes are often related[34, 35] – caregiver psychological wellbeing can influence

patient psychological wellbeing, and the effects of this wellbeing can have long-term health effects for both caregiver and patient.[34, 36, 37]

Psychosocial interventions can significantly improve patients' and caregivers' health, communication, knowledge, caregiving burden, self-efficacy, and overall coping.[34, 38-40] However, population specific empirical interventions to address caregivers' needs over the cancer care cycle are limited, especially among caregivers of HSCT recipients.[11, 17, 18] Despite recent efforts to develop interventions tailored for the unique needs of HSCT recipient caregivers, the results from the few existing studies have been mixed and inconclusive.[41] Additionally, to our knowledge, existing HSCT recipient caregiver interventions have focused on caregiving skills, distress management and cultivation of cognitive-behavior therapy skills. Despite the well established benefits (e.g., improved caregiver burden) of PPWB in caregivers of other serious illness populations (e.g., caregivers of patients with dementia), interventions that specifically cultivate PPWB have been limited among caregivers of patients undergoing HSCT.[3] Hence, interventions that promote PPWB and that potentially buffer against distress could be an excellent option for the HSCT caregiver population.

Positive psychological interventions (PPIs) are empirical interventions that promote PPWB and have been efficacious in various serious illness populations (e.g., heart failure, diabetes) and their caregivers.[42, 43] PPIs are simple, well-accepted, cost-effective, and can be delivered via phone either individually or in groups by clinicians with a wide range of training, including bachelor level clinicians. PPIs entail positive psychological exercises (e.g., writing a letter of gratitude, performing acts of kindness, recalling positive life events, leveraging previous successes, and expressing optimism) completed in a systematic and deliberate manner.[22-26] Although PPIs have been successfully used in other medical and caregiver populations to boost mood and QOL,[27, 28] they have never been tested in the cargivers of HSCT recipients. If PPIs are feasible and enhance PPWB in caregivers of HSCT recipients, this could have a substantial impact on mood, caregiver burden, and overall function.

Scientific Premise of the Proposed Project: Informed by the Broaden and Build Theory of Positive Emotions,[44] the revised Stress and Coping Theory,[45] and our team's efficacious PPI for cardiac patients,[43] we have developed the Positive psychology for Allogenic Transplantation of Hematopoietic stem cell intervention (PATH). The PATH intervention is a novel 9-week phone-administered PPI. Preliminary testing of the PATH intervention via a one-arm proof-of-concept study (18-225) demonstrated that our intervention was feasible and acceptable in patients undergoing HSCT and led to very small-to-medium effect size improvements in patient-reported outcomes (e.g., symptoms of depression and anxiety, QOL, fatigue).[46] Since PPIs have not been tested in caregivers of HSCT recipients, we hope to use an open-pilot (phase-1) to refine the PATH intervention and then use a one-arm trial (phase-2) to establish feasibility and acceptability in caregivers of HSCT recipients. Results from this study will assist in the refinement of our intervention for future larger efficacy trials in the HSCT caregiver population.

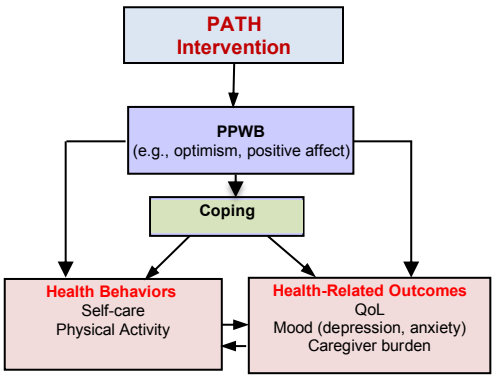

Figure 2: Conceptual Model

Conceptual Model: Our conceptual model in Figure 2, adapted from the Broaden and Build Theory of Positive Emotions[44] and the Revised Stress and Coping theory,[45] proposes that PPWB could increase caregivers' emotional and cognitive resources for problem-solving strategies and coping.[44] Using this framework, we anticipate that the PATH-C intervention, our caregiver-centered,

and low-burden PPI, could lead to improved psychological outcomes (e.g., decreased depression, anxiety,[47] and caregiver burden), coping, QOL,[48, 49] and self-efficacy.

3.0 Inclusion and Exclusion Criteria*

We will recruit 25 (5 for phase-1 and 20 for phase-2) consecutive caregivers of patients undergoing HSCT at Dana Farber Cancer Institute (DCFI) to participate in this study. Caregivers will be recruited during the patient transplant consent visit, or over the telephone if patient identifies a potentially eligible caregiver at the consent visit.

3.1 Screening Procedures:

Screening and eligibility procedures will be the same for both phases of the project. Caregivers of patients undergoing HSCT will participate in this study. Caregivers will be identified by the patient as the primary caregiver for HSCT. The primary caregiver must either live with the patient or have in-person contact with them at least twice per week.The research team will review the transplant clinic schedule to identify potentially eligible patients to be approached to identify their primary caregivers for study participation. The research team will contact eligible patients' oncology clinicians to inform them that we plan to approach the patient's primary caregiver and inquire about any concerns regarding the caregiver's participation in the study. If the clinician objects to the caregivers' participation, we will document the reason and not approach those individuals. If the oncologist has no concerns regarding the caregivers' participation, the research staff will approach eligible caregivers. We will approach caregivers to participate during the HSCT hospitalization, until the patient's day 100 post-transplant. The clinical research coordinator (CRC) will approach the patient during their HSCT hospitalization or after discharge until their day 100 post-transplant and ask them to identify their primary caregiver and request permission to contact the caregiver for study participation. We will attempt to contact caregivers over the telephone up to three times and leave up to two voicemails [Appendix A]. Caregivers will have the option of enrolling in the study over the telephone with a verbal consent [Appendix B] - we advocate for a waiver of written informed consent because this study is no more than minimal risk and the goal is to prioritize participant safety and reduce their exposure to study staff in the setting of the ongoing COVID-19 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 caregivers. 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 with their caregivers. The CRC will review the consent form with potential caregiver participants, which will clearly detail the nature of the study procedures and the time requirement.

Phase-1: Caregivers who provide informed consent will then be registered with ODQ and scheduled for their first study intervention visit via telephone. Caregivers who withdraw from the study during the study period will not be replaced and they will count towards the accrual numbers.

Phase-2: Enrolled caregivers will complete baseline self-assessment questionnaires [Appendix C] within a week window from study enrollment. Caregivers who provide informed consent and complete the baseline questionnaires will then be registered with ODQ and scheduled for their first study intervention visit via telephone. If a caregiver signs the consent form but does not complete the baseline questionnaires, they will be

excluded from the study. Caregivers who withdraw from the study during the study period will not be replaced and they will count towards the accrual numbers.

3.2 Eligibility Criteria

Caregiver Inclusion Criteria:

1) Adult caregivers (≥18 years) of patients undergoing allogeneic HSCT at DFCI.
2) A relative or a friend who either lives with the patient or has in-person contact with him or her at least twice per week and is identified as the primary caregiver for HSCT.
3) Ability to speak English and able to complete questionnaires with minimum assistance of an interpreter.

Caregiver Exclusion Criteria:

- Cognitive deficits impeding a caregiver's ability to provide informed consent or participate adequately in the study assessed via a commonly used 6-item cognitive assessment with the Brief Interview for Mental Status (BIMS) screening tool that is sensitive and specific for screening for cognitive impairment in research subjects [Apendix D].

Special Populations:

- Individuals who are unable to verbally consent or are not yet adults (including infants, children, teenagers), pregnant women or prisoners will be excluded from the study.

4.0 Study-Wide Number of Subjects*

We propose to recruit a total of 25 caregivers (5 for phase-1 and 20 for phase-2) of patients undergoing HSCT from one site – Dana Farber Cancer Institute (DFCI). We chose our sample size because these are the numbers commonly used in behavioral intervention refinement and single-arm feasibility testing trials.[50, 51] 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 schedule to identify potentially eligible patients. The CRC will approach caregivers for study participation during a patient's HSCT hospitalization and can approach them until their day 100 post-transplant. The CRC will obtain permission from the patient to contact their caregiver via phone [Appendix E]. Interested participants will be screened with the BIMS and if eligible, will undergo verbal consent procedures. Caregivers will have the option of enrolling in the study in-person at their patient's scheduled clinic visit or over the telephone with a verbal consent [Appendix B].

We are requesting a HIPAA Waiver of Authorization to review Preparatory to Research from the IRB. This Waiver is being requested to identify potential participants from a minimal chart review. In accordance with the DF/HCC policy, this waiver: 1) is being sought solely to review Protected Health Information as necessary to prepare a research protocol and for recriuitment; 2) will not include Protected Health Information

from the Covered Entity by the researcher; and 3) the Protected Health Information for which we are requesting access is necessary for research purposes.

Participants will be registered with the Clinical Trials Management System after they have verbally consented and completed baseline assessments. 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 caregiver has been enrolled, they will be asked to complete baseline study measures. Registration Process for DF/HCC Institutions DF/HCC Standard Operation Procedure for Human Subject Research Titled Subject Protocol Registration (SOP#: REGIST-101) must be followed. For each study participants, we will complete the following registration procedures:

- We will obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- We will complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Only eligible participants will be registered. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criteria as described in this protocol and reflected on our eligibility checklist.
- We will fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295.
- The ODQ Registrar will (a) review the eligibility checklist and (b) register the participant on the protocol.
- An email confirmation of the registration will be sent to the PI, study RA, treating investigator and registering person immediately following the registration.

6.0 Multi-Site Research

Not Applicable. This research is located at one site – the Dana Farber Cancer Institute (DFCI).

7.0 Study Timelines*

Table 1. 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** ❖ Train CRC in study procedures, recruitment, data collection and intervention delivery.

Months 5-12	**Open Pilot and One-Arm Feasibility study:** ❖ Enroll 5 caregivers to the open pilot trial to provide feedback for intervention refinement. ❖ Enroll 20 caregivers to the one-arm feasibility trial.
Months 9-15	**Data Collection:** ❖ Complete baseline data collection within a week of participant enrollment. (Only for Phase-2 participants) ❖ Conduct 9-week PATH intervention via telephone. ❖ At the 9-week period, complete exit interviews.
Months 15-18	**Data Analysis:** ❖ Complete data analysis and submit primary manuscripts. ❖ Prepare and submit grant proposal for efficacy study.

8.0 Study Endpoints*

Primary Endpoint:

- Establish the feasibility and acceptability of the PATH intervention and completing the assessment battery in 20 caregivers of HSCT recipients.

Secondary Endpoints:

- Establish the feasibility of study procedures (e.g., use of assessment measures like actigraphy for physical activity) in caregivers of HSCT recipients in preparation for larger preliminary efficacy trial.
- Determine the proportion of caregivers completing intervention visits
- Establish the duration of the intervention visit
- Determine the proportion of caregivers completing study assessments

Primary or secondary safety endpoints:

- None

9.0 Procedures Involved*

9.1 Study Design

The proposed project entails two phases. Phase one is an open-pilot trial in 5 caregivers of patients undergoing HSCT to refine the PATH intervention. Phase two is one-arm trial evaluating the feasibility and acceptability of the PATH intervention in 20 caregivers of patients undergoing HSCT. All participants will be approached in person during patient's HSCT hospitalization or during a patient's routine clinic visit anytime up to the 100-day post-transplant period, or with patient permission over the phone if caregiver is not physically present at the consent visit for eligibility determination. Interested participants will be screened based on the inclusion/exclusion criteria and verbal consent would be obtained (via phone).

Upon consent to participate in the study, participants in Phase-2 will be asked to complete baseline questionnaires either in-person, over the phone, or via a REDCap survey link to participants. After baseline assessments are completed, participants will be given an intervention manual with 9-weekly PP exercises and an explanation of the exercises and intervention.

Participants in Phase-1 will complete the intervention after consenting for the study. All participants in Phase-2 will be asked to complete the 9-weekly PP exercises starting after the baseline questionnaires (i.e., after the

patient transplant consent visit) are completed in the pre-transplant phase and to speak with the study interventionist, a trained CRC, 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. After the Week 9 intervention phone session, participants in Phase-2 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 will be asked to complete a recorded exit interview over the phone. These individual, semi-structured exit interviews will elicit feedback about the intervention (e.g., relevance and applicability of the chosen PP exercises, intervention length, timing, and delivery), study procedures, and the questionnaires. Exit interviews will be recorded, transcribed, coded and thematically analyzed. With the Oppenheimer Grants Program funding, participants who complete study procedures will receive $100 renumeration for their time and feedback. At study completion, we will inquire about participants' potential interest in being contacted about our future studies.

9.2 The PATH Intervention

After the initial phone visit to introduce the concept of positive psychology and the PATH intervention, participants will be asked to complete 9 weekly positive psychology exercises with the study interventionist over the phone.

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[52]	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[52]	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[53]	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[52]	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[54]	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[55]	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 from our prior work (17-154 and 18-225) in HSCT recipients. 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 and CRCs will engage in several training exercises prior to study initiation. Dr. Amonoo has substantial experience in delivering PP exercises from prior work which will inform the training of other study team members. 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 patients undergoing HSCT (18-225). Also, we will use rigorous training procedures for our CRCs. To ensure fidelity of the intervention delivery, the Dr. Amonoo will meet weekly with the CRCs to 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[42, 43] to measure the extent to which domains of each session are addressed. On a monthly basis, Dr. Amonoo 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 and prior work in several medical populations - 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, Dr. Amonoo and interventionist (CRC) will meet for ongoing training of consistent intervention delivery - Dr. Amonoo will help problem-solve issues as they come up during the intervention delivery - On a monthly basis, Dr. Amooo 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 Selection of Instruments

While the primary aim of this study is to refine the intervention and assess its feasibility, we will also determine the feasibility of study procedures, including administering study assessments at baseline and at the end of the intervention for future efficacy studies. During phase 1, we will utilize feedback from participants regarding the length of the assessment battery and revise the assessments incorporated in phase 2. In Phase 2, we will then assess the feasibility and acceptability of completing the assessment battery. Study instruments were selected based on their appropriateness for measuring the important outcomes pertinent to caregivers in this population. All measures were used in prior studies and demonstrated strong psychometric properties. All measures are valid, reliable, and frequently used within cancer patient and caregiver populations.

The demographic questionnaire will ask study participants to provide their email address to allow us to email study assessments if preferred. If participants do not have an email address, we will either send them paper copies of the survey or ask them to complete them verbally over the telephone. We will track the methods of survey completion among participants. The entire study assessment battery will take approximately 15-20 minutes to complete.

Self-reported measures:

- ***Demographic questionnaire:*** Participants will self-report their age, sex, race/ethnicity, marital status, relationship satisfaction, religion, and education level, relationship status, relationship to the patient, and living situation [Appendix F].
- ***QOL:*** We will use the CareGiver Oncology QOL questionnaire (CarGOQOL) to measure caregiver QOL [Appendix G].[56]
- ***Caregiving burden:*** We will use the Caregiver Reaction Assessment (CRA) to assess caregiving burden [Appendix H].[57]
- ***Mood:*** We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety in all study participants [Appendix I].[58]
- ***Self-efficacy:*** We will use the Cancer Self-Efficacy Scale-transplant (CASE-t) to measure caregivers' confidence in managing the impact of HCT [Appendix J].[17]
- ***Perceived coping skills:*** We will use the Measure Of Current Status (MOCS) to assess caregivers' self-perceived status on skills targeted by the intervention including ability to relax, recognizing stress-inducing situations, restructuring maladaptive thoughts, and coping [Appendix K].
- ***Optimism:*** We will use the 10-item Life Orientation Test-Revised (LOT-R) to measure dispositional (trait) optimism. Higher scores indicate greater optimism.[59] [Appendix L]
- ***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.[60] [Appendix M]
- ***Satisfaction:*** We will use the 5-item Satisfaction with Life Scale (SWLS) to measure satisfaction with life; higher scores indicate greater satisfaction with life.[61] [Appendix N]
- ***Gratitude:*** We will use the 6-item Gratitude Questionnaire to measure dispositional gratitude; higher scores indicate greater proneness to experience gratitude in daily life.[62] [Appendix O]
- ***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.[63] [Appendix P]
- ***Physical activity:*** We will use the well-validated Actigraph GT3X+ accelerometer,[64]for 7 days of wear; minimum acceptable use is 4+ days with 10+ hours of recorded data as in prior guidelines[65-67] to measure minutes/day of light activity (100-1951 counts/min[68]) along with sedentary leisure time (SLT),[64, 69] given their links to health outcomes [Appendix Q]. Participants in Phase-2 will be given the actigraph either in person at a routine clinic visit or via mail for a 7-day wear by participants prior to the initiation of the intervention. Prior to the end of the intervention at week-8, participants will receive the actigraphs again for follow-up data collection during the last week of the intervention.

9.4 Qualitative Interview Guide

We will use a semi-structured interview guide to explore the following: 1) caregiver perception of the acceptability and content of the intervention; and 2) caregiver perceptions of the benefits of receiving the intervention. Facilitators will use probes to obtain a comprehensive understanding of the caregivers' perspectives. The semi-structured interview guide is detailed in Appendix R. The interview will last approximately 30 minutes. The qualitative interview will be conducted in-person or over the phone.

9.5 Data from the Electronic Health Record

Since this is a caregiver study and caregivers are not patients, we will not be obtaining any patient information from the electronic health record.

9.6 Data Collection

We will collect and enter all caregiver-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 a remote access link to the REDCap system [Appendix S] 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. 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.

Table 4: Administration of Self-Report Measures

Participant	**Baseline**	**Week-9 (+ 1 week window)**
Patient Measures:		
Demographics	X	
CarGOQOL	X	X
CRA	X	X
HADS	X	X
CASE-t	X	X
MOCS	X	X
Accelerometer	X	X
LOT-R	X	X
PANAS	X	X
SWLS	X	X
GQ-6	X	X
Flourishing Scale	X	X

9.7 Overview of Research Procedures

Initial/Enrollment phone call: During this initial approach during the patient's HSCT hospitalization or during a routine clinic visit up to their day 100 post-transplant, or with patient permission a phone call after the consent visit, the study procedures will be explained to potential participants. Those who are interested will be screened for eligibility. Eligible participants will be enrolled and asked to complete verbal consent procedures. Consented participants will also be mailed (or given in person at a routine follow-up visit) the study intervention manual.

Baseline Assessments: At enrollment all participants will be mailed the Actigraph GT3X+ with instructions on how to use the Actigraph for 7 days of wear; minimum acceptable use is 4+ days with 10+ hours of recorded data prior to the intervention initiation. After baseline physical activity data collection, participants will mail back the Actigraph in prepaid envelopes we will provide. Within a week of consenting to participate in the study, 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 before intervention initiation.
After completion of the baseline survey, the interventionist will review the mailed treatment manual with weekly PP exercises. Participants will be assigned the first exercise (gratitude for positive events) in preparation for their first phone session.

Weekly phone sessions for positive psychology intervention: All participants 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 so that a percentage (10%) of these recordings can be reviewed by Dr. Amonoo, 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 among HSCT recipients, and 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.

Follow-up assessments: At Week 9, participants 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. A week prior to intervention completion, participants will be mailed the Actigraph GT3X+ for follow-up physical activity data collection and participants will mail back the Actigraph in prepaid envelopes we will provide. Furthermore, participants 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 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 Brigram/DFCI server. Recordings will contain no personally identifiable information (names or other identifying information on the recordings will not be used) and will be erased following review.

10.0 Data and Specimen Banking: Not Applicable

10.1. Data analysis

We will use descriptive statistics (e.g., mean) for continuous variables and proportions for categorical variables to summarize the demographic and clinical characteristics of caregivers enrolled in the study.

Specific Aim 1 (Phase 1: Intervention Refinement): To refine a positive psychology intervention, PATH, in caregivers of HSCT recipients based on findings from an open-pilot study. Informed by our prior work,[46] our planned sample size (N=5) will allow us to obtain comprehensive feedback about the intervention for refinement. The qualitative exit interviews will explore the following themes: 1) caregiver perception of intervention content; 2) barriers/challenges with the delivery method; and 3) modifications to promote caregiver engagement. All exit interviews will be recorded, transcribed, coded, and thematically analyzed using a directed content analysis.[70] Findings from phase-1 will be used to refine and finalize the intervention for feasibility testing in phase 2. Participant feedback of the study assessments/questionnaires will also help to refine the study procedures for the phase-2 of this project.

Specific Aim 2 (Feasibility and Acceptability): To assess the feasibility and acceptability of the PATH intervention for caregivers of patients undergoing HSCT. Based on prior work, we define feasibility as >60% of eligible participants enrolling for the study and >60% 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[42, 43] and other behavioral intervention studies.[71-73] 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 will be calculated, and we will use a threshold mean combined score of 7.0/10 for acceptability that was used in prior studies.[19,57]

Qualitative Data Analysis: For all exit interviews, two research staff will independently review the transcripts to create a thematic framework for interpretation. Dedoose 8.0.35 software (SocioCultural Research Consultants, LLC: Los Angeles, CA) will be used for data organization and management. We will code and analyze the data using directed content analysis, a descriptive approach to qualitative analysis.[74] Codes will be informed by the interview guide and qualitative interview data, and the framework for the coding tree will be informed by conceptual models per existing qualitative methods.[70] Overall with qualitative data, we will explore intervention acceptability, proposed intervention content (e.g., PP exercises), and delivery preferences (e.g., intervention duration, call frequency).

10.2 Sample Size Calculation & Power Analysis:

Given that this pilot is a one-arm feasibility study, we will not be able to estimate sample sizes or complete a power analysis. Although we will be administering patient reported outcomes for phase 2, the primary reason is feasibility of study procedures and we are not powered to detect statistically significant group differences.

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 CRC, 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 CRC 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:

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.
- 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:

- 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 verbal informed consent from patients; 5) monitor participants longitudinally and administer study questionnaires; and 6) deliver the PATH intervention. In addition, Dr. Amonoo will meet with the CRC weekly to address any study issues or concerns.
- Assessment of Intervention Fidelity: To ensure the appropriate delivery of the intervention, 10% of all intervention calls will be recorded and reviewed with Dr. Amonoo for consistency with explanation and delivery of positive psychology exercises. These measures will also provide accurate data on

intervention feasibility. Dr. Amonoo will also discuss any issues or concerns regarding the intervention fidelity.

Informed Consent Requirements:
The Dana Farber Harvard Cancer Center approved informed verbal 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: Not likely for this study as this is for caregivers and not patients.
- 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 this is a one-one feasibility study without many follow-up data collection. Also, the intensive and frequent outpatient follow-up visits for the caregivers of patients with hematologic malignancies during the first six months post-HSCT.

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 caregivers, 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.
- 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 data
- Number of participants completing the study

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

- Number and types of SAEs
- Number and types of reportable AEs

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 verbal informed consent is being obtained from patients, we will emphasize to participants 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 caregiver-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 caregivers of patients undergoing HSCT.

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: Verbal 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, the study staff will notify both the study PI and primary transplant clinician. 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 social work or 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 and assessments. We have been thoughtful to use the briefest methods necessary to assess emotional states and other outcomes to reduce participant discomfort.

As with any study, there is the risk of a breach of confidentiality of the data collected. To minimize the potential loss of confidentiality, we will employ multiple safeguards and measures. Study procedures and intervention sessions will be administered by a trained interventionist. Study participants will be assigned a unique study identification number, 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. We will ensure to not provide any data to third parties. 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 caregivers of patients with any form of malignancy. To our knowledge, this trial is the first of its kind testing a positive psychology intervention in caregivers of 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. Additionally, some participants may enjoy the opportunity to complete study measures and reflect on the illness experience of the patient. Some may also value the possibility that their contribution to the study may benefit other caregivers of patients with serious illnesses. 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 the patients our caregivers are caring for may die during or within months of completing the study. We do not wish to cause unnecessary distress to caregivers by attempting to contact them after their loved one undergoing HSCT has 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 – participants 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), caregivers of patients who are adult (age ≥18) and English speaking recruited from the Dana Farber Cancer Institute (DFCI) HSCT Program will be eligible for the study. Eligible study participants will be identified using the DFCI HSCT database. Caregivers will be contacted during the patient's HSCT hospitalization and before their day 100 post-transplant, for eligibility determination and to obtain verbal consent. Upon agreement to participate in the study, caregivers will complete consent and enrollment procedures. Enrolled participants 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 will be called on a private phone they designate. 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 CRCs on a 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 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 caregivers would be ineligible for study participation. Therefore, we will have approximately 495 patients and their caregivers 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 and their caregivers to meet our recruitment goal of approximately 25 subjects – enrolling 3-4 patients per month will help us reach our accrual goal of 25 participants in 6 months.

Dr. Amonoo currently has 75% of her time protected to conduct research activities.

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' and caregivers 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 and their caregivers for study participation.

Eligible study participants will be identified using the DFCI HSCT database. Caregivers will be approached at the HSCT consent visit or with patient permission over the phone shortly after this visit or during patient's HSCT hospitalization for eligibility determination and to obtain verbal consent. Upon agreement to participate in the study, participants will complete baseline assessments and receive a study intervention manual. 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. Caregivers who refuse study participation will be asked the reason for deferring.

Caregivers who complete informed consent and complete baseline questionnaires will then registered with the Clinical Trials Management System. If participants 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.

22.0 Local Number of Subjects

We anticipate that we will recruit approximately 25 caregivers locally during the study period.

23.0 Provisions to Protect the Privacy Interests of Subjects

We will use REDCap to collect participant data. Participant 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 verbal consent process, it will be emphasized to the participant 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 patients' 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

With the Oppenheimer Grants Program funding we will renumerate participant with a $100 check after completing all study procedures.

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 obtain verbal consent from potential participants via phone. 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)*:** Written informed consent will not be obtained. Instead, verbal consent will be obtained, and participants' willingness to partake in the study will be indicative of consent. 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 caregivers. 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 with their caregivers. As part of the verbal consent process, a study information sheet will mailed to all study participants in the study.

27.0 Process to Document Consent in Writing

As stated earlier, written informed consent will not be obtained. Instead, verbal consent will be obtained, and participants' willingness to partake in the study will be indicative of consent. 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 and caregiver safety and reduce their exposure to study staff in the setting of the ongoing COVID pandemic and intermittent restrictions on caregivers accompanying patients with their visits. 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 caregivers. Electronic consenting may also result in a selection bias in participation procedures.

28.0 Drugs or Devices

No drugs or devices will be utilized in this study.

29.0 References

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