ACT to Reduce Morbidity and Mortality in Hematopoietic Stem Cell Transplant (HCT) Patients (ACTivate)

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1. **Protocol Title**

ACT to Reduce Morbidity and Mortality in Hematopoietic Stem Cell Transplant (HCT) Patients

2. Purpose of this Research

The goal of this project is to develop and test a novel protocol to reduce physical and psychological vulnerabilities to treatment intolerance and treatment-related morbidity and mortality among HCT patients. The specific aims and associated hypotheses of this 3-year project are:

Aim 1: Optimize a brief ACT protocol (ACTivate) for HCT patients (NIH Stage IA). Acceptance and Commitment Therapy (ACT)[1] is an evidence-based CBT that improves human functioning and adaptability via increasing psychological flexibility. The current protocol will leverage ACT to improve diet and exercise pre-transplant and help patients continue to eat and move during and following transplant procedures. We will optimize our protocol in an iterative fashion with three sets of three HCT patients each. Our goal will be to maximize: 1) the acceptability of the intervention (treatment duration, content and implementation) for key stakeholders and 2) target engagement. Target engagement will be assessed via repeated measurement of psychological flexibility over the course of the intervention and continuous measurement of step count (a behavioral indicator of engagement in value-guided action and behavioral mechanism to maintaining post-transplant mobility).

Aim 2. Evaluate the preliminary efficacy of ACTivate in improving physical function and other outcomes in HCT patients (NIH Stage IB). As standard of care, all HCT patients undergo comprehensive functional evaluation (physical, cognitive, mental health, nutrition, social/financial, global, and quality of life) between sign-off (~10 days before HCT) and year 3. This will allow us to compare outcomes in the nine patients in Aim 1 plus an expansion cohort of 11 patients receiving the final iteration of ACTivate (total n=20) to contemporaneous controls matched for age, gender, and disease.

H1: Patients receiving ACTivate will have a shorter hospital stay and better physical function (six-minute walk, primary endpoint) at year 3.

3. Background and Significance

Allogeneic hematopoietic stem cell transplant (HCT) has the potential to cure patients with hematologic malignancies and other diseases, but treatment is arduous and there is significant risk of treatment-related morbidity and mortality. Worse clinical outcomes are predicted not only by advanced chronological age, but also by modifiable behavioral factors such as decreased physical function and comorbid psychological conditions, such as depression. Targeted interventions to reduce physical and psychological vulnerabilities during the pre-HCT time period could therefore improve treatment tolerance and HCT outcomes.

ACT [1] is a transdiagnostic, mindfulness-based treatment that has been effective in reducing psychological distress and symptom interference in a variety of clinical populations [2-5], including individuals with cancer [6-15]. Unlike more traditional cognitive-behavioral therapy (CBT), which focuses on changing thoughts/feelings themselves, ACT emphasizes psychological acceptance: voluntarily adopting an open, receptive posture with respect to moment-to-moment experience. This may be well-matched to individuals with cancer for whom distressing thoughts/feelings may not be illogical or irrational, but rather perfectly normal or expected responses to having a life-threatening illness (and embarking on a journey that could cure their disease but could also cause death), or simply inevitable during the course of treatment.

Rather than change the form or frequency of difficult thoughts and feelings, ACT aims to increase psychological flexibility, such that patients' behavior remains flexible and effective in the presence of any and all thoughts/feelings that may arise, and guided by personal values (i.e., what is most important to the individual or how they want to live the moments of their lives) [16].

Among HCT patients, increased psychological flexibility may decrease unnecessary suffering (by reducing patients' struggle with unwanted thoughts and feelings) and help patients adapt behaviors to improve or maintain physical activity and nutrition as they approach HCT, as well as in the presence of chemotherapy/radiation-induced fatigue and anorexia/nausea (rather than succumbing to these experiences, e.g., declining to walk and developing critical illness myopathy; declining to eat and getting placed on total parenteral nutrition). This is particularly important for older adults undergoing HCT, who typically have less functional reserve and less experience with intensive chemotherapy.

We will develop a brief ACT-based protocol ("ACTivate") for adults undergoing HCT. Intervention will aim to increase psychological flexibility and optimize health behaviors from HCT initiation to year 3. Intervention will include the patient, as well as the caregiver who will function as a "coach" for the patient particularly during hospitalization when physical activity and nutrition may be most difficult to maintain. Caregivers will practice the same ACT skills that their loved one is learning with their own difficult thoughts/feelings that arise as their loved one undergoes treatment, allowing them to also remain flexible and effective throughout the process. The health care team will also be oriented to the strategies and goals of ACTivate, to insure consistency in messaging to patients and reinforcement of psychological acceptance and values. The current study will establish a protocol that maximizes both acceptability with key stakeholders and target engagement and evaluates treatment efficacy in a pilot case-control design.

Significance. The curative potential of HCT is balanced by the significant risk of treatment-related morbidity, and mortality ranges from 10-30% [23-25]. Outcomes are worse in patients of advanced age, decreased physical function, and depressed mood [26-29]. Targeted interventions that reduce physical and psychological vulnerabilities pre-HCT have the potential to increase treatment tolerance and dramatically change illness trajectories and maintain long-term mobility and quality of life post-HCT, particularly for older adults. ACT is a newer CBT that has significant potential for this purpose [4]. ACT has decreased psychological distress and symptom interference and produced behavior change in a variety of clinical populations, including individuals with depression, anxiety, disordered eating, diabetes, and chronic pain [2-5]. Unlike traditional CBT, which focuses on correcting cognitive distortions, the target mechanism in ACT is psychological flexibility (the ability to allow experience to be what it is and move in the direction of values) [16]. Increased psychological flexibility may help HCT patients accept their situation (and the distressing thoughts/feelings that arise) and direct their attention to how they want to live the moments of their lives and to the things they can control.

For example, chemotherapy/radiation creates adverse interoceptive signaling (nausea, pain, fatigue) that may elicit maladaptive behavioral response patterns in HCT patients (sedentary behavior, disengagement, suboptimal nutritional intake). Individuals must actively choose to override these signals and engage in behaviors that may briefly intensify uncomfortable experiences in the service of improving treatment outcomes (walking, drinking protein shakes). Through ACT, individuals may better accept the discomfort associated with HCT and adapt behaviors in ways that improve function and survival. Further, the infusion of personal values in ACT may increase patient motivation to engage in health behaviors, even in the face of uncertain outcomes.

The effects of ACT may be enhanced by including a caregiver, which has been important with other populations with disturbances in eating and activity levels, particularly when patients may experience fluctuations in cognitive faculties (e.g., during chemotherapy) and periods of severe symptom interference. Integrating the caregiver into treatment sessions will not only increase their attunement to their loved one's goals and behavioral coping strategies, but also allow them to use ACT themselves to remain flexible and effective despite the difficult thoughts/feelings that arise as their loved one undergoes HCT (Figure 1).

ACTivate will be designed as a brief treatment and integrated into routine HCT procedures, aiding implementation. The intervention, grounded in ACT and include additional features of behavioral interventions known to enhance behavior change, including self-monitoring, personalized SMART goals, accountability to

others and reinforcement for behavior change. Optimizing patients' activity levels pre-transplant may not only improve function and treatment tolerance but also decrease depression (via behavioral activation) and promote activity during HCT. This is particularly important for older adults who are both more physically vulnerable (frail) [30, 31] and less likely to have primary medical experiences that may prepare them for HCT (younger adults are more likely to receive more intense inpatient chemotherapy before referral to HCT while older adults are more likely to receive less intense outpatient therapy due to concerns around frailty) [32, 33].

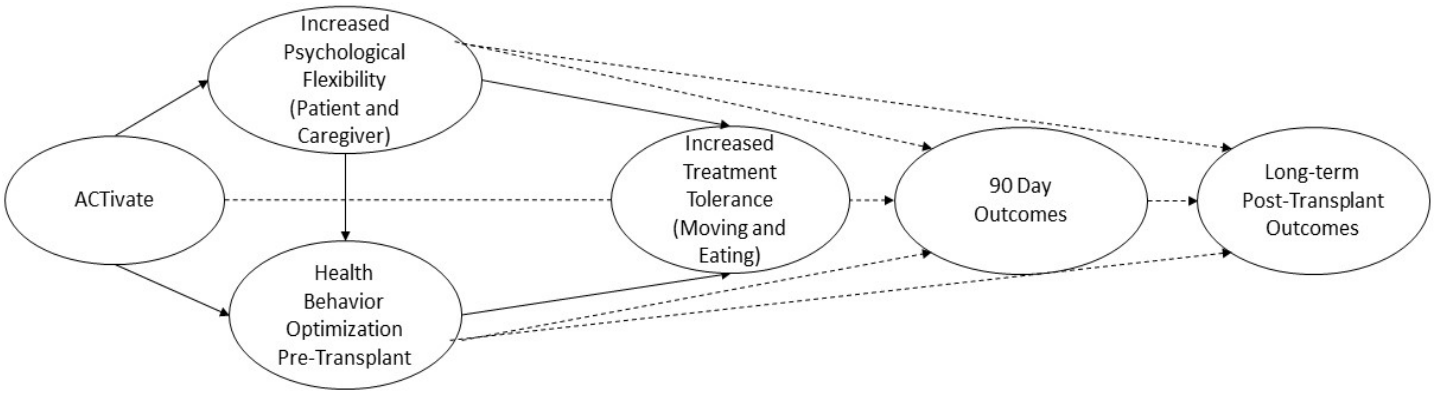


Figure 1. Model of treatment processes and outcomes

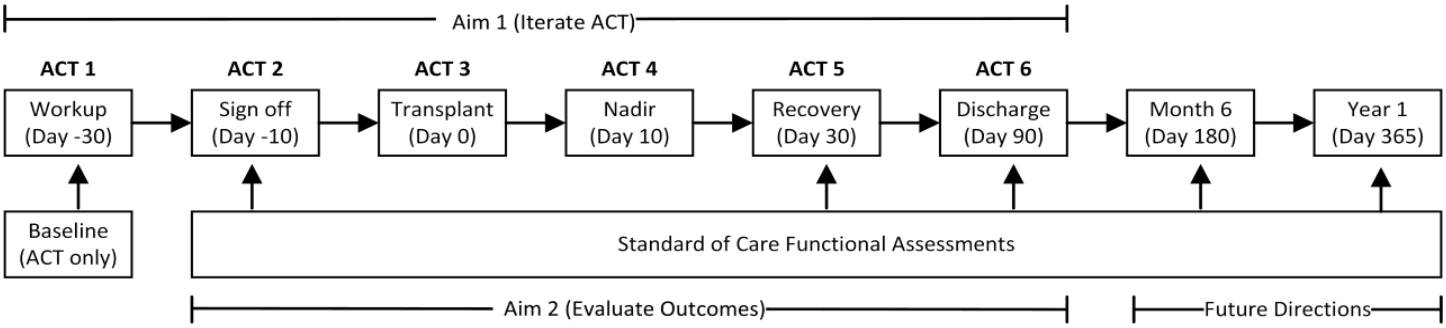
4. Design and Procedures

We will recruit 20 adults around HCT workup (when patients undergo medical testing and commit to HCT). To be eligible, participants must be ≥18 years old (*n*=10 <60 years, *n*=10 ≥60 years), English speaking and receiving allogeneic HCT. They must also have a caregiver who is willing to participate. This age range is selected because the Duke Adult Blood and Marrow Transplant Program only cares for adults ≥18 years, and because we want to evaluate the impact in older and younger patients, we plan to recruit 10 <60 years and 10 ≥60 years. Patients and their caregivers will complete a 1-6 session ACT protocol tailored to the clinical challenges of HCT. Assessments (outlined in Table 1) will be administered at key points to assess target engagement (process of change) and treatment outcomes. Self-report measures will be administered via a secure online survey tool (REDCap). Please see appendix A for REDcap survey distribution details. The caregiver will participate in the baseline and exit interviews, complete the acceptability measures, psychological assessments (with themselves as the identified person), and stool and skin collection. All other measures will only be completed by the patient. Patients will also use a custom HCT mobile application (or app) -- either Technology Recordings to better Understand BMT (TRU-BMT) (used in our previous studies (Pro00068979 and Pro00092963)) or SplendoFit -- to report things such as symptoms, diet and exercise, and wear an activity tracker (Apple Watch) during the intervention. Step data will be passively transmitted to the treatment team daily from the Apple Watch. We do not expect that there will be technical difficulty with the use of TRU-BMT or SplendoFit apps. The TRU-BMT app has already been piloted in Duke HCT patients (Pro00068979, PI Shah, co-I Sung) and was rated favorably as both easy to use and helpful (abstract presentation at the American Society of Hematology 2017 Annual Meeting).

In rare circumstances, and with the permission of the principle investigators, subjects may be allowed to use their personal activity tracking devices (such as an Apple Watch or FitBit) to track activity metrics such as step count. The activity tracking data from a subject's personal device will be shared with only key personnel on this study and with the subject's permission as outlined in the informed consent form. If subjects are allowed to use their personal activity tracker, we will only export activity data from their devices (such as a csv file) and will not be downloading the TRU-BMT or SplendoFit app on their personal device. Rare circumstances may include that subjects refuse to use the Duke provided Apple Watch and they have their own activity trackers.

Participants will complete informed consent procedures before the baseline assessment. Following the baseline assessment, patients and their caregivers will complete the first ACTivate session, and treatment will continue as outlined in Figure 2. ACTivate sessions will be audio recorded for training purposes to allow Dr. Merwin to train others on how to conduct ACTivate sessions. Participants will be made aware that their sessions will be audio recorded at the time of informed consent procedures. Audio files will be recorded using a Duke encrypted Olympus DS Digital Voice Recorder on loan through the Duke Research Navigators program or using the Audacity software (Duke IRB approved) on an encrypted and password-protected Duke computer. The Olympus DS Digital Voice Recorder is password protected and has DSS Pro real-time 256-bit file encryption. Audio files will be saved to the project's secure folder behind the Duke server. Only IRB-approved key personnel will have access to the recorder and the audio recordings.

During Aim 1, we will make rapid iterations of the protocol after each cohort of *n*=3 to maximize acceptability and effectiveness (Stage 1A). All intervention will be conducted by Dr. Merwin (a licensed psychologist with ACT expertise). For Aim 2, a second interventionist will be trained in the protocol, and we will continue to enroll patients in the final iteration of ACTivate until reaching 20 patients total (Stage 1B).



ACT Session Schedule

Given that this is a treatment development project, the precise timing of the sessions may vary as we iterate the protocol and determine what works best for the patients and caregivers. The number of sessions may also vary from 1-6 as we iterate the protocol or based on the needs of particular patient-caregiver dyads.

Pro00078566

Pro00105683 participants will be offered the opportunity to participate in the Pro00078566 repository. For those who do provide separate consent for the repository, their Pro00105683 specimens and data (e.g., questionnaires, assessments) can be incorporated into the repository for the broader future cancer research and research methods uses described in the Pro00078566 consent form.

Skin swab and Microbiota Assessment:
20gm (plum size) stool samples will be collected from patients, designated for this study following standard clinical protocols (e.g. for Clostridium difficile collection) and may be stored at 4°C for up to 24 h before freezing at -80°C for batch sequencing and microbiome analysis. Stool samples will be obtained prior to conditioning and at day 0, 7, 14, 21, 30, 60, 90, 180, year 1, year 2, and year 3 (year 3 samples will be optional).

Stool samples may also be collected with a OMNIgene-gut collection kit for each time point, which includes a paper hat, spatula, collection tube, biohazard bag, and gloves, as well as instructions for collection. The OMNIgene-GUT contains a RNA preservative that will maintain the integrity of the sample for up to 60 days at

ambient temperatures. The tube will be mailed back in the provided prepaid return packaging and frozen at -80 degrees for batch analyses.

Skin microbiota assessment will include a sample of a 2×2-cm area of the target region collected by swabbing the skin to pick up bacteria located on the skin. Specimens may be obtained from the following sites: (1) Forearm, (2) antecubital fossa, (3) Retroauricular region, (4) Buccal, (5) Abdomen, (6) Back, (7) in addition, if a rash affects a patient, that site may be swabbed as well. Samples will be snap frozen and stored for batch sequencing and microbiome analysis. Skin samples will be obtained prior to conditioning, and at day 30, 90, 180, year 1, year 2, and year 3 post-transplant (year 3 samples will be optional).

To analyze the gut microbiome, DNA will be extracted from fecal samples[1] and gut flora bacterial density will be quantified using real-time quantitative polymerase chain reaction (qPCR) as described.[2] We will amplify 16S ribosomal RNA (rRNA) using Illumina HiSeq platform and analyze the data using the Qiime script package with parallel processing.[3] Sequences will be de-noised and clustered at 97% identity using USEARCH and aligned to the 16S rRNA gene, using the align.seqs.py wrapper with the PyNAST algorithm and Greengenes reference alignment. Based on these results, we will calculate diversity (Shannon Diversity, primary endpoint, and Chao1) and construct phylogenetic trees using computational analysis software. We will also make longitudinal evaluations within individual patients.

Blood Collection: Biomarkers, Metabolomics, and Flow Cytometry:
Research blood samples will be collected prior to transplant and Day 14, 30, 90, 180, year 1, year 2, and year 3post-transplant (year 3 samples will be optional). Research blood samples will include no more than 16ml of blood per collection event (two NaH green top + one EDTA purple top) or 128ml (about 2 fluid ounces) in an 8-week period.
Subjects may be consented to multiple studies that contain the same research blood collection and analysis (specifically Pro00051024, Pro00089697, Pro00092963). If this situation occurs, duplicate research blood samples will not be collected. Instead, data derived from either Pro00051024 or Pro00089697 may be transferred to this study for analysis and reporting purposes.

Research blood samples will be processed as follows prior to biomarker, metabolomics, and flow cytometry analysis:

<u>For Biomarker and Metabolomics analysis:</u>
1. Draw one 4ml lavender top (K_2EDTA) tube.
2. Invert tube 10 times to mix blood.
3. Centrifuge at 4°C at 2500 x g for 15 minutes.
4. Remove plasma from tube and transfer into sterile 15ml conical tube.
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes.
6. Aliquot ≥1.0ml of plasma equally into 2.0ml cryovials, one for metabolomics, one for plasma biomarkers
7. Freeze at -80°C.

<u>For Flow Cytometry analysis:</u>
1. Draw two green top (Sodium Heparin) tubes.
2. Dilute sample with phosphate-buffered saline (PBS) at a ratio of 1:1.
3. Ficoll sample in accordance with laboratory SOP.
4. For every 1mL of PBMCs (peripheral blood mononuclear cell) collected add 100 µL DMSO (dimethyl sulfoxide).
5. Immediately freeze sample at -80°C.

Metabolomics

Approximately 1ml of plasma from the EDTA tube will be used for metabolomics analysis.

Targeted metabolomics: acylcarnitines and amino acids are analyzed using stable-isotope-dilution techniques. Measurements are made by flow-injection, tandem mass spectrometry, using serum or plasma sample preparation methods described previously (57, 58). Data are acquired using a triple-quadrupole detector equipped with an Acquity ultra-high-pressure liquid-chromatography system and controlled by the MassLynx 4.1 software platform, all from the Waters Corporation (Milford, MA).

Exploratory, non-targeted metabolomics: via gas chromatography/mass spectrometry (GC/MS), metabolites are extracted from blood (serum or plasma) with methanol, methoximated in dry pyridine, and then silylated with *N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide. Samples are analyzed on a 7890B GC connected to a 5977B MS (Agilent Technologies, Santa Clara, CA), equipped with two wall-coated, open-tubular (WCOT) GC columns connected in series (Agilent part 122-5512, DB5MS, 15 meters in length, 0.25 mm in diameter, with an 0.25-µm luminal film), separated by a microfluidic flow splitter to enable hot back-flushing at the end of each run (59). Data are acquired by scanning from *m/z* 600 to 50 as the oven ramped from 70 to 325 °C. Data are then deconvoluted using AMDIS software (60). Metabolites are identified using our retention-time-referenced spectral library (24, 61, 62), which is based in part on that of Kind *et al.* (2009) (63). Reported data are log-base-two transforms of the areas of deconvoluted peaks.

Blood-based biomarker analysis

Approximately 1ml of plasma from the EDTA tube will be used for metabolomics analysis

Assay methodology: Our collaborators art Duke, Dr. Andrew Nixon and Dr. Virginia Krauss, have developed and optimized an innovative multiplex assays evaluating angiogenic, stromal, and inflammatory markers and markers of aging (the Pepper Panel). For these assays, all collected samples are platelet-poor EDTA plasma. Briefly, plasma samples to be used in these analyses will be identified and cross-checked for provision of informed consent and the availability of relevant clinical data. Approved samples will be aliquoted and stored in -80°C freezer, ready for analysis. Plans for optimal sample allocations as well as customized ELISA plate arrangements will be developed. Any study sample that falls outside the linear portion of the standard curve will be retested. Samples that read below the limit of detection will be retested, if possible. Samples that read above the linear portion of the standard curve will be serially diluted and retested to obtain accurate measurements. Any analytes that do not meet the aforementioned criteria will result in the sample being re-evaluated. All research personnel are blinded to clinical outcomes.

In order to develop the optimal arrays, we have the opportunity to leverage 3 multiplex protein array systems from Aushon Biosystems (Billerica, MA), ProteinSimple (San Jose, CA) and Meso Scale Diagnostic (MSD), LLC. (Rockville, MD).

Regulatory Considerations: Blood-based biomarkers have many advantages compared to tissue-based markers, including lower risk to the patient, lower cost, and easy collection along the continuum of care, including at the start of treatment, in the setting of response, and at the time of progression. Therefore, any blood-based biomarker approach would provide an easier and more cost-effective method for the detection of cancer or the guidance of cancer treatment decisions. The development of blood-based biomarkers utilizing standard or multiplex ELISA techniques is readily adapted to clinical diagnostics. Importantly, many of the markers are drug targets, either in development or already approved. These features make any findings from our blood-based approach highly actionable, both diagnostically and therapeutically.

Statistical considerations for the blood based biomarker analysis: The characteristics of blood analytes will be investigated using a variety of measures. Baseline and on-treatment samples will be assessed. Coefficients of variation will be used to assess the dispersion of each marker. Pair-wise correlations among the analytes will be estimated using Kendall's Tau. For additional visualization of these analytes, plots of dendrograms and/or heat maps with clustering relationships among the analytes will be presented. Descriptive statistics will also be presented.

Overview of some key QA/QC considerations: The validation protocol described in more detail below will assess and provide data for all markers tested, including but not limited to: standard curves for each marker, sensitivity, dynamic range, precision (intra-assay and inter-assay), and cancer patient marker ranges,

sample type (serum, EDTA plasma, citrated plasma), assay specificity, and sample stability evaluating key timing and temperature considerations.

Standard Curves and Dynamic range: The standard curves for each marker will be determined according to each platform manufacturer. For the plate-based systems (Aushon Biosystems (Billerica, MA) and Meso Scale Discovery (MSD) platform (Rockville, MD)), we will provide representative 8-point standard curves for each marker assessed, demonstrating the dynamic range of the assay, expected to exhibit 3-4 orders of magnitude. Protein standards are added in duplicate for each multiplex array tested. The standard curve values will be generated by averaging 2 replicates of each calibrator in each plate. We will optimize the dilution used for each array in order to maximize the linear part of the standard curve. The microfluidic ELLA system has built-in, preset standard curves that are imported into the system during analysis. Use of these factory-calibrated standards facilitates the work flow and directly correlates with daily in-lab calibration experiments.

Sensitivity: For the markers of interest, we will establish the Limits of Detection (LOD), Lower Limits of Quantitation (LLOQ) and Upper Limits of Quantitation (ULOQ). LOD is the mean of the zero calibration standards + 2 standard deviations, LLOQ is the lowest calibration standard with back-calculated concentrations having CVs <20% and relative error <25%, and ULOQ is the highest calibration standard with back-calculated concentrations having CVs <20% and relative error <20%.

The Coefficients of Variation (CV): The average %CV will be determined for all markers. The data will be representative of intra-assay variation. In our previous analyses, we have demonstrated that most makers have %CV in the range from 2 -10%.

Assay Specificity: Specific multiplex arrangements will be evaluated for specificity by evaluating: 1) all detection Abs in the well and 2) only the specific detection Ab of interest.

Flow Cytometry

Whole blood samples, will be analyzed and monitored for outcomes such as immune cell differentiation, immune response and development of GVHD**.** Flow cytometry will be performed -b(7) Briefly, whole blood will be used for isolation of about 1×10^6 mononuclear cells. The mononuclear cells will be incubated with titrated antibodies for 15 minutes at room temperature in the dark. mononuclear cells will be lysed with FACS lysing solution (BD Biosciences, San Jose, CA). Cells will be stained with appropriate antibody cocktail and then analyzed using a FASCanto flow cytometer equipped with FACSDiva software (BD Biosciences). Absolute cells counts will be determined using a Flow-Count Fluorospheres (Beckman Coulter, Brea, CA). Examples of antibodies include: FITC-conjugated anti-CD62L (clone MEL-14), R-PE–conjugated anti-CD45.1 (clone A20), cy-chrome-conjugated anti-CD44 (clone IM7), and their isotype controls (all from BD PharMingen); and FITC-conjugated anti–H-2Db (clone CTDb), PE-conjugated anti-CD4 (clone CT-CD4), B220 (clone RA3-6B2), PE-Texas red–conjugated anti-CD4 (clone RM4-5), tricolor-conjugated anti-CD4 (clone CT-CD4), CD8α (clone CT-CD8α), and their isotype controls (Invitrogen, Carlsbad, CA).

For any assessment in which the patient completed as part of their standard of care, we will share that data as part of our analysis for this protocol. We will also review their charts to abstract clinical information on these subjects.

Figure 2. Project Overview and Timeline

Table 1. Assessments	Baseline	Every 2 Weeks	Continuous from Baseline	Day 30, Day 90, Day 180, Year 1, Year 2, Year 3
Physical function				
6-minute walk	X			X
Short physical performance battery	X			X
30 second sit-stand	X			X

Step count (activity tracker data)			X	
Falls question	X			X
PROMIS Fatigue*	X			X
PROMIS Physical Function*	X			X
Cognitive function				
Montreal Cognitive Assessment	X			X
PROMIS Cognitive Function*	X			X
Emotional / Psychological				
PHQ-9 (Depression)**	X			X
Valuing Questionnaire (VQ)*	X	X		
PC-PTSD/PCL**	X			X
PROMIS Depression**	X			X
PROMIS Anxiety**	X			X
PROMIS Emotional Support**	X			X
PROMIS Social Isolation**	X			X
HHI-12*	X			X
Brief COPE*	X			X
AAQ-II*	X			X
Nutrition				
Albumin	X			X
Body-mass index			X	
PONS	X			X
Clinician SGA	X			X
PG-SGA*	X			X
ASA-24*	X			X
Social/financial				
CMS Social determinants of health	X			X
FACIT-COST	X			X
Sociodemographics**	X			
SES (caregiver only)*	X			X (only Day 180, year 1, 2, 3)
Financial Assessment	X			X
Global				
Fried Frailty	X			X
OARS IADLs	X			X
Quality of life				
FACT BMT	X			X
FACT GP (caregiver only)*	X			X
EQ-5D-5L	X			X
Lorig Self Efficacy *	X			X
Self-Efficacy Preparedness for Caregivers (caregiver only)*	X			X
Miscellaneous				
PROMIS Global Health*	X			X

PROMIS Sleep*	X			X
HCT-CI (completed by MD)	X			
Clinical outcomes				
Adverse events (e.g., graft-host disease)			X	
Resource utilization (e.g., length of hospital stay)			X	
Symptoms				
PRO-CTCAE core symptoms*	Weekly through year 1			
Sample collections				
Stool**	X			X + Day 0, 7, 14, 21, 60
Skin**	X			X
Blood*	X			X + Day 14
Treatment development				
Acceptability survey**	X			X (only during ACT session time points as listed above)
Exit Interviews**				X
Note: Measures not collected as part of routine care are marked with an *. Measures marked with ** are assessments taken by caregivers too. All year 3 biosample collections will be optional.				

Measures. Measures are outlined in Table 1. The majority of the assessments are collected as part of routine HCT procedures or tracked in the Duke Adult Bone Marrow Transplant (ABMT) database. Assessments that are not typically collected during HCT procedures have been marked with an (*). Primary outcomes will be the 6-minute walk and length of hospital stay. Target engagement (process of change) will be assessed with the Valuing Questionnaire (VQ) (or equivalent), administered to the patient and the caregiver every 2 weeks for the first 30 days, and once a month thereafter.

ACTivate sessions will be conducted in person or via the Duke extended care platform used for telehealth visits. Participants will also receive reminders of concepts from sessions and reinforcement or prompting from the study team via the custom HCT app (e.g., “Great job completing your steps yesterday!”). All sessions will be audio taped for fidelity review. Fidelity will be assessed with the ACT Measure (ACT-FM), along with an ACTivate protocol checklist (developed after finalization of the protocol in Aim 1). Session tapes from the second interventionist will be reviewed by Dr. Merwin for ongoing training/consultation to maintain fidelity to the intervention.

Participants’ functional outcomes at Day 30 and Day 90 will be compared to age, gender, and disease-matched controls (case-control design), collected as standard of care.

Use of previously collected data: If a subject is simultaneously on another study and the same assessment or sample is required for both studies, we will only collect once and share the data between studies to avoid subjects having to duplicate efforts.

5. Selection of Subjects

Eligibility criteria: (1) Over the age of 18 (2) undergoing allogeneic HCT for any cancer or non-cancer illness, (3) English-speaking (4) has a caregiver who is willing to participate. Caregiver eligibility criteria: (1) Over the age of 18 and (2) English-speaking.

6. Subject Recruitment and Compensation

Potential participants will be recruited from the Duke ABMT Program. Patients may learn about the study at the end of their new patient class, where the presenter will give the option for patients to stay after class and view a slideshow that briefly introduces the study. Under the current standard of care practice, ABMT physicians evaluate all new patients. If the patient's ABMT physician deems the patient to be an allogeneic transplant candidate and he/she meets basic eligibility criteria, the patient will be informed about the study. If the patient expresses interest in participating, they will be referred to research staff, who will review inclusion/exclusion criteria and tell the patient more about the study. Our target *N* is 20, and we anticipate achieving this target by recruiting 24 patients and caregivers. All recruited participants will be assigned to the intervention group, consistent with our use of a historical control group.

Participants will not receive direct compensation for participation in the study.

7. Consent Process

The ABMT physician and the research staff will make clear that participation in this research is voluntary, and patients may decline to hear more or to participate in the study without penalty; these patients will receive standard of care. Patients who are interested in learning more about the study will speak with study staff who will explain details, answer questions, and confirm inclusion/exclusion criteria. Caregivers will be identified by the HCT patient as a primary caregiver. They will be approached by study staff who will explain details, answer questions, and confirm inclusion/exclusion criteria. Patients and their caregivers will review the consent form with study staff in-person or over the phone. Potential participants will have ample time to ask questions and have those questions answered and consider whether they would like to participate. Only those who voluntarily provide full informed consent will proceed to study enrollment. Individuals who are screened but do not want to participate (do not give informed consent) will not be recorded and will receive standard care.

Subject's Capacity to Give Legally Effective Consent

We will exclude from participation anyone who does not have the capacity to give legal consent.

8. Study Interventions

All recruited participants will be assigned to the experimental intervention. The intervention will be 6 sessions of ACT adapted for HCT patients, and integrated into HCT procedures. Intervention sessions will be 45-60 minutes and include both the patient and caregiver.

ACT helps individuals remain flexible and effective in the presence of unwanted experiences. Acceptance and mindfulness skills are taught as an alternative to avoidance and overcontrol, and personal values are evoked as a motivation and guide for daily decision-making. ACT strategies will be used to increase HCT patient's capacity to accept their situation and the experiences that accompany it, while engaging in health behaviors that maximize the likelihood of survival and minimize post-HCT morbidity. This includes optimizing diet and exercise pre-HCT, during chemotherapy/radiation and in the weeks/months that follow transplant.

Session 1 will set the course for treatment. Patients and caregivers will be oriented to the ACT model and the patient will set personalized SMART goals to optimize health behaviors (diet, exercise) pre-transplant. Values

will be evoked for the first time, and explicitly tied to behavior change goals, and elaborated in subsequent sessions. Sessions 2-5 will teach acceptance and mindfulness skills and content will be adapted to individual experiences (unwanted thoughts and feelings that arise during treatment etc.) as patients proceed through HCT. Patient optimization goals will be updated throughout treatment to match the patient and treatment stage/needs. Session 6 will be a consolidation session and skill review. Caregivers will practice ACT skills with their own difficult thoughts/feelings that arise as they support their loved one undergoing transplant. Between sessions, HCT patients will receive messages from the study staff via the HCT mobile app. Messages will reinforce adaptive behavior, evoke values to maintain motivation and remind patients to practice skills.

Session content is not overspecified at this stage, given that this is a treatment development study. However, will be grounded in empirically established ACT principles and techniques (Hayes et al., 2012), and draw on existing ACT protocols for health populations, including our own (e.g., R21 DK106603, Merwin et al., 2013; 2019)[36-38]. Sample exercises include the Matrix, Choice Point and Passengers on the Bus exercises, Guests in Home metaphor and practices in present moment awareness/willingness (open, nonjudgmental awareness of thoughts/feelings; watching thinking without entanglement; centering on the breath)[1].

9. Risk/Benefit Assessment

Risks associated with the study procedures and procedures for protecting against/minimizing risks or discomfort are as follows:

There are risks inherent in HCT that are unrelated to the experimental intervention. Risks specifically associated with participation in the experimental intervention which is psychological in nature include:

- Completing the questionnaires or taking part in interviews may make some participants uncomfortable. Participants will be reminded they are not required to answer any questions that make them uncomfortable and they can stop participating at any time.
- HCT is a stressful time, and safety concerns may be identified. All participants will interface with trained professionals at each appointment. All study personnel will be trained in assessment of safety risk, and identification of other serious symptoms that interfere with tasks of daily living (e.g., severe mood symptoms). Self-report measures of psychological symptoms will be screened for areas of immediate safety concern (e.g., suicidal ideation). Participants who indicate suicidal ideation either via self-report or during one of the clinic visits will be assessed for suicidal plan and intent and the PI will be immediately notified by pager. Any individual who poses an immediate risk to self or others will be escorted to the emergency room (adjacent to the Duke Clinic where the study is being conducted). Participants who indicate other severe psychological symptoms without immediate danger will be assessed at the earliest time possible by a PhD-level psychologist affiliated with the study for treatment need, and if appropriate, referred to the appropriate level of care (inpatient or outpatient treatment) with a mental health professional. All study personnel and study participants will also be able to reach Dr. Sung and Dr. Merwin directly by either cellular telephone or pager for the duration of the study.
- As with any study, the collection and storage of data carry risk of loss of confidentiality. Section 12 in the e-IRB addresses fully all issues of Privacy, Data Storage & Confidentiality All staff will be trained in responsibilities for maintaining and protecting participant confidentiality.
- There are additional risks for loss of confidentiality associated with the use of mobile applications and devices.

Planned strategies for protecting against or minimizing all potential risks with devices

All data will be stored on a secure server, and study personnel will do everything possible to protect patient confidentiality. Nevertheless, there is a potential risk of loss of confidentiality specific to use of mobile

applications. These risks are clearly defined within the Informed Consent Form and discussed with the patient at the outset of participation. Information collected by mobile applications or 'apps' is subject to their terms of use, which each participant should read carefully. Many mobile apps that are developed are intended to be very secure, compliant with federal privacy regulations, and used and tested by other academic centers. However, any mobile app that is downloaded carries potential security risks.

The daily data collected via TRU-BMT will be kept on an EC2 server. AWS EC2 is a tool by Amazon Web Services (AWS) that provides cloud-based compute capacity, allowing developers to run applications on Amazon's computing environment. In the context of the TRU-BMT app, EC2 is the cloud computing machine powering the transfer of TRU-BMT's user-data. Specifically, it houses the logic used by the program to transfer data inputted by the user and collected via the Apple Health kit. EC2 is the "house" that the code that moves data from user phone to dashboard lives in. Only study personnel will have access to the data collected.

Security Measures for AWS:
Security/Access Control: Provider AWS accounts are locked so that they are only able to access the databases that are assigned to them. Authorized users have read-only access to their databases with no ability to access or tamper with any other AWS resources.
Breach: We will enable CloudTrail logs in our AWS account that will constantly generate detailed logs on what activity occurs within the account. **Refer to the Sicklesoft IR plan for actions taken in case of a potential Breach.*
Backups: S3 buckets and databases will have versioning enabled, allowing for recovery if files are accidentally deleted (although this is further mitigated by the providers having read-only access to the buckets/databases). On the AWS end, the data will be stored in at least 3 devices in the region to protect against failures.
HIPAA Compliance: The AWS resources being utilized are certified HIPAA compliant. Additionally, SickleSoft's AWS account is under the Business Associate Addendum (BAA), which certifies that the AWS account is approved to host PHI data. The SickleSoft team closely monitors HIPAA guidelines to ensure that all AWS resources are configured in a way that stays HIPAA compliant.

- Other Risks and Protections Specific to the Mobile Application

The TRU-BMT mobile application have been programmed to access only certain features of the participant's device (camera, microphone) that will enable study activities. Other applications on the device will not have access to data entered into the study app.

The SplendoFit app used industry standard SSL encryption. All Google Cloud components used by the platform store data with encryption-at-rest principles (AES256 based). The monitor app runs on a remotely managed iPad which enforces strong user credentials and encrypts the entire file system (using AES256) based on those. Identity platform stores passwords using the scrypt algorithm. Encryption keys and secrets can be used on the platform to communicate with 3rd parties or create additional layers of encryption within the platform. To protect the content of these keys and secrets, access to them is guarded by only providing certain (service) accounts access to them, using the unified IAM model from Google Cloud. Additional information about security and complicant for the SplendoFit app can be found here: https://splendo.health/privacy/ .

Patients enrolled in the study will be provided a device (e.g., iPhone, Apple Watch) with the study software. Patients will be instructed to run a current operating system (OS) on their device, review the privacy/security settings often, and restrict any unnecessary access. The application may run in the background of their device. Mobile apps may have unanticipated impact on the operations of the device (e.g., battery drainage). If the patient does not have an unlimited data/text plan, s/he may incur additional charges. At the conclusion of the study, the study team will provide participants with instructions on how to remove the mobile apps from their personal device.

While these apps are intended to help monitor symptoms, track physical activity and food group intake, provide encouragement to maintain or improve adherence and self-care, the app is not intended to supplant healthcare decisions discussed with the patient's healthcare provider.

As with all technology, we will ask patients and their families to wait until they are in a safe environment, use good judgment, and follow prevailing laws. While the devices are intended to only be used in the participant homes, patients and their families should not perform study-related activities while they are driving.

If a Duke device is used for non-study related reasons, this could add additional personal information onto the device and potentially result in it being sent to unauthorized persons. The Duke-loaned device will be preset with security settings and patients will be asked not alter these during the course of the study. When the device is returned at the end of the study, the device will be cleaned to remove any personal information. If the device is lost or stolen during the course of the study, patients will be instructed to contact the study team immediately.

In order to ensure that patient-reported variables are known to the health care team and research staff, all updates made by the study apps (and other information on the app interface) will be able to be viewed by providers (nurses and physician staff) on a data dashboard.

Participants may have their own personal health information on devices they own for their own personal use independent of this study. This protocol will not require devices to be used in ways that are different from their regular practice but will ask that participants use numerical or alphanumeric codes to unlock the device. The email addresses supplied by the participants for the purpose of this study will also be on the device. The daily data collected will be kept in a server password protected Citrix ShareFile with encrypted WebDAV access to allow two-way communication between participants and providers via the app. Only study personnel will have access to the data collected.

Patients may track their devices via GPS so that the phone can be located once on-line. Moreover, all devices and the website will be password-protected with unique logins and passwords for all personnel on the project, and the website server is protected by a firewall. Medical record login and access fall under the strict policies of the Duke institution. All study personnel will have received Collaborative Institutional Training Initiative (CITI) training to conduct studies involving human subjects. All key personnel are licensed, bondable, healthcare providers.

Other Risks:

Skin Swab – risk of mild discomfort and irritation from skin swabbing, self-limited and will stop on request, minimal risk

Stool Collection – risk of mess with transferring stool sample from hat into collection container, minimal risk

Blood collection – care will be taken to prevent excess blood draw, minimal risk

Relationship of Risks to Benefits: This is a low risk intervention study that does not involve the use of a study drug or investigational device. No adverse health effects had been established from the use of the iPhone or Apple Watch. There is risk of loss of confidentiality, as with any study, and with studies with mobile devices. Treatment-related morbidity is high among HCT patients and mortality ranges from 10-30%. The potential benefit of interventions to increase treatment tolerance is thus substantial. Given the minimal risks associated with the study methods, the risk-benefit analysis is highly favorable.

10. Costs to the Subject

There are no direct costs to subjects.

11. Data Analysis & Statistical Considerations

Study variables will be described using summary statistics and graphical methods. Continuous variables (e.g., 6 minute walk (primary endpoint), AAQ2) will use the generalized linear model with the outcome of interest at year 3 as the dependent variable and treatment assignment as the primary predictor of interest, with a priori selected covariates age, gender, and disease. Ordered categorical outcomes (e.g. Fried Frailty) will use ordered logistic regression models in the same form above. Other outcomes (e.g., length of stay) will be assessed using an adaptation of the Cox regression model [35]. Primary analyses will be followed by examining the extent to which engagement is associated with outcomes using appropriate modeling. We also will explore the trajectory of outcome changes using generalized linear repeated measures models. We will carefully examine model assumptions (e.g., residuals, linearity, influential cases) and reparameterize models accordingly. Assuming an alpha of 0.05 and 10% attrition at 90 days, for the continuous outcomes, a sample size of 60 (20:40) will afford 80% power to detect a standardized group difference of just over 0.8 SDs. This translates to about a 16 meter treatment group difference in the six minute walk test.

12. Data & Safety monitoring

All efforts will be made to insure protection of participant information. All study personnel will complete training on how to appropriately handle data. Hard copy materials (e.g., consent forms) will be stored in a locked cabinet in a locked office of the Clinical Research Coordinator. Data will be stored separately from subject identifiers. Only key personnel will have access to subject identifiers linking to study data. Electronic data will be stored on password protected computers in locked offices, and will be transferred for more permanent storage to secure Duke maintained drives that are backed up every 24 hours.

Any data that are entered by research assistants will be entered twice to cross check and verify accuracy. Questionnaires completed by participants using secure online survey tools will force response with the option to purposely skip a question. All materials will be on an 8th grade reading level to insure understanding of items and personnel will be available to answer participant questions regarding content. Data will be reviewed for completeness and anomalies within 24 hours of collection. The PI will provide regular oversight of all data collection and analysis procedures, meeting weekly with study personnel (Clinical Research Coordinator, Research Assistants). The PI will meet with co-investigators and statistician(s) to review data quality and study progress every other week to once a month as demanded by study tasks. The entire study team will meet within 48 hours in the event that a major data issue is identified that cannot be resolved with individual members of the study team and the PI.

13.1 DCI Monitoring

This clinical research study will be monitored both internally by the PI, and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;

- Data are being appropriately collected in a reasonably timely manner.

DCI Protocol Review and Monitoring systems (PRMS) review of this protocol begins with an initial review by the Cancer Protocol Committee (CPC). CPC new protocol review focuses on scientific relevance, study design, adequacy of biostatistical input, protocol prioritization, feasibility of completing the study within a reasonable time frame and risk assessment of the trial. The PI will abide by CPC assessment of the level of risk, which will determine the intensity of subsequent DCI monitoring. CPC also conducts annual scientific progress reviews on protocols that are open to enrollment and focus on protocol prioritization, accrual and scientific progress. These reviews are conducted at the time of IRB annual renewals and documentation of all CPC reviews will be maintained in eIRB/iRIS systems.

A determination for the degree of monitoring conducted by the DCI monitoring team is made at the time of initial CPC approval to commensurate with the type and level of intervention, phase, endpoints, degree of risk, size and complexity of the protocol. A formal, independent monitoring will be conducted by the DCI monitoring team according to the risk level and monitoring plan assigned by the CPC until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

13. Privacy, Data Storage & Confidentiality

Section 12 in the e-IRB addresses fully all issues of Privacy, Data Storage & Confidentiality

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Appendix A: REDcap survey distribution

Surveys will be distributed to the subjects via e-mail using the message below:

> Please [take this, click the link below to take your baseline, click the link below to take your] survey.
>
> You may open the survey in your web browser by clicking the link below:
> [survey-link]
>
> If the link above does not work, try copying the link below into your web browser:
> [survey-url]
>
> This link is unique to you and should not be forwarded to others.

If they do not complete the survey within 24 hours, they will be sent a reminder e-mail (same message as above) every day for up to 3 days.