

## A biobehavioral intervention to enhance recovery following hematopoietic cell transplantation: Protocol for a feasibility and acceptability randomized control trial

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### ABSTRACT

**Background:** Insomnia, fatigue, and depression are among the most persistent and distressing concerns for hematologic cancer patients recovering from hematopoietic cell transplantation (HCT). This study will evaluate a novel behavioral intervention, *Restoring Sleep and Energy after Transplant* (ReSET), designed to alleviate insomnia, fatigue, and depression by improving rest-activity patterns. Evidence-based behavioral strategies to improve nighttime sleep and increase non-sedentary daytime activity will be combined to optimize 24-h rest-activity patterns.

**Methods:** The protocol herein evaluates the feasibility and acceptability of ReSET by conducting a pilot randomized controlled trial to compare the intervention with usual care. Adults undergoing HCT will be randomly assigned to ReSET or usual care. The ReSET arm will receive 3 face-to-face sessions and telephone coaching delivered in an individual format tailored to each patient. Patient-reported insomnia, fatigue, and depression will be the primary outcome measures. Actigraphy will be used to objectively quantify rest-activity patterns. Semi-structured interviews will evaluate participant satisfaction with ReSET. The goals are to determine: (1) participant satisfaction with and acceptability of the behavioral techniques; (2) facilitator fidelity and participant uptake of key intervention components; (3) ability to recruit, retain, and collect complete data from participants; (4) participant willingness to be randomized and acceptability of the control condition; and (5) validity and acceptability of the assessment strategy.

**Conclusion:** The overarching goal is to optimize recovery following HCT with a brief, non-invasive intervention that can be implemented as a part of routine clinical care.

Hematopoietic cell transplantation (HCT) is a potentially curative but rigorous therapy for hematologic malignancies with significant morbidity and risk of mortality. Common adverse effects of HCT include nausea, diarrhea, anorexia, cognitive changes, mucositis, mood disturbance, and loss of muscle mass [1]. While many of these resolve within the initial weeks after HCT, functional recovery tends to occur slowly over 6–12 months [2]. It is typically a year or longer before patients can

return to work or resume a more normal schedule of activities, assuming a good outcome [3].

Insomnia, fatigue, and depression are among the most prevalent and distressing concerns after HCT, and these symptoms can persist for many months and even years after transplant [3–7]. Research from our lab and others has shown that up to 69% of HCT patients experience clinically significant sleep disruption during the acute recovery period, and recent

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research indicates that 24% meet criteria for a clinical insomnia diagnosis [6,8]. Further, 43–48% continue to experience clinically significant sleep disruption at 1 year post-transplant [6,7]. Fatigue is even more common, with 81% of HCT patients reporting moderate to severe fatigue in the early recovery period [9]. A large study of long-term HCT survivors who were an average of 7 years post-transplant reported continued problems with sleep, depression, and fatigue [4]. Insomnia, fatigue, and depression tend to co-occur as a “cluster” among cancer patients due to shared mechanisms, including inflammation and alterations in sleep and circadian rhythms [6,10–12]. The translational implication is that a single intervention targeting this cluster may be an efficient and effective means for improving multiple quality of life concerns [13].

Restoration of normal circadian rest-activity patterns has been proposed to be one of the most promising intervention strategies for this symptom cluster [10,12–14]. Circadian rhythms have a biological and behavioral basis; they are orchestrated endogenously by the central clock in the suprachiasmatic nucleus in the hypothalamus and are sensitive to external input including light-dark exposure, social patterns, physical activity, and sleep timing [15]. Stress and changes in daily routines are known to disrupt circadian rhythms among cancer patients [14,16–22]. Alterations in circadian rhythms may be even more marked for HCT recipients due to extended hospitalizations, the adverse physical side effects of the intensive therapeutic regimen that limit activity, and routine use of medications such as steroids and narcotics that are known to disrupt sleep (Fig. 1).

Interventions that optimize sleep or activity patterns have been demonstrated to be effective treatments for insomnia, fatigue, and depression in other cancer populations. Two randomized trials have shown that cognitive behavior therapy for insomnia (CBT-I) was highly effective for insomnia occurring in the context of cancer treatment, with secondary analyses showing reduced fatigue and depression [10,23,24]. A Cochrane review found that the most effective interventions for cancer-related fatigue incorporated activity management—a set of strategies to optimally schedule and pace daytime activity—as a central component [20,25–29]. The combination of behavioral techniques to optimize both sleep *and* daytime activity across the 24-h cycle may be even more powerful than focusing selectively on nighttime or daytime patterns. Attention to the 24-h rest-activity rhythm is the basis of a well-established treatment for mood disorders, Interpersonal and Social Rhythm Therapy [30,31]. Despite the promise and potential, none of these interventions have been tested in the HCT context.

## 1. Aims and objectives

The present study will examine the feasibility and acceptability of a novel behavioral intervention for cancer patients recovering from HCT, Restoring Sleep and Energy after Transplant (ReSET). ReSET uses behavioral strategies to enhance the quality of nighttime sleep and increase engagement in daytime activity. Participants will learn and apply

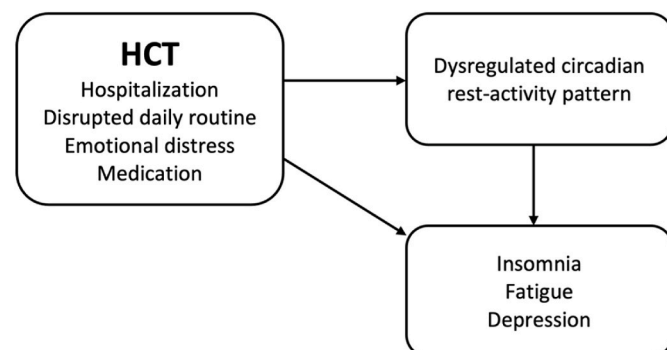


Fig. 1. Biobehavioral model informing the intervention.

well-established cognitive-behavioral techniques for insomnia and activity management strategies. The techniques will be delivered in an individual format tailored to each patient. These non-pharmacologic approaches are safe, inexpensive, and have no significant side effects. The approach emphasizes scalable implementation and minimal patient burden; the intervention is delivered in a few brief sessions that can easily be incorporated in routine clinical care.

Given the novelty of the proposed intervention and the unique implementation challenges of the HCT context, the aims of the current study are centered on establishing the feasibility and acceptability of both the ReSET intervention and the trial protocol. The specific objectives are to:

### ReSET Intervention.

1. Determine participant satisfaction with and acceptability of the behavioral techniques
2. Evaluate facilitator fidelity and participant uptake of key intervention components

### Trial Protocol.

1. Assess the ability to recruit, retain, and collect complete data from participants
2. Assess participant willingness to be randomized and acceptability of the usual care condition
3. Evaluate acceptability and validity of the assessment strategy with a particular focus on actigraphy and patient reported outcome measures

## 2. Method

### 2.1. Study design

We will conduct a Stage 1b randomized controlled trial (RCT) to compare a novel biobehavioral intervention with usual care. In the intervention, cancer patients who were treated with HCT will learn behavioral techniques to improve sleep and increase daytime activity with the goal of alleviating insomnia, fatigue, and depression. Participants will be enrolled at least one week prior to admission to the hospital for HCT. After successfully completing baseline assessments and infusion of stem cells (HCT), participants will be randomized to the intervention ( $n = 24$ ) or standard care ( $n = 12$ ). The University of Wisconsin Health Sciences Institutional Review Board (IRB) reviewed and approved all study procedures.

### 2.2. Participants

Participants will include 36 adults undergoing autologous or allogeneic HCT at the University of Wisconsin Carbone Cancer Center between the ages of 18–74 years. Autologous transplant recipients with multiple myeloma or lymphoma (both Hodgkin’s and Non-Hodgkin’s types) and allogeneic transplant recipients undergoing ablative transplants will be eligible to participate in the study. Autologous transplant recipients with other disease types will be excluded, as will allogeneic transplant recipients undergoing non-ablative regimens due to different treatment trajectories and side-effect profiles. As this is a feasibility study, we are purposefully including participants with a range of symptom severities.

Demographic information and previous experience with psychotherapy or complementary and alternative therapies will be collected at baseline. Information regarding diagnosis, disease stage, conditioning regimen, medications, physician-rated performance status [32], comorbid medical conditions [33], and psychiatric diagnoses will be abstracted from patient records. Incidence of post-treatment complications and disease recurrence will also be tracked during the study period.

## 2.3. Study procedure

### 2.3.1. Recruitment

Eligible patients will be identified by transplant coordinators and HCT physicians. Study personnel will meet with patients who express interest and agree to be contacted at a pre-HCT clinic visit. Those wishing to participate will be asked to sign the informed consent document.

### 2.3.2. Assessment timing

Participants will be asked to complete self-report and actigraphy assessments prior to hospitalization for HCT (baseline) and approximately 9 (mid-intervention) and 18 weeks (post-intervention) post-HCT. Study investigators will conduct one telephone interview to assess satisfaction and acceptability at approximately 18 weeks (post-intervention). See Fig. 2.

### 2.3.3. Randomization

Randomization to trial condition will occur approximately 3–4 weeks post-transplant prior to hospital discharge. The study will use a 2:1 allocation ratio to randomize participants to the intervention (n = 24) or usual care (n = 12) conditions. Participants allocated to the ReSET intervention will receive the first treatment session on the same day as randomization when possible. Randomization will be stratified by allogeneic versus autologous graft type due to differences in disease, conditioning regimen, post-HCT complications, and recovery trajectories, with the randomization sequence generated via blocked randomization by the study biostatistician.

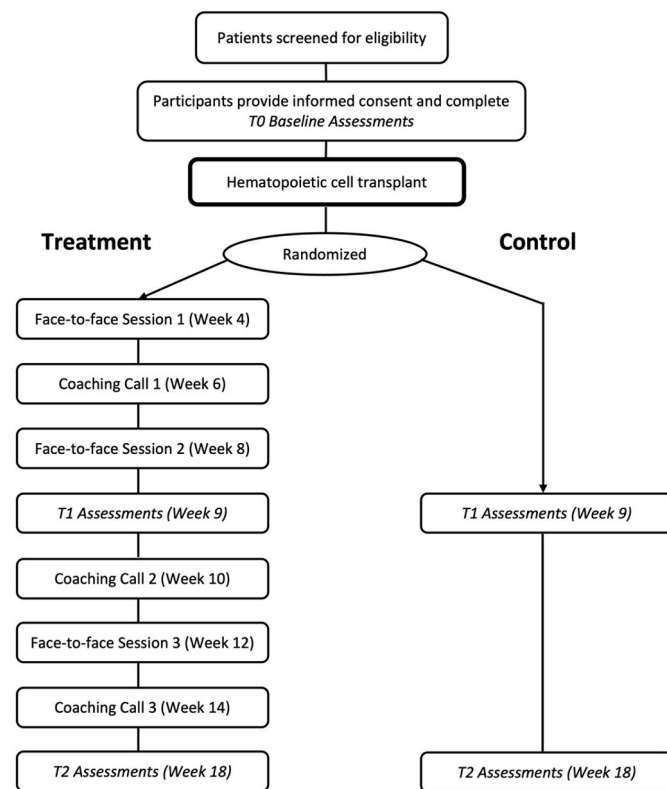


Fig. 2. Participant Flow

Note. Self-report, sleep log, and actigraphy measures will be collected at each assessment point. Phone interviews will be conducted at the final T2 Assessment (Week 18) timepoint.

## 2.4. The ReSET intervention

### 2.4.1. Timing

The intervention will be delivered in three 45–60 min face-to-face sessions at approximately 3–4, 8, and 12 weeks post-HCT with follow-up phone calls scheduled at the mid-point between sessions (see Fig. 1). The initial session will occur just prior to discharge from the hospital to allow patients to begin to practice the strategies as they return home. The final session occurs around 12 weeks post-transplant, an important clinical milestone during which disease outcomes are assessed and patients are beginning to re-establish more normal routines. Participants will be encouraged to use the behavioral strategies from hospital discharge through 18 weeks post-HCT. The timing of the sessions may be modified up to 2 weeks to accommodate timing with post-transplant clinic visits and hospital discharge. A major aim of this study is to develop an intervention that can be delivered as part of routine clinical care, so the timing is purposely flexible.

### 2.4.2. Administration

The intervention will be administered by a clinical or counseling psychology graduate student with at least 2 years of clinical training experience. Interventionists will use a treatment manual to guide the intervention sessions. In addition, they will have a weekly supervision session with a licensed clinical psychologist, at which time all study sessions will be reviewed and discussed to ensure correct delivery of the intervention components and adherence to the treatment manual and to address any problems that may arise. All intervention sessions will be audio-recorded. A selection of the audio-recorded intervention sessions for each time point will be evaluated using a fidelity checklist. In addition, the lead investigators will track any problems with delivery or lack of adherence to the treatment manual noted during weekly supervision sessions with the study interventionists.

The intervention will be adapted to the individual needs of the patient. While all participants will receive base modules of the primary intervention components, additional instruction and strategies will be implemented based on a brief assessment of sleep and activity patterns at the start of each session. For example, if a patient is already sleeping well but is having trouble sustaining activity during the day, additional coaching in activity management strategies would occur during the session and follow-up call. The proposed intervention attempts to strike a balance between patient burden and sufficient dose. We have timed the face-to-face sessions so that they can be conducted during the inpatient hospital stay and routine follow-up clinic visits to reduce burden and increase participation. Additional coaching will occur by phone so that participants do not need to make additional trips to the clinic.

The study has a formal plan for monitoring and reporting adverse events (AE) to ensure participant safety that includes notifying the participant's medical provider if concerning symptoms are noted. Participants will be specifically instructed to stop strategies and inform research staff if symptoms worsen and/or increasingly interfere with daily activities. Regular contacts between research staff and participants for study activities will provide frequent opportunities to assess and address any symptoms or unanticipated problems.

### 2.4.3. Intervention strategies

**Improve nighttime sleep quality.** Participants will receive an abbreviated, modified form of CBT-I with a primary focus on stimulus control, a set of techniques to strengthen the association between one's bed and sleep and weaken its association with stimulating behaviors. Stimulus control is a well-established stand-alone treatment for insomnia [34,35]. Sleep restriction will not be used due to the increased need for sleep in this population. Participants will also receive instruction in sleep hygiene, with cognitive restructuring utilized as needed. CBT-I is an established, evidence-based treatment for insomnia that has been effective in other cancer populations and has been shown to

improve fatigue and mood [10,23,29,35]. Moreover, abbreviated CBT-I can be effective in doses as small as one session [36]. Nighttime sleep intervention components are described in Table 1.

**Optimize daytime activity.** Participants will receive instruction in activity management strategies including prioritizing activities, planning activities during times of peak energy, activity pacing, and alternating between rest and activity with the goal of increasing ability to engage in non-sedentary, valued activities. In addition, participants will be provided with a basic step-counting pedometer to enhance ability to self-monitor activity across the day and over time and increase motivation for activity. These approaches have been shown to be among the most effective strategies for treating cancer-related fatigue [25–29]. Increasing engagement in meaningful activities is also a central component of established, evidence-based behavioral treatments for depression that are typically comparable or superior to other psychotherapeutic and medication strategies [37–39]. Daytime activity intervention components are described in Table 1.

#### 2.4.4. Session breakdown

Each session will begin with a brief, semi-structured assessment of current sleep and activity patterns. Questions will focus on ability to fall asleep, nighttime sleep disturbance, napping, and extent and patterns of engagement in activities of daily living, work inside or outside of the home, family and social activities, and hobbies. Sessions will incorporate all intervention components but will focus on areas of concern. A sample session outline is shown in Table 2. Session 1 (prior to hospital discharge) will include instruction in basic stimulus control and sleep hygiene strategies for re-establishing good sleep patterns after hospital discharge, introduction of the principles of activity management, and instruction on use of the pedometer. Session 2 will review progress with Session 1 components, introduce additional stimulus control and

**Table 1**  
Intervention components.

Nighttime sleep	Stimulus control	Techniques to strengthen the association between bed and sleep and weaken the association between bed and stimulating behaviors. For example, patients are asked to only use the bed for sleeping, go to bed only when sleepy, set a regular morning rise time, and leave the bed when unable to fall asleep.
	Sleep hygiene	Techniques to avoid behaviors that interfere with sleep and optimize the environment for sleep. For example, patients are encouraged to avoid stimulants such as caffeine before bed, establish a relaxing bedtime routine, and ensure the bedroom is dark, cool, and quiet.
	Cognitive restructuring	Techniques to correct maladaptive beliefs and attitudes about sleep (e.g., “Tomorrow will be terrible and I won’t be able to function if I don’t sleep well.”). Patients learn to recognize and correct problematic thought patterns with accurate information.
Daytime activity	Prioritizing and planning	Techniques to optimize energy resources and prevent energy depletion. For example, patients are assisted with prioritizing activities that are most fundamental to well-being, activities are planned at times of peak energy, and high-energy or non-essential activities are delegated or deferred.
	Activity pacing	Techniques to increase ability to sustain activity over the day and to avoid either prolonged rest or over-activity. Patients learn to alternate between planned, manageable periods of activity and rest.
	Pedometer	Pedometers facilitate accurate self-monitoring of activity and increase motivation for activity. Patients wear a basic step-count pedometer and learn strategies for monitoring and tracking activity across the day and over time.

**Table 2**  
Sample session outline.

5–10 min	Greeting, brief assessment of current sleep and activity patterns and concerns.
5–10 min	Review progress on behavioral strategies already introduced. Provide additional instruction and coaching as needed.
10–15 min	Instruction in new behavioral strategies in base module. Review patient take-home materials.
10–15 min	Instruction and coaching in additional behavioral strategies as needed based on assessment.
5–10 min	Planning and goal setting for incorporating strategies into daily life.
5–10 min	Address questions and concerns. Schedule interview and phone coaching sessions.

cognitive restructuring techniques for sleep if needed, and incorporate planning and goal setting for daytime activities. Session 3 will focus on the use and maintenance of strategies learned in previous sessions as participants begin to re-establish daily routines. Participants will receive educational handouts and worksheets at each in-person session outlining and personalizing key strategies and a 3-ring binder to store the materials for easy reference between sessions. All sessions will be followed with a scheduled phone call approximately 2 weeks later for additional coaching and troubleshooting focused on problem areas. Participants will also be asked to keep a daily checklist of sleep and activity strategies used between sessions.

#### 2.5. Usual care condition

Participants randomized to usual care will complete outcome measures. They will undergo the typical post-transplant medical care at the cancer center. The cancer center does not provide systematic education about symptom management but provides education and referrals to community support groups and health psychology as needed.

#### 2.6. Measures

##### 2.6.1. Actigraphy

The Actiwatch-2 (Philips Respironics), a wrist-worn actigraphy device, will be used to objectively quantify circadian rest-activity patterns over a continuous 7-day period at three time points: prior to hospital admission for HCT and 9 weeks (mid-intervention) and 18 weeks (post-intervention) post-HCT [40]. Data processing will yield the following indices: mesor (mean activity level), amplitude (rhythm height), acrophase (time of day the rhythm peaks), and R-squared (goodness-of-fit or robustness of the rhythm), as described in Rumble et al., 2015 [41]. These rest-activity indices will be the primary actigraphy outcomes of interest. However, we will also collect additional measures of sleep and daytime activity. Specifically, participants will complete a concurrent nightly sleep log, and traditional sleep parameters will be calculated from both the logs and actigraphy, including total sleep time, sleep onset latency, wake time after sleep onset, and sleep efficiency. For daytime activity, calibration thresholds will be used to aggregate activity data into steps and minutes spent in sedentary, light, moderate, and vigorous activity [42].

##### 2.6.2. Patient-reported outcomes

Participants will complete well-validated self-report assessments at the same three time points: prior to hospital admission and 9 and 18 weeks post-HCT. The sleep disturbance, fatigue, and depression modules of NIH Patient Reported Outcomes Measurement Information System (PROMIS) will be the primary outcomes [43–45]. The anxiety, pain, and physical functioning modules will also be used. We will compare performance with more established instruments that our team has previously used, including the Insomnia Severity Index (ISI), Fatigue Symptom Inventory (FSI), and Inventory of Depression and Anxiety Symptoms Depression Scale (IDAS) [46–48]. In addition, we will report PROMIS sleep, fatigue, and depression scores relative to population

norms, and we will report the percent of the sample with of mild, moderate, and severe insomnia symptoms on the ISI to estimate prevalence and severity to inform a future trial.

### 2.6.3. Patient interviews

Study investigators will conduct a semi-structured interview at the end of the intervention (approximately 18 weeks post-HCT) to determine participant satisfaction with and acceptability of a) the behavioral strategies, timing, and delivery mode of the intervention and b) the assessment strategy and time commitment of the RCT. Two trained research assistants will administer this interview; one will ask questions, the other will take notes and the interview will be audiorecorded. Participants will be asked about barriers to participation and problems encountered as well as areas of satisfaction. They will be cued to report both problems and satisfaction with each of the aforementioned elements. Notes and recordings will be reviewed to generate a list of barriers and facilitators of participation in the intervention. Details from participant narratives will be used to determine the significance of the issues and potential means to address them.

## 2.7. Data analysis

The primary outcomes will focus on feasibility and acceptability of the intervention and the trial protocol.

### 2.7.1. Feasibility and acceptability of the intervention

The goals are to determine the following:

**Participant satisfaction with and acceptability of the behavioral techniques.** Interview data will be examined to determine participant satisfaction with the intervention and behavioral techniques. We will also evaluate this indirectly through examining participant attrition.

**Intervention fidelity.** All intervention sessions will be audiorecorded. A selection of the audio-recorded intervention sessions for each time point will be evaluated using a fidelity checklist. In addition, the lead investigators will track any problems with delivery or lack of adherence to the treatment manual noted in weekly supervision sessions with the study interventionists.

**Intervention uptake.** Participants will be asked to complete a daily checklist to indicate which behavioral strategies they used each day.

### 2.7.2. Feasibility and acceptability of the trial protocol

The goals are to determine the following:

**Ability to recruit, retain, and collect complete data from participants.** These will be evaluated by tracking recruitment rate and reasons for non-participation. Retention rates and those contributing complete data will be tracked at milestones of 4, 8, 9, 12, and 18 weeks. Woolf's method will provide confidence intervals for these rates [49].

**Participant willingness to be randomized and acceptability of the usual care condition.** Participant willingness to be randomized will be evaluated by examining attrition between enrollment and the first intervention session as well as attrition between randomization and the mid-point assessment. Participant willingness to be randomized and acceptability of the usual care condition will also be evaluated by examining responses to a semi-structured interview of usual care participants at 18 weeks post-transplant.

**Acceptability and validity of the assessment strategy.** Acceptability will be assessed by examining interview data and rates of completion of actigraphy, logs, and self-report measures. To address validity, we will assess the ability to predict PROMIS measures with the legacy measures of the same symptoms we have previously used successfully with this patient population. Strong prediction ( $r > 0.5$ ) will imply that the PROMIS measures are a statistically valid approach to quantifying the effects of our intervention.

### 2.7.3. Determination of estimates of variance and effect sizes

The exploratory goal is to conduct a preliminary test of the efficacy of

the intervention to determine estimates of variance and effect sizes for determination of power and sample size. The primary outcomes will be PROMIS sleep disturbance, fatigue, and depression scores. Actigraphy index scores (mesor, amplitude, acrophase, R-squared) will also be compared to determine the effects of the intervention on rest-activity patterns. We will use linear regression to compare groups, and we will obtain mean differences and within-group standard deviations. It is important to emphasize that this is an exploratory analysis only as we are likely underpowered to test the efficacy of the intervention. Our sample size will provide 80% power to detect a group difference of 1.0 within-group standard deviations (a large effect). In sum, we will have sufficient information to gain a sense of whether there is an effect and to quantify within-group standard deviations. These within-group standard deviations will be essential for study planning for a full-fledged 2-arm larger, confirmatory RCT.

Finally, we will examine the extent to which actigraphy index scores are associated with—i.e., predictive of—the patient-reported outcomes listed above. For outcomes that are highly skewed, ordinal logistic regression will be used to model the data. For more continuous or symmetrically distributed outcomes, we will use linear regression models.

## 3. Discussion

Despite the prevalence and persistence among HCT survivors, insomnia, fatigue, and depression are undertreated in this population [1], and a key barrier is the lack of practical, evidence-based strategies for addressing these concerns in the HCT setting. ReSET was designed to address this gap and optimize recovery from HCT with a brief, non-invasive intervention that can be implemented as a part of routine clinical care.

Strengths of ReSET include the attention to scalability and minimizing patient burden by integrating face-to-face sessions into existing clinical care and using telephone coaching. To increase benefits and efficiency, ReSET will target sleep and rest-activity patterns across the 24-h cycle. While similar approaches have been established in the treatment of mood disorders, prior research in cancer has focused selectively on either sleep or management of daytime activity, but not both. This approach also applies emerging models of biobehavioral symptoms in cancer to treat prevalent and debilitating symptoms occurring in the context of HCT. Specifically, ReSET will capitalize on the shift in focusing on treating symptoms individually to developing interventions with the potential to alleviate multiple quality-of-life concerns [10,12,13]. Finally, while ReSET is manualized and includes standardized base content, it is also designed to be flexibly tailored to patient needs based on brief assessments at the start of each session. This flexible approach is designed to optimize engagement, efficiency, and benefits.

Strengths of the assessment approach include the use of both patient-reported outcome measures and the objective assessment with actigraphy, a sophisticated and non-invasive measure that uses a highly sensitive accelerometer to objectively quantify circadian rest-activity rhythms. These novel indices of circadian rest-activity patterns, in addition to more traditional sleep parameters, will be brought to bear on this project. Semi-structured interviews will further be utilized to evaluate patient satisfaction and acceptability.

There are also some limitations that should be noted. The protocol was specifically designed to assess feasibility and acceptability of ReSET. Therefore, the sample size is likely underpowered to test the efficacy of the intervention. However, the statistics generated will be key ingredients to power and sample size calculations that will be needed to plan a larger, confirmatory RCT.

Another potential limitation is the heterogeneity of the patients with respect to diagnosis, treatment, and stem cell source. We opted to include both allogeneic and autologous transplant recipients based on research from our laboratory and results from another large study

showing comparable levels of fatigue, sleep disturbance, and depression in both groups [3,7,50]. We will stratify randomization based on transplant type. If findings are promising, subgroup analyses would be planned in a future trial.

While ReSET is designed to minimize patient burden, it is possible that the dose may not be sufficient to improve target symptoms. However, there is already evidence that behavioral interventions as short as one session can have a clinically meaningful impact on insomnia [36], and most activity management interventions are similarly brief [28]. Given barriers to implementing behavioral interventions in the cancer care setting, there is a high need for developing efficacious, brief interventions that can be successfully implemented under real world conditions. Preliminary effect sizes and participant feedback will guide optimization of ReSET for a future trial, which could increase number, frequency, or duration of sessions.

Finally, while it might be ideal to evaluate patients for a longer period of time, the 18-week follow-up will allow us to answer the critical questions concerning the feasibility and initial effects. The acquired data will lay the groundwork for a larger trial where a longer follow-up period can be employed.

All intervention research reflects a balance between practical considerations, burden and time constraints, and ethical concerns, when seeking to achieve desired goals. We believe our approach maximizes the potential gain and has high potential to make a meaningful contribution with respect to the care of HCT patients. The current protocol will focus on HCT recipients due to the severity and persistence of the quality-of-life impairments; however, if shown to be effective, this approach could easily be extended to other cancer populations.

While the overarching goal is to improve quality of life by minimizing the impact of distressing symptoms for HCT patients, our research group has recently demonstrated that insomnia, fatigue, and depression occurring pre-HCT and in the early post-HCT recovery period predict important clinical outcomes following HCT. Specifically, pre-HCT sleep disturbance, fatigue, and depression symptoms and post-HCT fatigue and depression symptoms predicted higher risk for mortality by 6 years post-HCT, after adjusting for known clinical risk factors. Similarly, pre-HCT sleep disturbance was a risk factor for disease relapse [6]. The findings underscore these symptoms as important targets for intervention and extend the possible benefits to improving the clinical outcome and extending survival.

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## Author contributions

Kirvin-Quamme: Conceptualization, Writing – original draft. Rumble: Conceptualization, methodology, writing – review and editing. Cadmus-Bertram: Conceptualization, methodology, writing – review and editing. Juckett: Methodology, resources, writing – review and editing. Rathouz: Conceptualization, methodology, biostatistics, writing – review and editing. Schell: Methodology, project administration, writing – review and editing. Callander: Methodology, resources, writing – review and editing. Hematti: Methodology, resources, writing – review and editing. Costanzo: Conceptualization, funding acquisition, methodology, resources, supervision, writing – original draft.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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