Systematic Programmed Illumination of Hospital Rooms to Prevent/Reduce Cancer-Related Fatigue during Autologous Stem Cell Transplantation for Multiple Myeloma
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Mount Sinai	Protocol Name:	Systematic Programmed Illumination of Hospital Rooms to Prevent/Reduce Cancer-Related Fatigue during Autologous Stem Cell Transplantation for Multiple Myeloma
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	Study Number:	IF# 2517160 HS# 15-00777 GCO#: 15-2009

Brief Summary of Research (250-400 words):

Patients who receive autologous hematopoietic stem cell transplantation (HSCT) in the treatment of Multiple Myeloma (MM) are typically hospitalized for 14-21 days during their transplant and medically stabilize afterwards as part of standard care. It is before, during, and after this hospitalization for transplant that our study will take place.

A sample of 60 patients scheduled for HSCT in the treatment of MM will be recruited in the weeks to months prior to their hospitalization. Light therapy incorporating ambient systematic programmed light illumination (sPI) will be used in patient hospital rooms (during scheduled transplant) to control cancer-related fatigue (CRF). The FDA has certified that light therapy, like that used in this study, is a low-risk intervention. After initial assessment of CRF, depression, and sleep quality/quantity (baseline assessments), participants will be randomized to one of two treatment conditions: one with an active intervention, and one with a non-active comparison. During inpatient hospitalization, the active intervention will consist of the following regimen: high intensity bright-white light (1300 lux at the eyes) during morning hours (7AM to 10AM). The non-active comparison condition will receive half the intensity dim-white light of the active group (i.e., 90 lux at the eyes) during 7AM-10AM. These differences in lux intensity are not easily discernable. Following baseline, assessment of fatigue, sleep activity, depression, circadian rhythms, and quality of life will continue through the course of hospitalization (14-21 days of treatment, to determine immediate impact of sPI), then repeat at one month and threemonths post-discharge follow-ups (to determine lasting effects). Outcomes will be assessed through standardized scales (e.g., FACIT-Fatigue Scale) and objective measures (e.g., actigraphy, daysimeter for light monitoring, melatonin from urine collection, blood inflammatory markers, all explained below). This trial will: 1) be the first randomized clinical trial (RCT) to investigate the effects of sPI to prevent CRF and other biopsychosocial side effects of transplant; 2) focus on a distinct, relatively homogenous patient population (MM-HSCT patients) with high prevalence of CRF; and 3) explore possible circadian rhythm mediation via melatonin analysis and blood analysis. This investigation will have major public health relevance as it will determine if an inexpensive and low patient burden intervention (sPI) is able to control fatigue associated with medical illnesses and related problems.

1) Objectives

Specific Aims:

- **Aim 1: Determine if sPI results in significant prevention/reduction of the development of CRF, depression, sleep problems, circadian rhythm disruption and diminished quality of life compared to the comparison light condition.** Hypothesis 1a: HSCT patients exposed to sPI will report less CRF (measured by FACIT-Fatigue Scale), less depressive symptoms (measured by the CES-D/BDI-II), better sleep (measured subjectively by the Pittsburgh Sleep Quality Index, FACIT Fatigue Scale and objectively by actigraphy), and more synchronized activity circadian rhythms (measured by actigraphy) during the course of HSCT hospitalization compared to those patients in the low light comparison condition. Hypothesis 1b: HSCT patients receiving sPI will report positive effects on CRF, depression, sleep, and circadian rhythm disruption at one month and three-

months after discharge and completion of the sPI intervention than those in the comparison condition.

- **Aim 2: Explore whether the effects of sPI are mediated by changes in sleep, depressive symptoms, activity circadian rhythms, melatonin and/or inflammatory markers.** Hypothesis 2a: The effects of sPI on CRF are mediated by changes in sleep quality. Hypothesis 2b: The effects of sPI on CRF are mediated by changes in depressive symptoms. Hypothesis 2c: The effects of sPI on CRF are mediated by changes in activity circadian rhythms (measured via actigraphy and melatonin rhythmicity). Hypothesis 2d: the effects of sPI on CRF are mediated by changes in inflammatory markers.**Aim 3: Determine the feasibility and acceptability of sPI, actigraphy, urine collection and monitoring of light exposure**. Hypothesis 3a: Initiating the sPI environment in patient hospital rooms during inpatient procedures (HSCT and initial chemotherapy regimen to treat MM and related oncological diseases) will be tolerable among MM-HSCT patients and medical professionals. Hypothesis 3b: sPI will be feasible as an inpatient treatment method to prevent common circadian rhythm-based side effects observed with HSCT and subsequent chemotherapy. Hypothesis 3c: sPI implementation inpatient hospital rooms will maximize potential patient benefit while minimizing deviation from normal lighting fixture end-user experience for both HSCT patients and medical professionals. Hypothesis 3d: Actigraphy collection among HSCT patients will be acceptable as an assessment method before, during, and after HSCT. Hypothesis 3e: Urine collection among HSCT patients will be tolerable as an assessment method before and during hospital visit for HSCT. Hypothesis 3f: Monitoring of light exposure via Daysimeter data among HSCT patients will be acceptable as an assessment method before and during HSCT.

2) Background

Debilitating fatigue – a persistent sense of exhaustion frequently associated with a number of serious medical conditions, including cancer – can interfere with mood, activities of daily living, treatment compliance. Such fatigue is often associated with sleep problems, depression, quality of life, and agitation. Unfortunately, currently available interventions for CRF are, at best, only modestly effective. Pharmacological agents have been studied for CRF, but there is insufficient evidence to recommend their use. Non-pharmacological interventions have shown clinical benefit, but they can be labor-intensive, expensive, and cumbersome for patients. A promising alternative is light therapy.

Although CRF is well documented, it is difficult to characterize because it has a poorly delineated etiology. Circadian rhythm disruption (CRD) has been hypothesized to play an important role in the etiology of CRF by affecting multiple domains of psychosocial and physiological functioning. Circadian rhythms are generated and regulated by an internal biological clock located in the suprachiasmatic nucleus of the hypothalamus; they are biological cycles (e.g., changes in hormone secretion, body temperature, and sleep-wake activity cycles) that are slightly longer than 24 hours and are entrained to the 24-hour day by environmental time cues.

Bright light is one of the strongest synchronizers of circadian rhythms, which are maintained through entrainment by light exposure to the retina. Light therapy incorporating systematic exposure to bluish-

white light is hypothesized to entrain circadian rhythms, which play a crucial role in the cellular and physiological functions of the brain and body. Indeed, disruption of these rhythms has been shown to affect sleep quantity and quality, depression, and fatigue among cancer patients. The proposed research will investigate the delivery of sPI via a novel delivery system to treat CRF, experienced by up to 80% of all cancer patients. Although CRF has been found to be related to CRD and it is known that bright light improves rhythms, the effect of sPI on CRF has not been investigated. Further, CRF has been found to be related to sleep disturbances, as well as to depression, yet the effect of sPI on these effects has not been explored.

Inflammatory response have been proposed to underlie CRF. There is an association between CRF among cancer patients and activation of pro-inflammatory signaling. For example, breast cancer survivors with persistent fatigue have elevated levels of markers associated with pro-inflammatory cytokine activity including Interleukin-1 receptor antagonist (IL-1ra), Interleukin-6 (IL-6), soluble tumor necrosis factor receptor type II (sTNF-RII), soluble intercellular adhesion molecule-1 (sICAM-1), and C-reactive protein (CRP). It has also been shown that chemotherapy leads to significant elevations in inflammation which is associated with increases in fatigue.

In the proposed preliminary feasibility research, sPI will deliver appropriately timed ambient, low-level, bluish-white light to patients during their hospital stay with floor lamps designed to deliver high circadian stimulation in the morning. We have selected cancer patients who are hospitalized for HSCT to treat MM because this population: (1) is relatively homogenous with a high prevalence of CRF, (2) can be studied prospectively across the course of HSCT, (3) permits careful monitoring of circadian rhythm entrainment through analysis of melatonin from urine obtained before, during and after HSCT, (4) regularly has blood drawn for clinical purposes and (5) allows assessment and control of confounding variables.

Preliminary research:

The proposed exploratory study builds on Redd's, Figueiro's, and Ancoli-Israel's complementary areas of research. Redd, Ancoli-Israel and colleagues' ongoing investigation of BWL to treat CRF in cancer (including HSCT) survivors has formed the conceptual template for the proposed study and points to the potential importance of sPI in the prevention and treatment of CRF. In previous studies, they were able to retain 71% of participants, a retention rate that we also expect for the proposed protocol.

Both Redd's and Ancoli-Israel's work supports the proposed study in 6 ways: (1) It provides the conceptual rationale for light as an intervention for negative sequelae of cancer treatment; (2) It established the acceptability of light treatment by cancer patients; (3) It determined the overall feasibility of lighting interventions with a cancer population, indicating that patients were: a) able to implement the light intervention with minimal involvement by research staff, b) adherent to home-based treatment regimens, and c) able to successfully complete all study assessments; (4) It confirms a low-lux light treatment as an

appropriate comparison condition; (5) It provides clear procedural guidelines; (6) It demonstrates the importance of examining sPI for the treatment of negative cancer sequelae as patients exposed to daily light entrainment showed clinical benefit.

Figueiro has shown that using an ambient light treatment can improve sleep and behavior in patients with Alzheimer's disease and related dementia. Using knowledge of human circadian phototransduction, which is how the retina converts light signals into neural signals to the brain, Figueiro was able to provide most of the ambient light's radiant power in a range that has the greatest effect on circadian rhythms. This allows us to reduce overall sPI light levels and make the emitted light more comfortable for patients, possibly increasing treatment compliance.

Recent work by Ancoli-Israel, Redd, and Liu revealed that breast cancer and HSCT patients were light-deprived. Compared to healthy adults in an illumination study who received 58 minutes of bright light per day, breast cancer patients during chemotherapy received only 35 minutes of bright light per day, and HSCT patients in our preliminary light exposure study for cancer-related fatigue only received 30 minutes of bright light per day. Their findings provide additional evidence that sPI may hold promise for patients who are light deprived.

3) Setting of the Human Research

Research procedures will be performed at the Icahn School of Medicine at Mount Sinai (MSH) and the Rensselaer's Lighting Research Center (RLC).

The RPI LRC Biomarker Lab staff will be responsible for processing urine specimens, informing and assisting with all protocols performed at MSH, processing and analyzing data, and writing reports. The IRB at Rensselaer Polytechnic Institute is a full board review, and will assess and approve the proposed research protocol at one of their regularly scheduled meetings.

Mount Sinai's Human Immune Monitoring Core Shared Resource Facility staff will be responsible for storing and processing blood samples.

4) Resources Available to Conduct the Human Research

Cancer survivors who will receive autologous HSCT for treatment of MM will be recruited from Mount Sinai. All patients will be randomly assigned to either the active or comparison condition. We expect to recruit 60 patients over the study course. It is estimated that over 100 MM patients are seen at MSH annually to receive their first HSCT.

Research study personnel are very experienced with these types of studies. Research coordinators are highly qualified to assume these roles of screening and evaluating subjects, obtaining informed consent, analyzing and interpreting complex clinical research data, ensuring accurate and complete compilation of subject data, and liaising with the IRB of Protection of Human Subjects issues.

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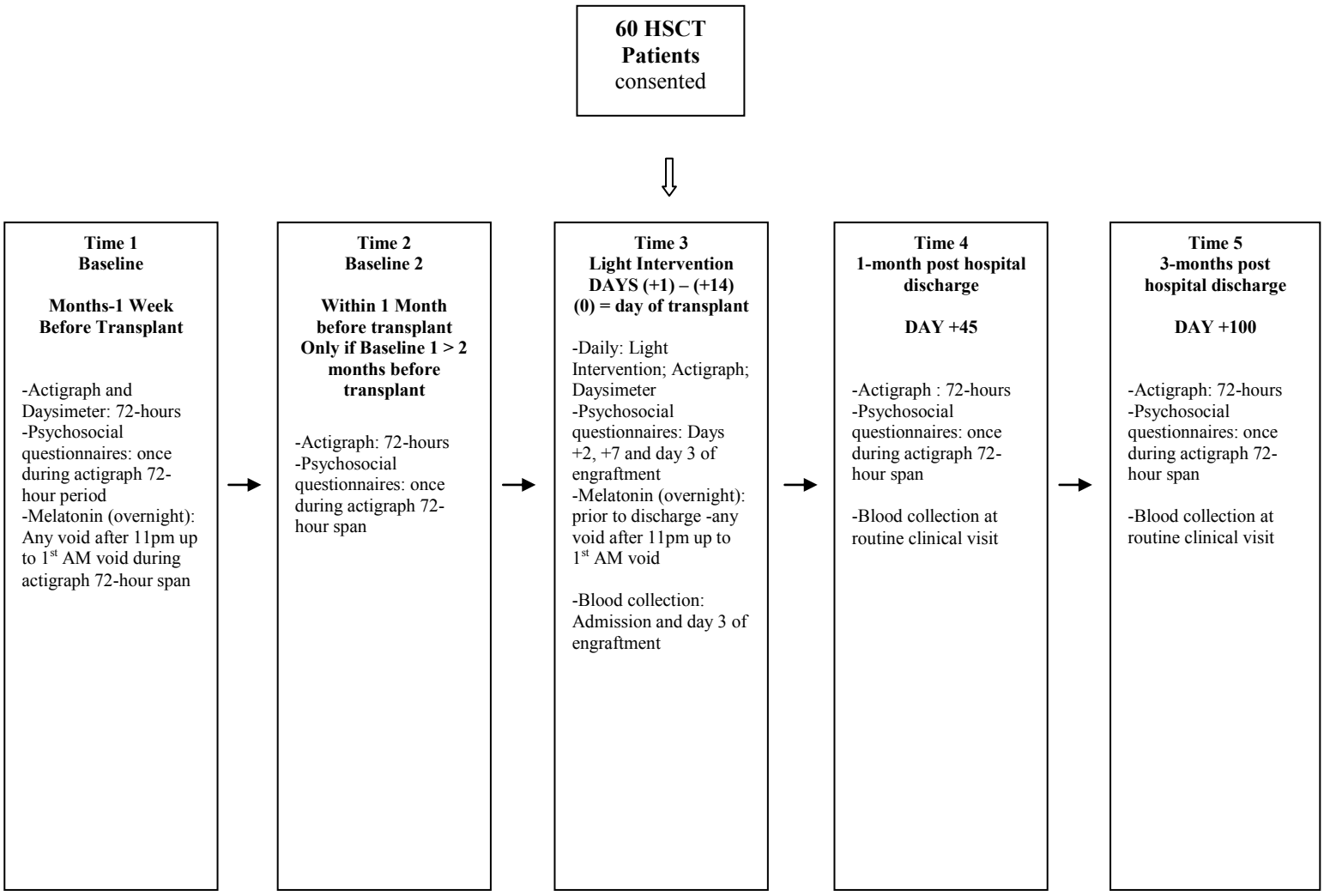
To ensure that all study personnel are adequately informed about the protocol, all investigators, consultants and research coordinators will be required to read the protocol and to review the measures and equipment. We will also develop a recruitment script that the research coordinator will practice before reaching out to potential participants.

5) Study Design



a) Recruitment Methods

Potential participants will be identified by Eileen Scigliano, MD, and staff from the group of patients who will be undergoing their first autologous HCST and meet the additional inclusion criteria in EPIC. Prior to

autologous HCST, the treating physician will discuss the study to their patient and inform them that they may be approached by a RA for participation. Additionally, a letter will be given to the patient, signed by the Director of the Multiple Myeloma program, introducing the study, team members, and to seek interest in participation. The following week, the RA will approach patients at their medical appointment at MSH in the months leading up to transplantation, unless the patient has expressed an unwillingness to participate. Physicians will inform RAs of those patients who have asked to not be approached for recruitment. The RC will then describe the study to determine their interest in participating, answer questions, and obtain Consent/HIPAA approval. A brief screening will subsequently be given to assess patient eligibility based on inclusion/exclusion criteria as listed in b) below. If there are any incidental findings during the screening and consent process, the subjects will be put in contact with a supervising licensed psychologist. The research team will look at each subject's CES-D scores at all timepoints to determine if they are at risk for severe depression. The protocol states that if a CES-D score is above 16, then the supervising psychologist will call the patient to determine if they need to be referred to get professional help regarding potential clinical depression. The BDI-II also can be used as a screener for depression. If a subject endorses suicidal ideation (by answering 2 or 3 for question 9, or scores in the severely depressed range between 29-63), then the supervising psychologist will also call the patient.

b) Inclusion and Exclusion Criteria

Our eligibility criteria includes:
Patients:

- Who will undergo their first autologous HSCT procedure as treatment for multiple myeloma

AND:

- Who are currently 21 years of age or older
- English language proficient
- Able to provide informed consent

Exclusion criteria will be:

- Under age 21
- Previous HSCT procedure (autologous or allogeneic)Pregnancy
- Eye Diseases which limit the ability of light to be processed (e.g., untreated cataracts, severe glaucoma, macular degeneration, blindness, pupil dilation problems or retina damage)
- Secondary cancer diagnosis within the last 5 years
- Severe sleep disorders (e.g., Narcolepsy)
- History of bipolar disorder or manic episodes (which is a contra-indication for light treatment)
- Severe psychological impairment (e.g., hospitalization for depressive episode in the past 12 months)
- Previous use of light therapy to alleviate fatigue or depressive symptoms

c) Number of Subjects

For this feasibility study, we will recruit 60 participants drawn from the pool of upcoming HSCT admissions to treat MM at the MSH bone marrow transplant (BMT) clinic. Our previous research has demonstrated that at least 40% of this group either suffers from or will develop clinically significant fatigue related to cancer or its treatment.

d) Study Timelines

Total participation in this study is 16-18 weeks, and may vary by hospital admission, length of hospital stay, and expediency of returning study related materials.

Endpoints

The primary endpoints in the proposed study are: 1) Fatigue as measured by a simple Graphic Rating Scale, Multidimensional Fatigue FACIT Fatigue Scale, and The Pittsburgh Sleep Quality Index; 3) Depression as measured by the CES-D; 4) Quality of Life measured by the SF-36 scale; 5)Sleep/wake activity measured using anactigraph; and 7) Biological variables melatonin and inflammatory markers (i.e., IL-1ra, IL-6, MCP-1/CCL2, MIP-1a/CCL3, sTNFr1, sIL-6R, CRP) as obtained via urine and blood analysis.

The secondary endpoints include: 1) the amount of light received by the patient as measured by the Daysimeter;2) treatment satisfaction using the FACIT-TS-G scale, and 3) Psychological moderators (e.g., emotions, symptom burden) that may affect for whom the treatment is effective.

With regard to safety endpoints, there are no known major risks associated with the use of bright white light in the treatment of either fatigue or depression. However, we will monitor those who decide to cease treatment because they find the treatment approach unacceptable along with their concerns regarding treatment.

e) Procedures Involved in the Human Research

Approach: We will explore the acceptability, feasibility and potential efficacy of sPI exposure to prevent CRF in patients undergoing initial autologous HSCT, as provided during their inpatient hospital stay for approximately two weeks following transplant. We will also determine the feasibility of investigating biological markers (i.e. melatonin, inflammatory markers) as mediators of the clinical impact on CRF. Urine samples will be collected at two timepoints to assess melatonin rhythmicity. Blood samples will be collected at four timepoints to assess the inflammatory response in relationship to the light treatment.

The proposed approach will be informed by procedures Figueiro developed for her recent research on sLE treatment in Alzheimer's patients. Additionally, we will be building on our previously established protocols to inform our ability to research sPI treatment. The two teams of investigators will work closely, carrying out weekly conference calls and quarterly face-to-face meetings alternating between MSH and Rensselaer Polytechnic Institute (RPI). The MSH team will recruit study participants and oversee use of the light fixtures, monitoring equipment, assessment scales, and facilitate with Figueiro's laboratory regarding proper storage and analysis of urine samples. MSH will also collaborate with the Mount Sinai's Human

Immune Monitoring Core Shared Resource Facility at Mount Sinai to process and analyze blood samples to assess and track inflammatory markers.

Actigraphs will be used to monitor bio-behavioral indicators of circadian rhythms. The Actigraph is attached to the non-dominant wrist and measures movement and activity. The Daysimeter is worn around the neck and measures light exposure.

Acuity Lighting Brands will be providing the lighting fixtures in patient rooms at no cost. The fixtures will control all emitted wavelengths and provide both treatment and comparison conditions from the same fixture, as controlled by the investigators.

Methods: MM patients who will receive an autologous HSCT as part of their treatment plan will be recruited from MSH, and will be randomly assigned to either the BWL or the DWL conditions. Participants in both treatment arms will complete baseline 1 assessment at the time they are recruited. If Baseline 1 is completed more than two months before transplant participants will complete baseline 2 approximately one month before their transplant. After the baseline(s) assessment participants will be assessed: (A) during the inpatient hospital stay at day of transplant, day + 2, day + 7; (B) engraftment day 3 (most likely during week 2-3): (C) one month after hospital discharge; and (D) three months after hospital discharge. Outcome measures include standardized questionnaire measures of CRF, depression, sleep quality, and quality of life, as well as analysis of urinary melatonin and blood inflammatory marker levels at both outpatient and inpatient timepoints to monitor the biological processes believed to be influenced by sPI. This assessment schedule will allow us to evaluate the immediate and post-treatment benefits of the sPI treatment.

The proposed statistical analyses examine a number of related questions. The first consists of a comparison of the impact of the sPI exposure intervention to a comparison condition on CRF, depression, sleep quality, circadian rhythmicity, and quality of life using both the self-report and objective outcome measures (i.e. actigraphy data) in MM patients undergoing autologous HSCT. The second will examine the possible mediating role of depression, sleep quality, circadian activity rhythms, and fatigue on the effects of sPI. Lastly, the third will assess the feasibility and acceptability of an sPI intervention, actigraphy, urine melatonin analysis, and light exposure monitoring during HSCT. We will also look at possible co-moderators that may influence for whom the treatment works as defined by the list of additional measures we have included. In addition, we will explore whether the light treatment improves fatigue and depression through biological mediators analyzed in blood, i.e. inflammatory markers.

Please see the Data Safety and Monitoring Plan in section 5h for procedures taken to lessen the probability or magnitude of risks.

Data about subjects will be collected from medical charts, urine samples, blood samples, questionnaires that the participants will fill out, and output from the equipment (i.e., Actigraph and Daysimeter data).

If there are any adverse events during the screening and consent process, the study participants will have the option to be put in contact with the a licensed clinical psychologist. The suicidality protocol will be in place throughout the entire study. It will be in the judgment of the consenting professional and/or as per medical record to determine if a patient may have severe psychopathology or cognitive impairment likely to interfere with the participation or completion of the protocol or ability to provide meaningful information. In this case, professional will decide not to include potential participant in the study.

The following questionnaires will be completed during the study:

Background Measures:

- Background Information Questionnaire – Socio-demographic data regarding gender, age, ethnicity, religion, income, marital status, and employment status will be gathered during the screening assessment and any changes in information will be gathered at the follow-up assessments. We will assess co-morbid medical conditions and current prescription sleep-related and non-sleep-related medications.

- Chronotype (MEQ) – We will collect data on baseline circadian predispositions using the Morningness-Eveningness Questionnaire, a 19-item self-rated survey designed to measure whether a person's peak alertness is in the morning or the evening. Takes approximately 2 minutes to complete.

Credibility Measures:

- Credibility/Expectancy Questionnaire – This questionnaire will ask whether the patient feels the light box is a useful and/or effective treatment for CRF.

Sleep and Fatigue Measures:

- Sleep Log – The sleep log will ask the participant to note what time she/he went to bed, what time she/he got out of bed, any times the Daysimeter and/or Actiwatch was removed, and whether she/he spent any time sitting very still (such as at the movies). The sleep log will be used to help edit actigraphy data.

- FACIT-Fatigue Scale – The FACIT-Fatigue scale will be used both for selection of patients into the study and as an outcome measure of fatigue. Smith et al. (1999) report that this 13 item scale has excellent test-retest reliability (r = 0.90) and internal consistency reliability (alpha = 0.93-0.95). In addition, criterion related validity studies using objective measures of physical function as the outcome show that patient reported fatigue based on the FACIT-Fatigue can predict these objective measures. This measure is the main tool for measuring fatigue in the Patient-Reported Outcomes Measurement

Information System (PROMIS) initiative. Cella (personal communication) has indicated that a FACIT-Fatigue score equal to or less than 33 constitutes clinically significant fatigue.

- Fatigue Line Scale – Simple numeric graphic rating scale, marked on a line numbering 0-100. Replaces the FACIT fatigue scale for daily fatigue assessment during inpatient procedures.

- Multidimensional Fatigue--The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Tested for its psychometric properties in cancer patients receiving radiotherapy, patients with the chronic fatigue syndrome, psychology students, medical students, army recruits and junior physicians, it was found to have good Test-retest Reliability (r=0.80) and great Internal Consistency (Cronbach's alpha = 0.92).

- The Pittsburgh Sleep Quality Index – The Pittsburgh Sleep Quality Index consists of 19 self-rated items. Scale reliability is excellent using both an internal consistency criterion (Cronbach's alpha = 0.83) and test-retest reliability (r = 0.85). The validity of the instrument is based on its ability to discriminate patients (those having either sleep problems and/or depressive symptoms) from controls (healthy participants without sleep complaints).

- SF-36 scale - Quality of life will be assessed using the SF-36 scale. The SF-36 is a multi-purpose, short form health survey consisting of 36 questions. Both test-retest and internal consistency reliability exceeded 0.70 in studies of this scale's psychometric properties. The scale also has demonstrated content, criterion, and predictive validity.

Depression Measures:

- CES-D (Center for Epidemiologic Studies Depression Scale) – 20 item questionnaire that comprise six scales reflecting major dimensions of depression: depressed mood; feelings of guilt and worthlessness; feelings of helplessness and hopelessness; psychomotor retardation; loss of appetite; and sleep disturbance. The CES-D has been shown to be a reliable measure for assessing the number, types, and duration of depressive symptoms across racial, gender, and age categories (Cronbach's alpha ≥0.80). Concurrent validity by clinical and self-report criteria, as well as substantial evidence of construct validity has been demonstrated.

Emotion Measures:

- PANAS – The Positive and Negative Affect Schedule (PANAS) is a 20-item self-report measure of positive and negative affect developed by Watson, Clark, and Tellegen (1988). NA and PA reflect "dispositional imensions, with high-NA epitomized by subjective distress and unpleasurable engagement, and low NA by the absence of these feelings." Conversely, PA represents the extent to which an individual experiences pleasurable engagement with the environment. Consequently, emotions such as enthusiasm and

alertness are indicative of high PA, whilst lethargy and sadness characterize low PA. Both the PA and NA have decent Test-retest reliability (r=0.68 and r=0.71 respectively) and decent Internal Consistency (Cronbach's alpha = 0.87).

Symptom Measures:

- Brief Symptoms Inventory-18 (BSI-18) - BSI-18 is one an integrated series of instruments designed to measure psychological distress. A more concise version of the 53 item BSI, the BSI-18 boasts 18 items and, according to its authors, this inventory presents satisfactory reliability indexes, both for the dimensions (ranging from .74 to .84) and the general distress index (.89). It has decent Test-retest Reliability (r=0.76) and good Internal Consistency (Cronbach's alpha = 0.89).

Medical tracking form - Medical data will be gathered through medical chart review and interview including comorbid and excluded medical conditions, medical information related to transplant, current prescription sleep-related and non-sleep-related medications, history of treatment with light therapy, and remaining exclusion criteria. During the final timepoint, research coordinators will check the participant's medical chart using the medical tracking form and enter updated relevant health information into a password protected file.

f) Specimen Banking

Urine Samples –

All 60 participants will be assessed using biological measures (via urine samples) at two points. Samples will be collected once during baseline 1 before their transplant admission and once during inpatient treatment (on Day Three of engraftment)..

Outpatient urinary samples will be collected at home by the participant, according to the provided timetable. Exact times will be noted on the samples in case of any variance in sample timing. Participants will be instructed to collect any void after 11pm up to 1st AM void overnight during the 72-hour span of wearing the actigraph and daysimeter at baseline, and then during hospitalization prior to discharge. Urinary sample containers will be provided by the study team. Collection time of samples will be written on the outside of the containers by participants. Samples will be refrigerated and mailed directly to RPI LRC Biomarker Lab for analysis using a pre-paid shipping label provided by RPI.

Biological samples collected in the hospital will be gathered according to regular BMT procedures by a registered nurse or physician, and processed as with at-home collections.

Blood samples –

Research related blood draws will be performed at four time points corresponding with routine clinical blood draws: First blood draw upon admission to the hospital, at the third day of engraftment (T3e, at the clinical visit about one month post-transplant (T4) and at the clinical visit about three months post-transplant (T5). Blood will be collected at MSH by a licensed phlebotomist. At each time point 16.7mL (approximately 3.5 teaspoons) will be collected in red top SST tubes, yellow top ACD tubes, and blue top Tempus tubes, delivered within 30 minutes, and processed immediately in the laboratories of Mount Sinai's Human Immune Monitoring Core Shared Resource Facility according to established blood processing protocols.

g) Data Management and Confidentiality

All data obtained will be placed into individual research participant folders and stored in a locked file cabinet in the department of Oncological Sciences. Only study personnel will have access to this file cabinet. All folders and data pertaining to individual subjects will be identified only by a code number and only the PI (Redd) and Co-investigator (Valdimarsdottir) the research coordinators will have access to electronic file that links the numbers to patient identities. Upon completion of the study, the file that links patients to the codes will be deleted.

Data sent between RPI, Mount Sinai, and the participants will be shipped via UPS. Patient names and dates of birth will not be included in mailed data to protect patient privacy. Mailed data will only be identified with study-ID numbers. RPI will be assessing melatonin levels, and will not receive any protected health information (PHI) other than the results of the biological assessments as well as assessments taken over the course of the study.

Data from any web-based assessment tools will be accessible to research study team using password protection and will only be identified by participant ID number. Paper files and printouts of assessment scores will be kept in a locked cabinet with access only by authorized project research staff. The use of email will be in accordance with MSH policy (i.e. secure email, obtaining consent from subject to send email, etc.).

Urine and blood samples will be marked only by study ID number and no other identifying information.

Data Analysis:

Descriptive statistics will be calculated both for the entire group and separately for each treatment group. T-tests and Fisher's exact tests will be used to assess group differences at baseline for possible confounders (i.e., demographic variables, clinical characteristics, and medications). Any variables showing differences between the two groups will be used as covariates in subsequent analyses. Since there is no known seasonality effect to measures of fatigue or to measures of sleep, which are our main outcome measures, seasonality will not be controlled in these analyses. For the primary outcome (Fatigue), the secondary outcomes (Depression, Sleep, Circadian Activity Rhythms, melatonin (exploratory), and Quality

of Life), hierarchical random effects linear mixed models will be employed for Aims 1 and 2 using MIXED with repeated measures. Besides time (linear and possibly quadratic trends to allow for possible nonlinear trends), any covariates identified in the preliminary analyses and intervention group will be assessed in a fixed effects model. Each model will also include a random intercept. Post-hoc comparisons will be Tukey-adjusted. Since there are multiple secondary outcomes, the p-values will be Sidak adjusted for correlated multiple comparisons. Any variations in length of hospital stay (i.e., length of intervention) will be used as a covariate in all analyses. This is highly unexpected since 90% of ASCT patients are hospitalized for 14 days. In the Analysis of Aim 2, we will establish that the treatment is a significant predictor of the primary outcome (CRF) as well as the hypothesized mediators. Next, we will first examine the role of each of the mediators of the effects of sPI on CRF by introducing each individually into the equation which contains the time variable, the treatment main effect, and the time by treatment interaction. Each mediator which is a significant predictor of CRF in this equation will then be combined with any other significant mediating predictor of CRF into a single equation. We predict the introduction of each significant mediator will result in the decrease in the significance of the time by treatment interaction effect on CRF. However, the more important test of the mediating role by any variable will depend on the statistical significance of the indirect path from treatment to mediator and from mediator to the outcome. Following procedures suggested by Shrout and Bolger (2002), 1000 bootstrap samples will be employed to determine the significance of each indirect path.[50] Power: It is difficult to discuss power for **Aim 1** and **Aim 2** since there is no directly relevant past research. As a consequence, one of the goals of this project is to obtain estimates of the effect sizes that will eventuate from our proposed analyses. Although unknown at the moment, these effect sizes can guide decisions regarding sample sizes for a larger scale grant. In the interim, there are three lines of research that may provide some guidance. The first involves the work of Ancoli-Israel, who investigated the effects of light treatment on fatigue experienced by women undergoing chemotherapy for breast cancer.[9] Using her results, we calculated power for a repeated measures design with an autoregressive lag 1 structure and autocorrelations ranging from 0.40 to 0.60. With alpha equal to 0.05 and a sample size of 30 patients per group, power ranged between 0.96 and 0.98. We followed a similar approach using Redd's results but focusing only on MM survivors of ASCT.[10] In this case, power was 0.99 for autocorrelations ranging between 0.40 and 0.60. However, the latter results must be treated cautiously because these calculations were based on a very small sample (N = 17 survivors). Using the same small sample, our repeated measures analysis of depression indicated that the time by treatment condition interaction was marginally significant (p = 0.0568). The F-ratio for this interaction yielded an eta coefficient of 0.48 which would be considered moderately strong following Cohen's criteria.[49] We hypothesize that the interaction effect would have been significant had the sample size been larger as is being proposed in this study (N = 60). Because of the very small survivors sample and the variability of our indicator of circadian activity rhythms (the f-statistic), the Mixed program did not converge and it was not possible to obtain a power estimate for this outcome. The third line of research that is germane to power in the proposed pilot study was conducted by Sim and Lewis who applied the UCL approach and found that a pilot sample of n => 55 would minimize the overall sample size for small to medium standardized effect sixes (0.2-0.6).

References:

· Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012; 65: 301–308.

· Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Julious SA, ed. *Statistical Methods in Medical Research*. 2016;25(3):1057-1073.

Urine samples will be analyzed for melatonin excretion by RPI according to their laboratory protocol. Blood Samples will be analyzed for a panel of inflammatory markers according to Mount Sinai's Human Immune Monitoring Core Shared Resource Facility protocols.

Data, Safety, and Monitoring Plan

The following plan addresses the four essential elements noted in NCI's 2001 outline: "Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute."

1. Monitoring the progress of trials and the safety of participants.

The proposed research is a low-risk behavioral trial. Study staff will be available to participants who have any difficulty with their equipment or any unexpected reaction during the intervention period. Study staff will be required to report all serious adverse events (SAEs) to the Mount Sinai IRB according to policies and procedures outlined by that body. Study staff members are also responsible to report all SAEs to the study PI as well. As per Icahn School of Medicine at Mount Sinai's IRB policies, the study PI is required to notify the IRB promptly of any unanticipated problems involving SAEs and risks to subjects or others that occur. The study staff PIs will monitor the progress of the trial and safety of participants on an ongoing basis. The procedures of this study will ensure discussion and reporting of all possible outcomes including adverse events. If the adverse event is due to the intervention and is unexpected, the PI will draft a safety report and send a copy to the Mount Sinai IRB. The IRB committee will serve as an objective review mechanism. This policy/procedure means that any potential conflict of interest inherent in the PI being the sole reviewer of SAEs is avoided.

We will use screening procedures from our prior grants to assess depression/suicidality. If risk of suicidality or severe depression is revealed, a licensed clinical psychologist in New York State, will contact the participants the same day, taking emergency steps and making referrals as needed.

2. Plans for assuring adherence with requirements regarding the reporting of adverse events (AEs).

All serious AEs (e.g., medical occurrences resulting in either hospitalization or death) that occur during the study defined by the given protocol, regardless of the relation to the research, must be reported to the IRB by telephone, e-mail or fax within 24 hours of the investigator's awareness of the occurrence of the

event. The PI will report SAEs to the Mount Sinai IRB and will disseminate information to other sites or agencies as necessary. These safety reports are a written account of an SAE determined by the PI to be both related to the psychological treatment under investigation and unexpected in nature. Serious AEs will be summarized annually in the IRB application for continuation or termination of research.

All expected non-serious AEs that occur at a greater frequency or severity than anticipated and all unexpected non-serious AEs will be reported to the Mount Sinai IRB within 15 working days of the PI becoming aware of the event. Adverse events that will be reported include suicidal ideation, which will be monitoring at each check-in. These AEs are also summarized annually in the IRB application for continuation or termination of the research.

3. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant.

The Director of the Grants and Contracts Office at Icahn School of Medicine at Mount Sinai will provide prompt written notification of any action resulting in a temporary or permanent suspension of this protocol to the NCI grant program director responsible for the grant.

4. Plans for assuring data accuracy and protocol adherence.

Data that will be collected from study participants will be in the form of self-report measures, actigraphy data, urine collection, and information from Daysimeter light monitors. These measures will generate information concerning: 1) fatigue; 2) sleep patterns; 3) depression; 4) biological mediators of the investigated symptoms; 6) general quality-of-life and information on common cancer treatment-related sequelae; and 5) socio-demographic and medical variables. The study PI and research team will assess data from sleep journals and Actigraphs as indicators of protocol adherence. The research team will have conference calls as stated above to monitor any adherence or accuracy problems that may arise in the course of the study. To ensure the validity and integrity of study data, a research coordinator will be blinded to the treatment assignment. The blinded research coordinator will oversee data management responsibilities (e.g., data entry and data checking) while the unblinded research coordinator will oversee the active and comparison light intervention. All research coordinators and Meschian will discuss data accuracy and management issues with the study PI. RAs will be in close communication with RPI investigators to ensure proper data analysis.

h) Provisions to Monitor the Data to Ensure the Safety of Subjects

The safety of subjects will be assured by constant monitoring of study protocols by:

MSH Principal Monitor, Study PI:
Last Name: Redd

First Name: William
Academic Title: Professor of Psychology
Department: Oncological Sciences
Mailing Address: [redacted], New York, NY 10029-6514
Phone: 212-659-5515
Fax: 212-849-2566
E-mail: William.redd@mssm.edu

MSH Additional Monitor, Team Members:
Last Name: Valdimarsdottir
First Name: Heiddis
Academic Title: Assistant Professor
Department: Oncological Sciences
Mailing Address: [redacted], New York, NY 10029-6514
Phone: 212-659-5579
Fax: 212-859-2566
E-mail: Heiddis.valdimarsdottir@mssm.edu

The proposed intervention is low-risk, and has been heavily informed by prior investigation by Dr. Redd and Valdimarsdottir . They are familiar with the intervention and its potential side effects, and will be able to provide consistent oversight of the project. Coherence of the collected data will be assessed on a yearly basis, while treatment compliance, adverse events, and patient expectancy/blinding will be assessed once every three months by Redd, Valdimarsdottir and research coordinators. They will inform and alter study methods based on this information. Data management is described in section h above. If the study is put on hold, IRB will be informed of the change in study timeline.

i) Withdrawal of Subjects

Patients will be allowed to withdraw from the research at any time. They will also be allowed to skip any questions or questionnaires.

6) Risks to Subjects

There always exists the potential for loss of private information; however, all possible precautions will be set in place in order to prevent loss of confidentiality. See section 5h.

Other risks or side effects may include:

- Headache
- Nausea

- If used incorrectly (e.g. such as staring directly into the light) it may cause eye discomfort or eye strain
  - **Likelihood of Harm**: There will be minimal risk to the participants. Light levels will be much lower than those experienced when subjects are outdoors during a bright sunny day. The subjects will not be exposed to ultraviolet radiation.
  - Light levels used in this experiment are lower than the levels produced by typical bright-light boxes (which is 10,000 lux) or produced at midday in a clear sunny day (about 100,000 lux). Using hazardous light exposure levels specified by the American Conference of Government Industrial Hygienists, one would need to be exposed to this light source for more than 10 hours continuously before it becomes a risk.
- Major research has not found increased risks of using light therapy for most major eye diseases. However, in the unlikely event the participant feels that the light is affecting their eyes or vision, they will be advised to contact the research team immediately.
- Previous research suggests that light therapy can improve the effectiveness of some antidepressant drugs. No evidence to date suggests that it decreases the effectiveness. If the participant is concerned about this, they will be advised to consult their physician.
- Completing questionnaires during the study may cause some distress or discomfort, however, past research has shown that such distress is usually minimal and transient.
- Wearing the light monitor (Daysimeter) and/or activity monitor (Actigraph) may cause discomfort. If this discomfort is unmanageable, the participant will be asked to report such discomfort to the research coordinator.
- Risks associated with blood draws: There is a minimal risk of pain, bruising, swelling, dizziness, or infection when blood is drawn from your arm. Some people feel dizzy or may faint during or after a blood draw. To minimize risk, blood for research purposes will only be drawn at the same time as routine clinical blood draws.

7) Provisions for Research Related Harm/Injury

The proposed project is a low-risk behavioral study. We will inform participants during the consent process that there is a chance that they will experience potential side effects of light therapy, e.g., sleep disturbance, headache, eyestrain, nausea, and hyperactivity, and in very rare instances, photic maculopathy, photophobia, hypomania, and suicidal ideation/suicide attempts have occurred (in those with pre-existing severe depression). They will be informed that such side effects are usually minimal if the light is positioned correctly and when they do occur, resolve within a few days. During the course of the protocol, if after 3 days the side effects persist, we will withdraw them from the study. Additionally, their care provider at the BMT clinic will be notified and refer the patient to a specialist if necessary. We will also follow up with those who discontinue the study due to side-effects and refer them to their care provider should symptoms persist even after discontinuation of the light exposure. Medical concerns will be billed according to other procedures occurring during hospitalization, since this is an inpatient study.

We will also inform patients during the consent process that there is a chance participants will feel some distress or discomfort as a result of answering some questions asked during the study or completing the neuropsychological assessment. Participants will be assured that they can refuse to answer any questions or withdraw from the study at any time without penalty. Participants' psychological symptoms will be monitored throughout the study. If any participant expresses severe suicidal ideation, evidences acute or emergency psychiatric symptoms, or asks for psychiatric care, a referral will be made. The RA will be trained to identify participants who may be experiencing such problems and discuss them with Meschian (a Ph.D.-level licensed clinical psychologist). The PI will be notified of any adverse participant reaction and psychiatric referral will be made, if necessary. If additional psychiatric care is warranted, participation in the study will be discontinued. Any participants presenting with physical complaints will be referred to their oncologist for evaluation so that the oncologist can rule out organic causes and/or make additional referrals, if needed. Participants who are assessed as having significant cognitive impairment and significant sleep dysfunction will also be referred to their oncologist for evaluation.

8) Potential Benefits to Subjects

Subjects may feel less fatigued after their transplant by undergoing daily sPI as a feature of their inpatient treatment. Subject fatigue may return after they stop sPI at the time of their medical discharge.

9) Provisions to Protect the Privacy Interests of Subjects

All study data collected will be also stored electronically. The data will be stored on a MSH network drive, accessible only to the PI and members of the research team. The data will be password protected. During data summarization and analysis, individual participants will be identified by code number only. No data identifying individual participants will be published or disclosed to third parties without prior consent of the participant. A list matching names with code numbers will be kept in a separate computer file and folder from the one where the data is stored.

If a participant agrees to participate in the study, all questionnaires will be labeled with the participants' study ID number, not their name and not their medical record number. Subjects will be informed that they can choose to not answer any questions that make them feel uncomfortable. Subjects will need to give study personnel their home addresses to which the study materials and questionnaires can be sent. This data will be kept private on the MSH network drive in a password protected spreadsheet. Subjects will mail back all study materials in a pre-paid envelope with an ID number and an MSH address as the return address.

Participants will provide the study team with a telephone number on which we can call them to administer questionnaires and help with any issues. If we need to leave a message, we will ensure that no confidential information or any information about the patient's study participation is revealed.

Subjects can withdraw from the study at any time or not answer questions they do not wish to address.

10) Economic Impact on Subjects

We do not expect the subjects to incur any foreseeable costs through their participation in our study. We will be shipping all relevant study materials to each subject's home at our expense. Lights, actigraphs, and daysimeters will be provided to clients at no cost during the study. Blood draws at Mount Sinai will be scheduled on days of routine clinical visits, eliminating any additional transportation or cost to the subject.

11) Payments to Subjects

Study participants will receive a $25 reimbursement for each time-point (study is divided into five time points – baseline 1, baseline 2, hospital stay, 1-month post and 3-months post). For a participant who completes the entire study this will come to a total of $125 paid in two check installments of $50 (or $75 for the first installment if baseline 2 administered). This payment plan was established because subjects will not need to come into Mount Sinai specifically for the research study. Therefore, it will be more practical to request and send participants two checks, rather than five/six different checks throughout the duration of the study.

12) Consent Process

Informed consent will be obtained from participants in person before the collection of any data - Eligible patients will be contacted during their initial HSCT consult visit (time to transplant varies between patients) to MSH and given information on the study. The study coordinator will then administer the informed consent process. The RC will: describe the study, give the subject's time to read the consent form, allow the subjects to discuss their decision with whomever they like, allow the subjects to digest the information, and allow the patients to ask the member of the study team any additional questions they might have.

All consented participants will be informed about study procedures, extent of participation, and potential risks and that their participation is voluntary and will not jeopardize their relationship and participation in any activity they conduct or care that they receive at MSH. Participants will also be provided with a telephone number where they can call if they have any questions or concerns about the study or the consent form.

13) Process to Document Consent in Writing

We will be asking participants to sign the standard PPHS consent template.

14) Vulnerable Populations

Indicate specifically whether you will include (target) or exclude each of the following populations:

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g. infants, children, teenagers)
	X	Wards of the State (e.g. foster children)
	X	Pregnant women
	X	Prisoners

15) Multi-Site Human Research (Coordinating Center)

All information will be stored and managed by Redd at MSH. Actigraphs, Daysimeters, sampling materials, and questionnaires will be mailed between the participants and the study team at MSH. No identifying information will be included on the equipment and questionnaires will only include code numbers. MSH will send RPI the Actigraph and Daysimeter data via secure email. Blood samples will be analyzed at Mount Sinai's Human Immune Monitoring Core Shared Resource Facility. Urine samples will be analyzed at the laboratory at RPI LRC. Samples will only be identified by participants' study-ID numbers.

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

If patients request information about the study results (i.e., whether light exposure was clinically effective in reducing cancer related fatigue), we will provide them with a copy of the publication that details the results.

18) External IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Devices will be mailed to and from subjects via UPS. They are water resistant, and require no special care or attention from participants.