PROTOCOL TITLE:

Treating cognitive impairments in cancer patients via systematic light exposure: The "Light for the Brain" study

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1.0 Objectives

1.1 Specific Aims

- Aim 1: Determine the feasibility (e.g., recruitment, level of participation) and acceptability (treatment satisfaction) of bright white light (BWL) as an intervention for cancer-related cognitive impairments (CRCI) in autologous and allogeneic hematopoietic stem cell transplant (HSCT) survivors.
- Aim 2: Assess the preliminary efficacy of BWL compared to dim red light (DRL) on cognitive functioning in preparation for a large-scale randomized controlled trial.
- Exploratory Aim 1: Investigate the possible mediating effect of circadian activity rhythms (CARs) and sleep quality on cognitive functioning.
- Exploratory Aim 2: Explore a) whether BWL compared with DRL affects biological (inflammatory immune response) variables; and b) whether the effects of BWL compared to DRL on cognitive functioning are mediated by biological factors (i.e., inflammatory immune response).

1.2 Hypotheses

- Hypothesis 1: BWL treatment will be feasible and acceptable in autologous and allogeneic HSCT survivors.
- Hypothesis 2: Auto-HSCT and allo-HSCT survivors receiving BWL will have greater improvement in cognitive functioning than those receiving DRL.
- Hypothesis 3: The relationship between BWL and CRCI will be mediated by CAR and sleep.

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge.

Cancer-related cognitive impairment (CRCI) due to cancer and/or its treatment has been well-documented.[24, 25] Hematopoietic stem cell transplant (HSCT) patients often experience CRCI before and after completion of transplantation.[10-14, 16, 26] This pattern of CRCI is not surprising because, in addition to aggressive treatment during the transplantation regimen, many patients undergo radiation, chemotherapy, or biologic therapies prior to their transplant. Such therapies have been linked to neurological changes in the brain, including white matter abnormalities, atrophy, and electroencephalogram abnormalities.[27, 28] Immediately after HSCT, there is generalized decline in cognitive functioning with subsequent recovery for most survivors by one year post-transplant. However, recovery does not mean a return to "normal." Between 15 and 32% of these individuals demonstrate CRCI prior to transplant.[15] Additionally, 54% of patients not impaired before transplant have impairments at one year post-HSCT,[15] and 41.5% experience cognitive impairments 5 years post-HSCT, particularly in motor coordination, speed, and memory.[10] In a recent review and meta-analysis of changes in cognition in HSCT patients, 12 to 89% experienced deficits before HSCT and such symptoms were likely to persist post-HSCT.[29] In another recent study of autologous HSCT patients, nearly half showed impairments in learning/memory or executive function after induction therapy. Although the impact of CRCI on

quality of life can be significant,[17] there is a dearth of research on interventions to treat CRCI.[18, 19]

2.2 Relevant preliminary data

The proposed exploratory study builds on Wu's work with her mentors. Redd and colleagues' investigated BWL to treat cancer-related fatigue in cancer survivors (including HSCT). From that study, Wu initiated a pilot study in preparation for this application which parallels the design of the proposed study. To date, 14 patients have been randomized so far (BWL condition, n=7; DRL condition, n=7). 10 potentially eligible participants (71%) agreed to participate suggesting that patients are highly amenable to participation in this protocol. Ancoli-Israel's work also supports the proposed study. She and her colleagues conducted preliminary research to examine the effects of BWL on cognitive functioning in breast cancer patients undergoing chemotherapy (as part of a larger-scale study to investigate BWL to control cancer-related fatigue).[36] Ten patients were assigned to either BWL or DRL delivered via a commercially available light box (Litebook®, Ltd., Medicine Hat, Canada). A standard neuropsychological test battery (i.e., attention/working memory, psychomotor/processing speed, auditory and visual memory, and executive function) was used to measure cognitive functioning prior to chemotherapy and at the end of Cycle 4 of chemotherapy. Data suggested an improvement in overall cognitive functioning in the BWL group but no change in the DRL group *(a between-group difference of 0.33 standard deviations).* These results highlight the broad impact of light on cognition. Ancoli-Israel's work supports the proposed study in five ways as it: 1) provides the conceptual rationale for the proposal; 2) demonstrates the overall clinical importance of investigating BWL for the treatment of CRCI; 2) establishes the acceptability of BWL by another population of cancer patients; 3) demonstrates the overall feasibility of BWL intervention with another cancer population as patients were: a) able to implement the BWL intervention with minimal involvement by research staff, b) adherent to the CRCI home-based treatment regimen, and c) able to successfully complete all study assessments; 4) confirms the use of DRL as an appropriate comparison condition; and 5) provides clear procedural guidelines for the proposed study.

2.3 Significance of the research

Systematic Bright White Light Exposure

One novel non-pharmacologic approach for treating CRCI may be systematic bright white light (BWL) exposure. Bright light has been used to reduce depression, fatigue, and sleep disorders in other groups (e.g., seasonal affective disorder, breast cancer, traumatic brain injury)[33,34-36] and has been found to have beneficial effects on cognitive functions in non-cancer populations.[37-43] Indeed, a recent Nature Reviews article highlighted the important influence of ambient and systematic light on cognitive functioning.[1] It has yet to be tested for the treatment of CRCI. See Figure 1 for hypothesized direct and indirect impact of BWL on cognition.

Direct Effect of Light on Cognition: Light affects cognition directly through a non-image forming (retinal photoreceptor) system.[22] Neuroimaging research shows that light can modulate a) subcortical structures related to alertness, b) limbic areas related to mood and memory, and c) cortical areas related to higher level cognition.[22, 23] In other words, light impacts brain structures that are responsible for low- to high-level cognitive functions – from basic attention to executive functioning. Indeed, research shows that bright light exposure exerts beneficial effects on cognition.[37-43] Light exposure research has been undertaken in healthy populations and clinical

populations with cognitive deficits similar to those found in cancer patients. In one study, healthy participants given increased light exposure exhibited greater improvements in cognition (alertness, psychomotor vigilance, or neuropsychological test performance) than those in a dim light therapy comparison group or matched control group.[37-41] Bright light exposure studies in dementia patients has shown that patients exposed to bright light showed improvements in cognition but not when exposed to dim light.[42,43] However, the quality of this research has been marred by small sample sizes[44] and the use of a gross screening measure (i.e., Mini-Mental State Examination scores). Promising research has been undertaken in patients with mild brain injury with the range and severity of cognitive impairments more similar to that of HSCT survivors. Preliminary data from 18 participants indicated that 30 minutes of increased light exposure each morning for 6 weeks resulted in marked improvement in cognitive functioning (i.e., attention, processing speed, memory, and executive functioning). In addition, daytime sleepiness decreased and mood improved (all $p<.05$).[33] These studies suggest that bright light exposure may improve cognitive functioning in lower-level (e.g., attention) to higher-level domains (e.g., memory). Given that CRCI in HSCT patients also affects lower-level to higher-level skills, BWL may be an effective cognitive intervention for HSCT patients. In cancer patients, BWL has also shown promise in treating CRCI. Co-mentor Ancoli-Israel and colleagues pilot-tested a BWL regimen with breast cancer patients undergoing chemotherapy. Ten patients were randomized to BWL or a comparison DRL condition. Overall cognitive functioning and CAR improved in the BWL group only (see C.1. Preliminary Research). The results in this area of research are preliminary, underscoring the need for an examination of bright light exposure as a treatment for cognitive impairment. Individuals with CRCI represent a worthy target for this examination due to the broad nature of their deficits and their tendency to also suffer from sleep problems and fatigue (discussed below), thus, making them more amenable to this form of intervention.

Indirect Effects of Light on Cognition: Light may also affect cognition indirectly through several mechanisms that have been proposed to contribute to CRCI. An examination of all of the possible mechanisms is beyond the scope of this proposal. Mechanisms to be examined in this proposal are discussed below.

Psychological correlates of CRCI: Fatigue is a potential psychological correlate of CRCI and mechanism through which light affects cognition. While it is well-established that fatigue is related to cognitive functioning in both healthy and non-cancer populations,[51, 51-53] the few studies with cancer patients have yielded no association.[54,55] Our pilot work indicates BWL may reduce fatigue in cancer patients[36] raising the possibility that BWL affects CRCI via its effects on fatigue. Depressed mood is also a potential psychological correlate of CRCI and mechanism through which light affects cognition. Depressed mood is a well-established correlate of cognitive impairment in non-cancer populations,[45-47] but the few existing studies in cancer populations have yielded mixed findings.[48-50] Our pilot work indicates BWL reduces depressed mood in cancer patients (see C.1. Preliminary Studies) raising the possibility that BWL may affect CRCI via its effects on depressed mood.

Circadian Activity Rhythms (Chronobiological Variable) and Sleep: Another proposed mechanism is circadian activity rhythms (CARs). CARs serve the function of preparing the body and mind for restful sleep at some times of the day and for active wakefulness at others.[56] CARs are biological cycles that are slightly longer than 24 hours and are entrained to the 24 hour day by environmental Zeitgebers (time cue) such as bright light.[57]Several studies have observed dysfunction in CARs among cancer patients.[58-60] For example, Ancoli-Israel (co-mentor) and

colleagues showed that CAR variables including amplitude, mesor, and rhythmicity were significantly impaired during the course of chemotherapy in breast cancer patients.[61] Sleep is another proposed mechanism as sleep problems are often reported by HSCT patients.[62] Dysfunction of CARs and sleep affects several psychological and physiological processes[63] including multiple domains of cognitive functioning.[64-68] Effects on cognition range from low- to high-level functions including attention, working memory, motor, verbal functions, and executive functions – areas also affected in many HSCT patients. BWL has been found by co-mentors and others to improve CARs and sleep,[33, 69, 36, 70, 71] including in cancer patients.[71] By extension, BWL may improve cognitive functioning through its effects on sleep and CARs.[39]

Inflammatory Immune Response (Biological Variable): Another proposed mechanism is the inflammatory immune response. Evidence suggests that inflammatory mechanisms within the central nervous system contribute to cognitive impairment (including CRCI) via cytokine-mediated interactions between neurons and glial cells.[7273] Cytokines play an important role in normal central nervous system functioning[72] including modulation of neuronal and glial cell function; neural repair; and impact the metabolism of neurotransmitters important for cognitive functioning.[74] Despite the blood-brain barrier's protective mechanism, there is significant communication between peripheral cytokines and cytokines in the brain.[72] Certain cytokine levels are likely to be elevated in patients prior to and after autologous HSCT and are thought to be related to the cancer itself and/or tissue damage from conditioning therapy.[75-77] It is likely that excessive cancer- and treatment-derived inflammation leads to cognitive impairment via effects on central nervous system pathways and dysregulation of the hypothalamic-pituitary axis (HPA).[78] Connections between peripheral cytokine activation and cognitive function have been shown in animal and human studies of inflammatory cytokine activation.[54, 79-81] One animal study found that mice who received an injection of a cytokine-producing substance exhibited working memory impairment but mice with interleukin (IL)-6 knocked out did not exhibit impairment.[81] Additionally, IL-1β, IL-6, and tumor necrosis factor (TNF)-α are reported to induce synthesis of C-reactive protein (CRP)[82] that has been associated with cognitive impairment.[83] IL-10 has also been found to be critical for maintaining normal neuroimmune communication during infection thus protecting hippocampal-dependent working memory.[84] A study of healthy young men with low-grade inflammation induced by administration of an endotoxin showed a negative association between circulating IL-6 and memory functions.[85] Among cancer patients, one study showed that a significant proportion of acute myelogenous leukemia and myelodysplastic syndrome patients had impaired cognitive function prior to chemotherapy treatment.[54] IL-1, IL-1 receptor antagonist (IL1RA), IL-6, IL-8, and TNF-α levels were elevated compared with laboratory normative controls and elevated IL-1 was associated with poorer executive function. In a study of post-chemotherapy treated breast cancer patients, higher soluble receptors for tumor necrosis factor type II (sTNF-RII) levels were associated with increased memory complaints and this relationship was evident longitudinally.[86] In summary, animal and human studies highlight the importance of the inflammatory immune response as a potential mechanism that underlies cognitive changes in cancer patients, particularly with respect to IL-1RA, sTNF-RII (surrogate markers for IL-1 and TNF- α activity that are likely to be measurable in HSCT patients), IL-6, IL-8, IL-10, and CRP levels. BWL has been found to normalize HPA axis function[87] raising the possibility that BWL may affect cognitive functioning via proinflammatory cytokine activity's normalizing effects on the HPA axis.

Summary: CRCI is a major clinical problem affecting a significant proportion of HSCT survivors.[10, 15] This study will examine the effects of BWL on CRCI in autologous and

allogeneic HSCT patients – an intervention associated with improved cognitive functioning[42, 43] (Ancoli-Israel's pilot work). HSCT patients with CRCI are a worthy target for this intervention due to the broad nature of their deficits and tendency to also have sleep problems and fatigue.

3.0 Inclusion and Exclusion Criteria

3.1 How individuals will be screened for eligibility

The first part of the screening interview can be conducted by phone and internet. It includes questions based on inclusion/exclusion criteria. Participants who meet criteria for entry into the study will be randomly assigned to BWL or DRL. Participants who are ineligible or decline participation will be thanked for their time and informed that they have completed the study.

3.2 Criteria that define who will be included or excluded in final study sample

Eighty autologous and allogeneic HSCT survivors will be recruited at Northwestern University, Feinberg School of Medicine, Department of Medical Social Sciences from Northwestern Memorial Hospital (NMH) and Robert H. Lurie Comprehensive Cancer Center (RHLCCC).

In order to qualify for participation in the study, potential participants must meet the following eligibility inclusion criteria:

1. Have a history of autologous or allogeneic HSCT,
2. Be in at least partial remission and not on active treatment (maintenance chemotherapy is ok),
3. Have less than severe graft-versus-host-disease (GVHD)
4. 1 to 5 years post-HSCT,
5. Age 21 or older,
6. English language proficient
7. Able to provide informed consent
8. Endorse subjective cognitive impairment.

Potential participants will not be allowed to participate in the study if they meet any of the following exclusion criteria:

1. Being treated for, or been diagnosed with or suspected neurological, psychiatric (including bipolar disorder or mania), or medical condition that might impair cognitive functioning (other than those caused by the cancer or its treatment),
2. Visual, hearing, or physical impairment sufficient to interfere with cognitive testing or participation,
3. Have a history of whole brain irradiation or surgery,
4. Active diagnosis of autoimmune and/or inflammatory disorder or disorders that may influence immune processes,
5. Have a history of severe graft-versus-host-disease
6. History of systematic light exposure treatment,
7. Diagnosed sleep apnea or narcolepsy,
8. Use of photosensitizing medications (including antibiotics that render participants photo-sensitive),
9. Plan to travel across meridians during the study,
10. Work night, early morning, or swing shifts,

11. Adults unable to consent, individuals who are not yet adults, pregnant women and prisoners will be excluded from the study.
12. History of eye disease including, but not limited to, macular degeneration.
13. Undergone laser corrective eye surgery in the past 30 days.

The excluded conditions have been chosen due to their known impact on cognitive function, the biomarkers to be studied, or are contraindications for light treatment.

4.0 Study-Wide Number of Subjects

Eighty autologous and allogeneic HSCT survivors will be recruited at Northwestern University, Feinberg School of Medicine, Department of Medical Social Sciences from Northwestern Memorial Hospital (NMH) and Robert H. Lurie Comprehensive Cancer Center (RHLCCC).

5.0 Study Timelines

5.1 The duration of an individual subject's participation in the study is 13 to 15 weeks depending on how quickly they send back the equipment. The duration anticipated to enroll all study subjects is 4 years. The estimated date for the investigators to complete this study's primary analyses is 5 years.

6.0 Study Endpoints

6.1 The primary endpoints in the proposed study are: 1) the level of cognitive functioning (as measured by the neuropsychological tests and self-reported cognitive functioning using the PAOFI.)

Secondary endpoints are: 1) Circadian activity rhythms using an actigraph (a small device similar in size to a watch that measures sleep and wake activity); 2) The Pittsburgh Sleep Quality Index; 3) the FACIT Fatigue Scale; 4) Quality of Life measured by the SF-36 scale; 5) a Credibility/Expectancy Questionnaire; 6) levels of Inflammatory Immune Markers; 7) the amount of time that the light boxes are used; 8) treatment satisfaction using the FACIT-TS-G scale; 9) depressed mood as measured by the CES-D; and 10) neurobehavioral functioning as measured by the Frontal Systems Behavior Scale.

6.2 With regard to safety endpoints, there are no known risks associated with the use of the light boxes in the treatment of cognitive impairments. However, we will monitor those who decide to cease treatment because they find the treatment approach unacceptable along with their concerns regarding treatment.

7.0 Procedures Involved*

7.1.1 Description of research procedures

Approach: We will explore the acceptability, feasibility, and potential efficacy of BWL exposure to treat CRCI in survivors of autologous or allogeneic HSCT. The proposed approach will be informed by procedures Ancoli-Israel developed for her recent research on BWL treatment of CRF in breast cancer patients undergoing chemotherapy. We will recruit study participants and oversee use of the light boxes, monitoring equipment, assessment scales, and enter adherence and actigraph data. We will also determine the feasibility of assessing levels of inflammatory immune markers (i.e., Interleukin-1 receptor agonist [IL-1ra], interleukin-6 [IL-6], interleukin-8 [IL-8], interleukin-10 [IL-10], soluble tumor necrosis factor receptor type II [sTNF-RII], soluble intercellular

adhesion molecule-1 [sICAM-1], C-reactive protein [CRP], peripheral blood mononuclear cells [PBMCs], and intracellular RNA) as mediators of the clinical impact on cognitive functioning.

Methods: Potential participants will be identified via the Northwestern University Enterprise Data Warehouse service (EDW) and available transplant database from the transplant team after providing them with a list of inclusion and exclusion criteria for the study. The IRB number for that protocol is STU00012731. A query of eligible patients and their physicians will then be created for the research staff. The research study staff will also review their EMR to ensure initial eligibility. The study team member will then contact the treating physicians to request permission to contact their patient(s) about the study. An attempt will be made, via an email sent by the study team member to the physician on in-person, to request permission to contact their patient(s). If the physician authorizes contact be made, research staff will contact the patient to gauge whether or not they are interested in participating in the study. Following physician approval, initial contact will be made with the patient (potential participant) either in-person at their next clinic appointment, or (e)mailed a recruitment letter with a study brochure attached (if their next clinic appointment is over a month away). For in-person recruitment, the study team member will approach patients at their next medical appointment at Northwestern Medicine (identified by the medical database). For letter recruitment, the study team member will inform them that a) they will be contacted in the near future about a research study and b) instructions on what to do if they do not wish to be contacted further. Those potential participants who do not opt-out of further contact will be contacted by the research study staff via preferred method as indicated in their EMR (via telephone, mail, etc.)

We will also use a community recruitment method. For this method, participants will be recruited through:

1) HCST and hematological malignancy groups - We will obtain permission from support group facilitators and advocacy organizations to have members of our study team (PI and/or research staff member) to attend and/or disseminate information about the study (flyers and brochures)
2) Online listservs and websites for patient advocacy – After obtaining permission as necessary, we will post information about the study to these online listservs and websites (flyers)
3) Local oncologists who think their patients might be interested in participating in the study – We will approach local oncologists and request permission to disseminate and/or post information about the study (flyers and brochures).

The study team member will then contact patients who express interest in the study or respond to recruitment solicitations.

The study team member can then describe the study (either in-person or by phone) to determine their interest in participating. Consent can be obtained either in-person or by phone and the screening scheduled. Participants who self-refer (i.e. contact study staff directly after learning about the project through a support group, their oncologist, or another source) will also undergo the Northwestern University verbal consent via phone call.

After obtaining consent, the screening interview will be undertaken which includes the completion of questionnaires based on inclusion/exclusion criteria as listed in Section 3.0.

If the patient decides not to participate in the study, the research assistant will ask if he/she will complete the refusal questionnaire consisting of their age, ethnicity, type of transplant, time since transplant and time since diagnosis. The information collected by the refusal questionnaire will help inform the study team on what kinds of barriers to participation potential participants may have. If a patient does not want to fill out the refusal questionnaire, they will not be required to and will be thanked for their time. The suicidality protocol will be in place throughout the entire study (see Section 9.1.2).

Those who are screened to meet inclusion criteria will be invited to participate in the main intervention study. At their first appointment (described below), the study team member will take the participant through the written consent form which also requires HIPAA approval permitting access to their medical records. Participants who self-refer (i.e. contact study staff directly after learning about the project through a support group, their oncologist, or another source), will undergo the written consent/HIPAA approval process at Northwestern University, and will also sign a Northwestern University consent form. They will be provided a release of information form to provide study staff permission to contact their physician(s) for information in his/her medical records. Participants will be randomly assigned to BWL or DRL. Participants in both intervention arms will be assessed one week before the intervention (baseline), during the intervention (2 weeks into the intervention), at the end of the intervention (during the fourth week), and two months post-intervention at Northwestern Medicine.

Time 1 Assessment

Participants will answer interview questions about their background, complete questionnaires via RedCap, have blood drawn by a trained phlebotomist, and undertake a brief neuropsychological assessment. Participants will have the choice to complete questionnaires from home via RedCap prior to their visit via a link that will be sent to them by email. Actigraphy measurement will occur following the neuropsychological assessment and completion of questionnaires. It requires the participant to wear the actigraph for 7 consecutive days and complete a sleep log on which they will record time to bed, time awake and other information to be used in editing and scoring the data.

Description of Light Treatment (including Litebook)

Following the Time 1 assessment, participants will be instructed to self-administer light treatment for 30 minutes every morning for 4 weeks. Participants will be informed that "The Litebook is a compact portable lamp (approximately 5" x 5" x 1") and weighs less than a pound. It is very easy to use. The Litebook is directed toward the eyes for 30 minutes each morning in order to trigger light receptors in the retina to trigger a cascade of messages throughout the body. It is powered by a rechargeable lithium-ION battery which we provide and can also be connected to a power source." As indicated in the consent form, participants will be told that they will receive one of two different light boxes of different wavelengths that are being tested (i.e., the same light box but with different bulbs to emit different wavelengths). The 30 minute dose is used in the treatment of seasonal affective disorder and has been shown to have a low risk of side-effects. For participants who require assistance, we will work with a caregiver to ensure correct actigraph and light box

use. The assessment schedule and data analytic plan will allow us to address the Specific Aims. To increase the likelihood of adherence, email reminders will be sent to participants to use the light boxes and complete sleep and Litebook logs.

Litebook devices can only emit one wavelength – either BWL or DRL – but they are identical in all other ways. BWL Litebook emits approximately 1000 lux and the DRL Litebook emits < 50 lux. Safety precautions are the same for both as indicated by the research outlined below.

Use of Litebook in Previous Research

Redd and colleagues' (2014) investigated BWL to treat cancer-related fatigue in cancer survivors (including HSCT) using the same Litebooks for the current study. BWL was found to be more effective in reducing cancer-related fatigue than DRL. There were no safety concerns nor adverse events. This study was approved by Mount Sinai's IRB in 2011.

Wu and colleagues have also been undertaking a parallel study at Icahn School of Medicine at Mount Sinai (ongoing National Cancer Institute funded R21 study) also examining cognitive functioning in HSCT survivors but using a different measure of cognition (an online assessment). The same Litebooks have been used. Mount Sinai's IRB has approved this research continuously since August 2014. There have been no safety concerns.

Ancoli-Israel's pilot work that predated Redd and colleagues' study mentioned above (approved by University of California San Diego IRB) with breast cancer patients and cancer-related fatigue (with a secondary outcome of cognition) also used the same protocol comparing BWL with DRL using the same Litebooks as the current study. Again, there were no safety concerns in that study.

Indeed the use of light boxes with these wavelengths (both bright white light and dim red light) in research to treat depression, fatigue, sleep disorder, and cognition have existed for decades (e.g., Kripke, Risch, & Janowsky, 1983; Kripke, Mullaney, Klauber, Risch, & Gillin, 1992; Friedman, Spira, Hernandez, Mather, Sheikh, Ancoli-Israel,….& Zeitzer, 2012) with no safety concerns mentioned.

Nevertheless, we have included in the consent form and exclusion criteria information about possible risks/side-effects associated with the use of the Litebooks as extracted from the manufacturer's pamphlet and from research of which we are already aware.

Time 2 Assessment

Time 2 (end of the second week) – During the second week of the light treatment, the participant will complete questionnaires via RedCap.

Time 3 Assessment

Time 3 (end of the fourth week) – During the fourth week of the light treatment, the participant will be asked to wear the actigraph again for 7 days and complete sleep logs. Then the participant will be asked to come in to Northwestern Medicine again and bring the actigraph, sleep logs and Litebook with them. Prior or during the Time 2 visit, they can complete questionnaires via RedCap.

Then they will be asked to answer interview questions to get an update on their medical status, complete the neuropsychological assessment, and blood samples will be collected again.

Time 4 Assessment

Time 4 (8 weeks after the intervention) – The study team will send the actigraph and sleep logs to participants again 7 weeks after the intervention. During the eighth week after the intervention, the participant will be asked to wear the actigraph again for 7 days and complete sleep logs. Then the participant will be asked to come in to Northwestern Medicine again to complete the same procedures as at Time 2, except their blood will not be drawn at this appointment.

Note that the neuropsychological testing portion of each assessment will be audio recorded with the permission of the participant to optimize scoring accuracy by the study team. Participants can still participate in the study even if they choose not to be recorded.

Data about subjects will be collected from medical charts, interview questions, questionnaires that the participants will be administered in-person and via online portal (RedCap), output from the equipment (i.e., actigraph data), and blood samples. All questionnaire data collected through RedCap will be coded to each subject's unique study ID. RedCap will not collect any identifiable information and will not log the participants' IP addresses. Neuropsychological testing will be audio-recorded when permission is given by the participant, and those audio files will also be coded to each subject's unique study ID.

Subjects who wish to receive feedback about their neuropsychological test scores may receive a debriefing from the PI at the end of their participation upon request.

7.1.2 Procedures to monitor subjects for safety or minimize risks

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 unanticipated events to the Northwestern University's IRB within 24 hours of knowledge or notification. All reportable new information will be reported to Northwestern University's IRB within 5 business days of knowledge or notification. Study staff members are also responsible to report all such events to the study PI as well. The study staff 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 unanticipated 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 Northwestern University's 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 these events is avoided.

We will use screening procedures to assess depression/suicidality. If risk of suicidality or severe depression is revealed, the PI will contact the participant the same day, taking emergency steps and making referrals as needed.

7.2.1 Procedures performed to lessen the probability or magnitude of risks

Please see the Data Safety and Monitoring Plan in Section 10.0 for procedures taken to lessen the probability or magnitude of risks.

7.2.2 Source records used to collect data about subjects.

Data about subjects will be collected from medical charts, interview questions, questionnaires, blood samples, and output from the equipment (i.e., actigraph data and integrated meter data from the light boxes). Questionnaires will be administered in person and via an online portal (RedCap).

Participants who self-refer will be provided a release of information to access their medical chart from other institutions.

All data collected through RedCap will be coded to each subject's unique study ID. Any identifiable information will be coded in RedCap as an "identifier." This allows the study team to export ONLY deidentified data, whilst preserving the ability to run the study effectively (i.e., being able to access participant contact information and recording study-related communications). Redcap will not log the participants' IP addresses. Surveys, scripts and data collection forms are attached.

7.3 Data to be collected

Measures

1) **Background Information (Screening and Time 1):** Sociodemographic data regarding gender, age, ethnicity, religion, income, marital status, employment status as well as questions about inclusion/exclusion criteria will be gathered during the screening assessment and any changes in information will be gathered at subsequent assessments. 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. The Self-administered Comorbidity Questionnaire will be used to capture comorbid conditions and the Valdimarsdottir Infection Scale will be used to capture recent infections. Recent Changes in Care will be evaluated by asking questions about any changes in medical treatment in Times 2 and 3 assessment time points.
2) **Active Psychosis (Screening):** The 6-item Paranoia/Psychoticism Screener (PPS) based on the "Psychotic Symptoms" module of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)[45] that has good discriminant validity will be used to exclude participants with active psychosis.
3) **Suicidality (Screening):** Participants will be asked questions regarding suicidal ideation, including one item from the Brief Symptom Inventory (BSI),[46] "Over the last week, have you had thoughts of ending your life" that will be used to screen for active suicidal ideation. Additional questions will be asked to assess for active suicidality. Those who are actively suicidal will be referred for further assessment and treatment, and their physician and/or a psychosocial staff member will be contacted. The PI will also follow up with the participant.
4) **Substance Abuse (Screening):** Current substance abuse (not including tobacco use) will be assessed by combining the 4-item Rapid Alcohol Problems Screen (RAPS-4)[47] with the Two-Item Conjoint Screening (TICS)[48]. Questions endorsed will be followed up with additional questions to determine alcohol or drug abuse/dependence. Both measures have good sensitivity and specificity.[47, 48] Participants determined to have probable current substance abuse disorder will be ineligible for the study and referred for further assessment and treatment.
5) **Cognitive Screening (Screening):** Participants will be asked whether they have concerns about their cognition by asking a question derived from the two cognitive questions on the

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30).

6) **Neuropsychologically-assessed Cognitive Functioning (Times 1, 3, and 4)**: Standardized neuropsychological tests will be used to evaluate multiple cognitive domains. They include all of the tests recommended by the International Cognition and Cancer Taskforce in their Lancet article[6]chosen due to their frequent use in CRCI assessment and appropriateness for repeat assessments over time: a) Premorbid Intellectual Function will be assessed using the Wechsler Test of Adult Reading and the Vocabulary subtest of the Wechsler Adult Intelligence Scale - 4th Ed. (WAIS-IV) at Baseline only; b) Psychomotor vigilance will be assessed with the Psychomotor Vigiliance Task; c) Attention will be assessed with the Digit Span subtest of the WAIS-IV;[99] d) Visual motor performance will be assessed with the Grooved Pegboard Test and Block Design subtest of the WAIS-IV; e) Visuospatial ability will be assessed with the Rey Complex Figure Test. f) Sustained attention and vigilance will be assessed with the Conners Continuous Performance Test 3rd Edition will be used to assess sustained attention and vigilance; g) Information processing will be assessed with Trail-Making Test A.[100] h) Processing speed will be measured with the Coding subtest of the WAIS-IV; i) Verbal fluency will be assessed with the Verbal Fluency subtest of the Delis-Kaplan Executive Function System (D-KEFS). j) Verbal learning and Memory will be assessed with the Hopkins Verbal Learning Test - Revised.[102] k) Visual learning and memory will be assessed with the Brief Visuospatial Memory Test – Revised. l) Executive Function will be assessed with Trail-Making Test B[100] and the Paced Auditory Serial Addition Task[103] and the Stroop Color and Word Test.
7) **Subjective Cognitive Function (Times 1, 2, 3, and 4)**: The Cognitive Failures Questionnaire is a 25-item self-report measure of cognitive difficulties in everyday life using a 5-point Likert scale. Its reliability and validity are well-documented. Those who score ≥43 are deemed to have clinically significant impairment. This measure has been used widely in the measurement of cognitive assessment, including for cancer-related cognitive impairment (e.g., Calvio, Peugeot, Bruns, Todd, & Beuerstein, 2010; Scherling, Collins, MacKenzie, Lepage, Bielajew, & Smith, 2012). Patient Assessment of Own Functioning Inventory – a 33-item self- report measure of a patient's self-perceptions regarding their functioning in everyday tasks and activities.
8) **Neurobehavioral functioning (Times 1, 2, 3, and 4):** The Frontal Systems Behavior Scale is a reliable and valid measure of neurobehavioral functioning (Grace & Malloy, 2001)
9) **Sleep Quality (Times 1, 2, 3 and 4):** The Pittsburgh Sleep Quality Index consists of 19 self-rated items (35). 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).
10) **Chronotype (Time 1):** The Morningness-Eveningness Questionnaire: A reduced scale (MEQr) will be used to collect data on baseline circadian predispositions (Horne & Ostberg, 1976; Adan & Almirall, 1991). It is a 5-item self-rated survey designed to measure whether a person's peak alertness is in the morning or evening. This measure takes approximately 1 minutes to complete.
11) **Physical health (Time 1):** Physical health measures will be included as covariates in data analyses as they have been shown to be associated with fatigue, sleep, depressed

mood, and cognition.[57–66] We will include Body Mass Index (a measure of adiposity) calculated by dividing a participant's weight by the square of their height. The World Health Organisation classifies a body mass index of 25-29.9 as overweight, 30-34.9 as obese class I, 35-39.9 as obese class II, and ≥ 40 as obese class III.

12) **Fatigue (Times 1, 2, 3 and 4)**: The FACIT-Fatigue scale will be used 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 (34). 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.
13) **Depressed Mood (Times 1, 2, 3 and 4):** The Center for Epidemiologic Studies Depression Scale is a reliable and valid measure that will be used to assess depressed mood (Eaton et al., 2004). The Beck Depression Inventory - II will also be used to facilitate comparisons with light studies with international collaborators.
14) **Quality of life (Times 1, 3, and 4):** The Medical Outcomes Study 36-item Short Form (SF-36) is a multi-purpose, short form health survey consisting of 36 questions to assess quality of life. Both test-retest and internal consistency reliability exceeded 0.70 in studies of this scale's psychometric properties (37-39). The scale also has demonstrated content, criterion, and predictive validity (40). The Functional Assessment of Cancer Therapy – BMT scale will also be used. Cancer-specific health quality of life will be assessed with the 50-item Functional Assessment of Cancer Therapy-BMT scale (FACT; Cella et al., 1993; McQuellon et al., 1997). This 50-item scale is a commonly used and well-validated measure of the functional status of cancer patients who have undergone BMT (SCT). It differs from the MOS SF-36 in that it measures the specific impact of cancer and SCT rather than general quality of life.
15) **Credibility/Expectancy (Times 1, 3, and 4)**: The Credibility/Expectancy Questionnaire will ask participants whether they feel the light box is a useful treatment for their cognition.
16) **Treatment Satisfaction (Times 3):** The Functional Assessment of Chronic Illness therapy – Treatment Satisfaction – General (FACIT-TS-G) will measure treatment satisfaction after the intervention at Time 2. It takes about 2 minutes to complete.
17) **Usage (during light exposure):** To measure adherence and fidelity to the procedures, the integrated meter in the Litebooks® record time and duration the light box turned on each day. Participants will also record when they turn on and off the light box and reasons for non-participation in a Litebook Log.
18) **Actigraphy (Times 1, 3, and 4):** Sleep/wake activity and CAR will be recorded with the Actiwatch-2 (Mini Mitter /Phillips/Respironics), which is similar in size to a watch and worn on the nondominant wrist. Total sleep time, percent sleep, total wake time, number of awakenings per night, length of awakenings at night, percent awake, and napping behavior (number of naps; naptime) will be computed. The actigraph also records light and amount (lux) and duration (above 1000 lux) of light exposure. Each participant will wear the actigraph for 7 consecutive days at each of the 3 time points and complete a sleep log on which they will record time to bed, time awake and other information to be used in

editing and scoring the data. For CAR, the activity data will be fit to an extended cosine model[109] from which circadian variables will be computed: acrophase (time of maximum modeled activity), amplitude (difference between maximum and minimum activity), mesor (mean of the modeled activity curve), and pseudo F-statistic (measure of rhythm robustness). There was no evidence of phase advance in Ancoli-Israel's data, but we will control for it statistically if it exists.

19) **Inflammatory immune markers (Times 1 and 3):** The BMHO Laboratory will conduct an assessment of cytokines to examine cellular responses to antigen/mitogens and RNA for genetic molecular analysis. Venous blood will be used to assay proinflammatory and anti-inflammatory cytokines from serum using ELISA, and cytokine gene transcripts. Blood samples will be collected at Times 1 and 2. 11mL of blood will be collected for serum and intracellular RNA collection. Venous blood is collected into evacuated tubes containing serum-separating gel for serum and the PAXgene Blood RNA tube for intracellular RNA. To control for diurnal variation, samples will be collected in the morning whenever possible and processed immediately in the Biopsychosocial Mechanisms and Health Outcomes (BMHO) Program's wet lab using established blood processing protocols, or will be processed immediately in Northwestern's Clinical Research Unit CORE laboratory using established blood processing protocols, depending on the availability of the BMHO Program's lab technician. Drawn blood from participants will be brought to The Robert H. Lurie Comprehensive Cancer Center of Northwestern University by trained and certified lab staff under the supervision of the Office for Research Safety at Northwestern University. Blood will be processed using standard procedure to obtain serum. Bio-samples will be aliquoted and stored at -80°C for maximum preservation until assayed. All processing and assays will be carried out at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Evaluation of cytokines in serum will be performed using commercial ultrasensitive solid phase ELISA kits, following the manufacturer's protocol. A ratio of pro- to anti-inflammatory cytokines will be derived as an indicator of immune dysregulation. Molecular testing of intracellular RNA via RT-PCR will be processed using the PAXgene Blood RNA Kit under the manufacturer's protocol. IL-6, IL-8, and IL-10 will be assayed by High Sensitivity Multiplex assay. IL-1ra and sTNF-RII will be measured using enzyme-linked immunonsorbent assay (ELISA) analysis. Mono-plex will be used for CRP measurement. Assays will be performed in batch format to minimize experimental variation. Molecular testing of intracellular RNA via RT-PCR will be processed using the PAXgene Blood RNA Kit under the manufacturer's protocol.

8.0 Data and Specimen Banking

8.1 Data or specimen storage and access

Participants will be assessed using blood samples collected by trained phlebotomists at two time points: within one week before initiation of the systematic light intervention (Time 1), and during the fourth week of the intervention (Time 2). As indicated in Section 8.3 above, serum and intracellular RNA samples will be stored at -80°C at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University, or at the Northwestern Clinical Research Unit CORE laboratory. The facilities at The Robert H. Lurie Comprehensive Cancer Center or at the Northwestern Clinical Research Unit CORE laboratory will perform the assays on the biosamples. Assays will occur within the project period, which is 4.5 years. Only research team

members, lab staff in the BMHO wet lab, lab staff in the Northwestern Clinical Research Unit CORE lab, and approved staff at The Robert H. Lurie Comprehensive Cancer Center will have access to the samples for the purposes of storage and assay only.

All paper-and-pencil research data (from questionnaires and interviews) will be stored in a locked file cabinet and identified by number only. Consent forms and tracking data (e.g., contact information) will be kept separately. Only study personnel will have access to the data.

Data from the RedCap online tool will be accessible to research study team members only with the following exceptions: All questionnaire data collected via RedCap will be linked to a subject's unique code – but no other identifying information will be accessible via this program.

Electronic research and tracking data will be stored on a secured Northwestern University network drive. Records for the study will be retained for at least 6 years after the investigation is completed and accessible only to study personnel. Upon completion of the study, the data files will be fully anonymized and the links between patients to the codes will be deleted.

8.2 Data to be stored or associated with each specimen

See Section 8.1 above.

8.3 Procedures to release data or specimens

Only anonymized data in SPSS format will be released to collaborators upon request and with the permission of the PI. Such data will not be identifiable to others.

9.0 Data and Specimen Management

9.1 Data analysis plan

Descriptive statistics will be calculated 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, and clinical characteristics *including time since transplant*). Variables showing differences between the two groups will be used as covariates in subsequent analyses. Since there is no known seasonality effect on cognitive functioning, seasonality will not be controlled in these analyses.

Aim 1: Assess the feasibility and acceptability of BWL as an intervention for CRCI in HSCT survivors. Feasibility: We will adhere to currently accepted practice for feasibility studies[110] by measuring the number of eligible patients, willingness of participants to be randomized, follow-up rates, the number who cease the intervention and their specific concerns about the intervention. We will monitor adherence by examining integrated meter data (i.e., time and duration of light box use). We expect high adherence, but if there is variation in duration, we will use duration as a predictor of the outcomes. Participants will be asked to log light box use (beginning and ending time) and reasons for not using it if that occurs. There is no gold standard for what constitutes a "feasible" study and relevant CRCI intervention feasibility studies have not been home-based.[18, 111] Nevertheless, in an inpatient cognitive rehabilitation study of HSCT patients, 78% completed baseline, intervention, and time 2 assessments.[18] A light exposure feasibility study for seasonal affective disorder deemed a 68% completion rate as acceptable,[112] and this is the criteria we will use in this study. In Ancoli-Israel's pilot study, breast cancer

patients used the light box about 50% of the required days. This usage frequency was sufficient for cognitive improvement to occur in the BWL group. A 50% level of adherence will be considered acceptable in this study. Acceptability: As recommended in the literature, in addition to accrual rates, we will assess acceptability by evaluating participants' comments about the intervention after they have had experience with it.[113] Finally, a comparison of the BWL and DRL on the FACIT-TS-G will be conducted using t-tests. Significant differences in favor of the BWL condition are expected.
Aim 2: Examine whether BWL compared with DRL among HSCT survivors suffering from cognitive impairment yields significant improvements in cognitive functioning. We will examine the cognitive functioning subscales and composite scores in separate analyses. Linear mixed model analysis with repeated measures will be conducted using the SAS procedure MIXED. Contrasts will compare groups across assessments. The linear mixed model approach has a range of choices for the error variance/covariance structure and accommodates missing data thus protecting against a "completers only" bias. Since multiple outcomes will be correlated with one another, *p*-values for significance will be Sidak-adjusted for multiple comparisons. If there is variation in light box utilization, we will use duration time as a predictor of the outcome measures as in Aim 1. No pre-intervention bias favoring BWL over DRL is anticipated. However, we will test this assumption by crossing expectancy with the treatment condition. This interaction is not expected to be significant. These results will determine preliminary efficacy and sustainability of the intervention. Power: Based on Ancoli-Israel's pilot study with 10 breast cancer patients, the effect size indicated that we would need a sample size of 19 to achieve power at 0.80. However, the sample size is likely too small to provide reliable estimates of improvement in cognitive functioning. One of the main aims is to determine preliminary efficacy of the intervention in preparation for a larger scale trial. For a total sample of 80, we calculated the mean difference between the two treatment arms for the Neurocognitive (composite) Index and assumed a repeated measures design with an autoregressive lag 1 error structure and autocorrelation of 0.60. The difference able to be detected with power equal to 0.80 and alpha = 0.05, is 0.209.

Aim 3: Examine whether BWL compared with DRL affects sleep and psychological variables (depressed mood, fatigue) which have been implicated as correlates of cognitive functioning in cancer patients. Hypothesis 2: Sleep quality and psychological variables will improve in the BWL group compared to the DRL group. The Aim 1 analytic strategy will be used in the analysis of this aim. Power: Our preliminary R-21 study that examined BWL vs. DRL on cancer-related fatigue in a mixed cancer population (including HSCT) provided guidance for the power. Sleep Quality: While survivors in the BWL group had better sleep quality scores than the DRL group, the main effect for treatment was not statistically significant, no doubt due to sample size. Cohen's d was 0.63. For a repeated measures design with alpha equal to 0.05 and a sample size of 40 per group, power=0.99. CAR: There was significant time x treatment interaction (p=0.02) on the F statistic. We calculated power for a repeated measures design with autoregressive lag 1 structure and autocorrelation of 0.60. With alpha equal to 0.05 and sample size of 40 per group, power=0.99 Fatigue: As with CAR, there was significant time x treatment interaction (p=0.003). Using the same method as above, power = 0.99. Depressed mood: There was a significant (p=0.004) time x treatment interaction. Using the same method as above, power = 0.99.

Exploratory Aims: Explore a) whether BWL compared with DRL affects biological (inflammatory immune response) variables; and b) whether the effects of BWL compared to

DRL on cognitive functioning are mediated by sleep, chronobiological factors (i.e., circadian activity rhythms), biological factors (i.e., inflammatory immune response), and psychological factors (i.e., fatigue, depressed mood).

a) Assess whether the BWL intervention affects biological factors (IL-1ra, IL-6, IL-8, IL-10, sTNF-III, CRP, PBMCs, and intracellular RNA) that have been identified as correlates of CRCI. Biological variables will be measured at Times 1 and 2. The mixed linear model approach described in Aim 2 will be used here.

b) The results of Aim 2 will provide evidence that BWL reduces cognitive impairment. Mediation analyses using bootstrapping will provide estimates of the effect of light treatment on the mediators, the effect of the mediators on cognitive functioning, the direct effect of light treatment on cognitive functioning, and the indirect effect of light treatment on cognitive functioning whilst accounting for the mediators. Advantages of this method include: 1) it does not rely on the causal steps approach to mediation analysis;[114, 115] 2) bootstrapping of the sampling distribution does not rely on the assumption of normal sampling distributions of the indirect effects; 3) type II error is reduced because it requires fewer inferential tests; and iv) multiple mediators can be tested at once;[116] 4) allows for statistical control of covariates. For this exploratory analysis, we will examine each category of factors as mediators separately (i.e., sleep, chronobiological, biological, and psychological factors).

Missing data: We will be using a mixed linear model using a maximum likelihood approach to parameter estimates which means that not every participant has to provide full data.

9.2 Power analyses

Aim 1 Power: Based on Ancoli-Israel's pilot study with 10 breast cancer patients, the effect size indicated that we would need a sample size of 19 to achieve power at 0.80. However, the sample size is likely too small to provide reliable estimates of improvement in cognitive functioning. One of the main aims is to determine preliminary efficacy of the intervention in preparation for a larger scale trial. For a total sample of 80, we calculated the mean difference between the two treatment arms for the Neurocognitive (composite) Index and assumed a repeated measures design with an autoregressive lag 1 error structure and autocorrelation of 0.60. The difference able to be detected with power equal to 0.80 and alpha = 0.05, is 0.209.
Aim 2 Power: Our preliminary R-21 study that examined BWL vs. DRL on cancer-related fatigue in a mixed cancer population (including HSCT) provided guidance for the power. Sleep Quality: While survivors in the BWL group had better sleep quality scores than the DRL group, the main effect for treatment was not statistically significant, no doubt due to sample size. Cohen's d was 0.63. For a repeated measures design with alpha equal to 0.05 and a sample size of 40 per group, power=0.99. CAR: There was significant time x treatment interaction (p=0.02) on the F statistic. We calculated power for a repeated measures design with autoregressive lag 1 structure and autocorrelation of 0.60. With alpha equal to 0.05 and sample size of 40 per group, power=0.99. Fatigue: As with CAR, there was significant time x treatment interaction (p=0.003). Using the same method as above, power = 0.99. Depressed mood: There was a significant (p=0.004) time x treatment interaction. Using the same method as above, power = 0.99.

9.3 Steps to ensure security of data to maintain confidentiality

Biological samples will be de-identified with personal participant information before lab staff begin processing. Each participant will be assigned a unique ID# for the study. Lab staff will only have access to the ID# and date/time of collection of samples.

Confidentiality of each participant's medical, neuropsychological test data, questionnaire and interview data will be protected with utmost care. All paper-and-pencil research data will be identified by ID# only and stored in locked filing cabinets. Physical consent forms and tracking data (e.g., contact information) will be stored separately in locked filing cabinets. To ensure confidentiality, a "cross-over" file matching ID# with participant identifying information (name, address and phone number) will be maintained and stored separately from the data with password protection. Only study personnel will have access to the cross-over file.

Data from RedCap will be accessible to research study team members using password protection and will only be identified by participant ID#.

The use of email will be in accordance with Northwestern policy (i.e. secure email, obtaining consent from subject to send email, etc.).

Electronic research and tracking data will be stored on a secured Northwestern University network drive. All study personnel will undertake required CITI, HIPAA and Data Safety and Monitoring courses through Northwestern. The PI and research assistant will be responsible for secured receipt and transmission of all aforementioned data and only study personnel will have access to it. Upon completion of the study, the data files will be fully anonymized and the links between patients to the codes will be deleted.

9.4 Procedures for quality control of collected data

The PI will collect data from the first participant to ensure the procedures are clean. The research assistant will then be rigorously trained by the PI to undertake all assessments and will observe the research assistant administer assessments until he/she is fully trained.

After the completion of each interview, the research assistant will be required to carefully check all recorded answers, correct any possible errors and conduct re-questioning if necessary. The research assistant will sign his/her name on the front page of each questionnaire in order to be accountable for the quality of the data collection. The PI will check the scoring of the first 3 neuropsychological assessments and will randomly check 5 more during the course of the study.

Study scripts and questionnaires have been designed for ease of administration and to minimize confusion and data entry errors.

The PI and research assistant will meet at least once a week to discuss study procedures and any issues.

Results from RedCap are immediately captured by their software thus minimizing data entry errors.

10.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The proposed study does not involve more than minimal risk to subjects.

10.1 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. If a participant experiences minor side effects (e.g., sleep disturbance, headache, eye strain or 'stinging' sensation in the eyes, nausea, and hyperactivity), study staff will work with the participant to ensure they are using the Litebook correctly and for no longer than the prescribed length of time. If the side-effects do not abate within three days, the participant will be discontinued from the intervention. If a participant experiences a more serious side effect (e.g., mania), then the participant will be discontinued from the study immediately and referred to their physician for follow-up. Study staff will be required to report all serious adverse events to Northwestern University's IRB according to policies and procedures outlined by that body. Study staff are also responsible to report all adverse events to the study PI as well. As per Northwestern's IRB policies, the study PI is required to notify the IRB promptly of any unanticipated problems involving unanticipated adverse events 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 Northwestern 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 unanticipated is avoided. We will use screening procedures used in our prior studies with HSCT survivors to assess depression/suicidality. If risk of suicidality or severe depression is revealed, our staff psychologist will contact the participants the same day, take emergency steps and make referrals as needed.

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

As per Northwestern's IRB policies, the PI is required to notify the IRB promptly of any unanticipated problems involving risks to subjects or others that occur. The PI will monitor participant progress and their safety on an ongoing basis. The procedures of this study, such as regular meetings with research staff and mentors will ensure discussion and reporting of all possible outcomes including adverse events. If an adverse event occurs and is at least probably due to study involvement and is unexpected, the PI will report this information to the IRB within 5 business days as required by IRB policy.

10.3 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 Northwestern 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.

10.4 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 (questionnaires), cognitive assessments (online screening and in-person for Times 1 to 3), blood samples (Times 1 and 2), sleep logs, Litebook logs, information from Litebook integrated meters, and actigraphs. These measures will generate information concerning: 1) cognitive functioning; 2) sleep quality; 3) circadian activity rhythms; 4) inflammatory immune milieu; 5) fatigue; 6) depression; and 7) socio-demographic and medical variables. Wu will assess data from Litebook integrated meters as indicators of protocol adherence and fidelity of the dosage. Wu will meet primarily with her mentor Frank Penedo regularly and with the whole mentorship team quarterly

to monitor any adherence or accuracy problems that may arise during the course of the study. To ensure the validity and integrity of study data, the PI will be trained by Sonia Ancoli-Israel at University of California San Diego to learn how to evaluate data integrity from the Litebook integrated meters and actigraphs, and Wu will oversee all other data management responsibilities (e.g., data entry and data checking) with guidance from Frank Penedo and Daniel Mroczek.

11.0 Withdrawal of Subjects

11.1 Anticipated circumstances under which subjects will be withdrawn

If there is any significant worsening of a subject's medical or psychiatric condition that is likely due to participation in the study, then the subject will be withdrawn immediately.

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

11.2 Procedures for orderly termination

Procedures related to handling unexpected adverse events (Section 9.1.2) will be followed.

11.3 Procedures that will be followed when subjects withdraw from research

If a participant has already begun participation in the study, but then refuses to complete one aspect of data collection (e.g., blood collection), that person will be permitted to continue in the study to completion at the discretion of the PI.

12.0 Risks to Subjects

12.1 Risks related to subjects' participation in research

The proposed project is a low-risk primarily behavioral study. 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. There is also a chance that they will experience potential side effects of light therapy, e.g., sleep disturbance, headache, eyestrain, nausea, and hyperactivity, though this is rare. They will be informed that such side effects are usually minimal (i.e., not clinically significant) if the light is positioned correctly and resolve quickly. During the course of the protocol, if side effects persist, we will withdraw them from the study. There is also 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. Past research has shown that such distress is usually minimal and transient. There are minimal risks associated with blood draws, including pain, bruising, swelling, dizziness, or infection. Some people feel dizzy or may faint during or after a blood draw.

13.0 Potential Benefits to Subjects

13.1 Potential benefits from taking part in the research

Benefits of participation may include the ability to report their experiences of cognitive problems. Being able to report their experiences in this important area may help them feel understood and validate their experiences. Participants may also benefit from an improved understanding of their cognitive difficulties during the debriefing (upon request) at the end of the study. Our pilot work shows that systematic light exposure may help to ameliorate fatigue. Some

subjects may experience small to moderate improvements in fatigue from their participation that may be sustained till the end of the study.

14.0 Vulnerable Populations

14.1 Safeguards to protect vulnerable populations

Even though we are evaluating cognitive impairment, the severity of such impairment tends to be mild and thus, typically, does not meet the level of impairment indicated in HRP-417 that would affect decision-making capacity. Furthermore, cognitive competency is required to be able to implement the procedures at home effectively. Hence, only participants who are able to undertake the consent process and meet the 4 elements of decision-making capacity will be eligible to participate:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one's own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and;
4. The ability to express a choice about whether or not to participate.

15.0 Sharing of Results with Subjects

As mentioned earlier, if a subject requests a debriefing of their neuropsychological test scores, they may receive a debriefing session with the PI at the end of their participation in the study.

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

16.0 Setting

All study activities will take place in the Northwestern University, Feinberg School of Medicine, Department of Medical Social Sciences, located on the 19th floor of 633 N. St. Clair Street, Chicago, IL, 60611. Blood sample processing will take place in the Robert H. Lurie Comprehensive Cancer Center (RHLCCC) wet lab located at 303 E. Superior Street, Room 4-220, Chicago, IL, 60611, or at the Northwestern University Clinical Research Unit CORE laboratory, located in the Feinberg building of Northwestern Memorial Hospital, depending on the availability of wet lab staff.

17.0 Resources Available

17.1 Qualifications of staff

A qualified research assistant will be selected preferably with a degree in psychology. He/she will be trained in all aspects of the research by the PI herself, including neuropsychological assessment. The PI has extensive clinical supervisory experience in both clinical psychology and neuropsychology, and has supervised research assistants on numerous studies in the past. The PI

will directly supervise all of the research assistant's activities to ensure the smooth running of the study.

17.2 Other resources available to conduct the research

Northwestern completes approximately 180 autologous and approximately 54 allogeneic transplants per year. Based on these numbers, there will be more than sufficient numbers of HSCT survivors available to screen 227 across 48 months of recruitment.

We have wet and dry labs available to undertake all assessments with participants in the Biopsychosocial Mechanisms and Health Outcomes Program. The dry lab is located on the 19th floor of 633 N. St. Clair and includes a blood draw room and assessment suites. The wet lab is located in the Lurie Research Building with an on-site lab technician who will take care of the processing and storage of biospecimens prior to distribution to the Evanston campus for analysis. The Northwestern Clinical Research Unit CORE laboratory is located in the Feinberg Hospital building of Northwestern Memorial Hospital with on-site lab technicians who will take care of the processing and storage of biospecimens depending on the availability of wet lab staff (i.e. CORE lab will process if BMHO wet lab staff is not available).

This is a minimal risk study. However, we will have contact information for any participant's physician and the transplant team's social worker on hand should any medical or psychological issues arise.

All persons assisting in the research will be rigorously trained by the PI in the procedures from recruitment, to assessments, to how to deal with unanticipated adverse events.

18.0 Prior Approvals

Approval has been obtained by the National Cancer Institute to undertake this research (pending IRB approval). It was previously approved by the Icahn School of Medicine at Mount Sinai before transfer to Northwestern University.

19.0 Recruitment Methods

19.1 When, where, and how potential subjects will be recruited

Source of subjects: Participants will be HSCT patients from Northwestern Memorial Hospital through the Lurie Cancer Center's Hematopoietic Stem Cell Transplant Program. Participants will also be recruited through HCST and hematological malignancy internet support resources, brochures at local support groups, online postings on free classified websites and dissemination of brochures/flyers to local oncologists who think their patients might be interested in participating in the study. The study team member will contact patients who express interest in the study or respond to recruitment solicitations.

Methods used to identify potential subjects: Potential participants will be identified via the Northwestern University Enterprise Data Warehouse service (EDW) and from patient databases provided by the transplant team after providing them with a list of inclusion and exclusion criteria for the study. A query of eligible patients and their physicians will then be created for the research staff. The research study staff will also review their EMR to ensure initial eligibility. The study team member will then contact the treating physicians to request permission to contact their patient(s) about the study. An attempt will be made, via an email or in-person to request permission from the physician to contact their patient(s). If the physician authorizes contact be made, research staff will contact the patient to gauge whether or not they are interested in

participating in the study. Following physician approval, initial contact will be made with the patient (potential participant) either in-person at their next clinic appointment, or (e)mailed a recruitment letter (if their next clinic appointment is over a month away). For in-person recruitment, the study team member will approach patients at their next medical appointment at Northwestern Medicine (identified by the medical database). For letter recruitment, the study team member will inform them that a) they will be contacted in the near future about a research study and b) instructions on what to do if they do not wish to be contacted further. Those potential participants who do not opt-out of further contact will be contacted by the research study staff via preferred method as indicated in their EMR (via telephone, mail, etc.) Participants who self-refer (i.e. contact study staff directly after learning about the project through a support group, their oncologist, or another source), will be contacted by the research study staff if they express interest in the study or respond to recruitment solicitations. These individuals will also undergo the Northwestern University verbal consent via phone call.

Materials used to recruit subjects: See advertisements and brochures attached.

Amount, timing, and method of any payments: Each participant will receive $60 at each completed assessment (Time 1, Time 2, and Time 3) in the form of cash.

20.0 Number of Subjects

20.1 Total number of subjects to be accrued

We expect to recruit 80 study participants whom we will draw from the pool of auto-HSCT and allo-HSCT survivors at Northwestern. Northwestern undertakes approximately 180 autologous HSCTs annually. Based on these numbers, we expect to be able to approach the necessary 227 HSCT patients between 1 and 5 years post-transplant across 48 months of recruitment. Research that examined HSCT survivors in our earlier BWL research suggests that 11.9% of those eligible will refuse to undertake the screening leaving 200 patients who will participate in the screening assessment. Research suggests that more than 40% of those individuals (the most conservative estimate) will meet criteria for entry into the study, leaving 80 interested participants eligible to complete the baseline assessment and randomization into the study.

21.0 Provisions to Protect the Privacy Interests of Subjects

21.1 Steps to protect subjects' privacy interests

When participants are approached by the study team member at the clinic (after receiving permission from their physician to do so), all efforts will be made to ensure that the meeting is undertaken in a private room or where no one is present. If approached by phone (following the sending of an introduction letter signed by their physician and by the PI), the study team member will make sure to ask if it would be a good time to talk. All communications by phone or email, including phone messages, will only be undertaken with the permission of the participant. In addition, all questionnaire and online questionnaire/testing information will be undertaken using the confidential ID# as the only identifier of materials. All interviews, neuropsychological assessments and blood collection will be undertaken in private assessment rooms.

21.2 Steps to make subjects feel at ease with the research situation

The research assistant will be trained by the PI regarding how to approach potential participants in an empathic manner that minimizes the feeling of intrusiveness. As mentioned, where possible, all efforts will be made to maximize the privacy of the setting whether it by in-person or by phone. During the administration of all aspects of the research, including the neuropsychological tests, standard scripts will be used to ensure that participants are comfortable with the instructions and that they are free to withdraw from the study at any time for any reason.

21.3 Research team's permission to access sources of information

The PI, research assistant and research volunteers will be given training to use and be provided with access to medical records at Northwestern in order to obtain participants' basic transplant-related medical information that directly pertains to study questions.

22.0 Compensation for Research-Related Injury

The research does not involve more than Minimal Risk to subjects, so there is no compensation in the event of research related injury.

23.0 Economic Burden to Subjects

We do not expect the subjects to incur any foreseeable costs through their participation in our study. We will be paying for shipment of the actigraphs, and, where necessary, the light boxes, to and from each subject's home at our expense.

24.0 Consent Process

Informed Consent: Informed consent will be obtained from participants either:

1) By phone before the collection of any data - a consent form will be emailed (after obtaining the email address from the participant directly) or mailed to potential participants identified as being interested to participate in the study. The study team member will undertake the consent process with the participant over the phone. The telephone consent will include the explanation of the consent form and will give details regarding the screening interview as well as outline the duration of the study. The study team member will: describe the study, give the subject time to ask questions regarding their consent to be screened, allow the subject to discuss their decision with whomever they like, allow the subject to digest the information, and allow the subject to ask the member of the study team any additional questions they might have. There will be a waiver of documentation of consent. Individuals who then undertake the screening interview and are eligible to continue in the study will be presented with the regular consent form to sign at their Time 1 appointment. This will ensure documentation of HIPAA authorization for access to PHI. See verbal consent and regular consent document attached;

2) In-person before the collection of any data - Eligible patients will be contacted during their visits to Northwestern and given information on the study. The study team member will then administer the informed consent process. The study team member will: describe the study, give the subject time to read the consent form, allow the subject to discuss their decision with whomever they like, allow the subject to digest the information, and allow the subject to ask the member of the study team any additional questions they might have. The regular consent document will be used here in order to ensure documentation of

HIPAA authorization for access to PHI. See verbal consent and regular consent document attached.

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 Northwestern consistent with the SOP: Informed Consent Process for Research (HRP-090). 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.

25.0 Process to Document Consent in Writing

25.1 Use of SOP: Written Documentation of Consent (HRP-091)

The written documentation of consent will be used.

25.2

Waiver of documentation of consent

The research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context. Hence, for the screening portion of the study there will be a waiver of documentation of consent. Subsequently, regular signed consent will be obtained for the main study as described in 25.3 below.

25.3: Consent script

For the waiver of documentation of consent, the regular consent document will be sent to participants (sans signature section). The verbal consent script will be used by the study team member to explain the study to the participant. The regular consent document WITH signature section will be presented to eligible participants at their Time 1 appointment for signature. All of these consent documents are attached.

Title of Research Study: ***The "Light for the Brain" Study***

Investigator: ***Lisa M. Wu, Ph.D.***

Supported By: This research is supported by National Cancer Institute.

Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are a hematopoietic stem cell transplant (HSCT) survivor who is 1 year to 5 years post-transplant. In this research study, we are testing a light box therapy to see whether it might be helpful for the treatment of side-effects you may be experiencing. For example, maybe you have felt that it's hard to concentrate or remember things like you could before; perhaps you're feeling more tired than you used to; or maybe you're just not like feeling yourself.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

This research is being done to help us evaluate whether survivors of hematopoietic stem cell transplantation (HSCT) who are regularly exposed to light produced from a light box will experience changes to symptoms they may be experiencing.

How long will the research last and what will I need to do?

If you are eligible, we expect that you will be in this research study for 13 to 15 weeks depending on the timing of assessments.

You will be given one of two Litebooks to use at home for 30 minutes every day for 4 weeks. You will come in for 3 assessments: before and after you use the Litebook, and 8 weeks after you have completed using it. At these visits, you will complete a blood draw, testing of your memory and concentration, and questionnaires. You will also record your sleep habits and wear a small actigraph watch to record your activity and sleep at three separate points during the study.

More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk. There is also a chance that you will experience potential side-effects of light therapy (e.g., sleep disturbance, headache, eye strain or 'stinging' sensation in the eyes, nausea, and hyperactivity), though this is rare. Such side-effects are usually minimal if the light is positioned correctly and resolve quickly though please let the study team know if any occur. On very rare occasions and usually only with over-use which is unlikely in this study, you may experience changes in mood. If this occurs, please contact the PI. This research study involves

neuropsychological testing and questions that may feel sensitive and personal in nature. It is possible that answering some questions may cause some stress or anxiety. You may become bored while taking the tests. You may stop taking the tests at any time. There are also minimal risks associated with blood draws: 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.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include: the ability to report about experiences of cognitive problems which may feel validating; an improved understanding of cognitive difficulties (if they exist) during the optional debriefing. In addition, there may be benefits from the research for cancer survivors, in general, who experience difficulties with memory, thinking, and concentration.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled.

Your alternative to participating in this research study is to not participate.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the Principal Investigator, Dr. Lisa Wu, at (312) 503-7722.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 80 people will be enrolled this research study.

What happens if I say "Yes, I want to be in this research"?

If you agree to participate in this research study, you will be enrolled in the "Light for the Brain" study which, briefly, involves 3 visits to the Department of Medical Social Sciences at Northwestern Medicine (633 North St. Clair, 19th floor), possible use of a Litebook (light box) each morning for 30 minutes over the course of four weeks, completion of questionnaires, ***two blood draws,*** and tests of memory, concentration, and other thinking abilities.

Start of Study (Visit One – three hours)
You will begin with the baseline assessment for the study in the Department of Medical Social Sciences at Northwestern Medicine (633 N. St. Clair, 19th floor). You will have about 11mL (approximately 1 tablespoon) of blood drawn from your arm by a trained phlebotomist. Then, in a private room at the Department of Medical Social Sciences, a study team member will ask you some background questions and questions about your medical history. You will then be guided through tests of your memory, concentration and other thinking abilities (neuropsychological tests) and complete questionnaires. With your permission, we will audio record these tests so

we can perform quality control checks. Upon completion of the tests, you will complete questionnaires on the computer.

At this first appointment, you will also receive one of two Litebooks of different wavelengths that we are testing (identical except for different bulbs emitting different wavelengths). You will be instructed to use your assigned Litebook every morning upon awakening for 30 minutes for four weeks. The Litebook is a compact portable lamp (approximately 5" x 5" x 1") and weighs less than a pound. It is very easy to use. The light box is directed toward the eyes for 30 minutes each morning. It is powered by a rechargeable lithium-ION battery which we provide and can also be connected to a power source.

We will then give you an actigraph (a small device similar in size to a watch that will measure your sleep and wake activity) to wear for 7 days and instructions for completing a sleep log.

Second week (At Home – 30 minutes)
During the second week of using your Litebook, you will be asked to complete questionnaires again on the computer, and asked for an update on any medical changes. These questionnaires will be completed at home. You will *not* need to come into study offices at Northwestern for this part of the study.

Last week of Litebox Use (Visit Two – Two and a half hours)
During the last week of the study, you will again wear the actiwatch and complete a sleep log for another 7 days. Then you will be invited to come in to complete an in-person assessment. You will again have about 11mL (approximately 1 tablespoon) of blood drawn from your arm by a trained phlebotomist. Then, in a private room at the Department of Medical Social Sciences, a study team member will guide you through the tests of your memory, concentration, and other thinking abilities. Upon completion of the tests, you will complete questionnaires on the computer.

Eight weeks after end of Litebox Use (Visit Three – Two hours)
This procedure will be repeated 8 weeks later. You will again wear the actiwatch and complete a sleep log for another 3 days (72 hours). A study team member will ship you an actiwatch via Fedex. You will be invited to come in to study offices at Northwestern and be guided through the tests of your memory, concentration, and other thinking abilities. Upon completion of the tests, you will complete questionnaires on the computer.

The study assignment you get, i.e. which of the Litebooks you receive, will be chosen by chance. There is a 50% chance of being in one of these groups. Neither you nor the research assistant or Principal Investigator will know which Litebook you are getting during the study.

Once you have completed your participation in the study, you may request to speak to the Principal Investigator if you wish to learn more about your neuropsychological test results.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time and it will not be held against you.

If you decide to leave the research, contact the investigator so that the investigator can collect the materials you may have and withdraw you from the study.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

If you stop being in the research study, all collected information will continue to be used to complete the research analysis. You may be asked whether the investigator can collect information from your routine medical care. If you agree, this data will be handled the same as research data.

Detailed Risks: Is there any way being in this study could be bad for me?

There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk. There is also a chance that you will experience potential side-effects of light therapy (e.g., sleep disturbance, headache, eye strain or 'stinging' sensation in the eyes, nausea, and hyperactivity), though this is rare. Such side-effects are usually minimal if the light is positioned correctly and resolve quickly though please let

the study team know if any occur. On very rare occasions and usually only with over-use which is unlikely in this study, you may experience changes in mood. If this occurs, please contact the PI. This research study involves neuropsychological testing and questions that may feel sensitive and personal in nature. It is possible that answering some questions may cause some stress or anxiety. You may become bored while taking the tests. You may stop taking the tests at any time. There are also minimal risks associated with blood draws: 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.

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include: the ability to report about experiences of cognitive problems which may feel validating; an improved understanding of cognitive difficulties (if they exist) during the optional debriefing. In addition, there may be benefits from the research for cancer survivors, in general, who experience difficulties with memory, thinking, and concentration.

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution and our sponsoring agency: the National Cancer Institute.

Data will be retained for 6 years for the purposes of data analysis directly related to the study and stored on password protected network drives.

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data

Can I be removed from the research without giving my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include: if the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

You will receive $60 for each completed assessment for your time and effort.

At the conclusion of data collection for the study, publication of findings (in the form of abstracts and manuscripts) will be given to participants upon request.

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs
- Records about study devices
- Mental Health information: i.e., history of psychiatric symptoms

Illinois State Law prohibits use and disclosure of your mental health information if the use and disclosure is not specifically permitted by this document.

The following groups of people may give the researchers information about you: Northwestern University's Robert H. Lurie Comprehensive Cancer Center and Northwestern Memorial Hospital (NMH).

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of Northwestern University and its clinical partners (or affiliates), the Northwestern University Institutional Review Board Office and Office for Research Integrity, the US Office of Research Integrity, the US Office for Human Research Protections, the US Food and Drug Administration will not contain your name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is necessary for review by such parties or is required by law [except that such information may be viewed by the Study sponsor and its partners or

contractors at the Principal Investigators office].

- Authorized members of the Northwestern University, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study).
- Study monitors and auditors who make sure that the study is being done properly,
- The National Cancer Institute who is sponsoring the study, and that company's contractors and partners.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

The use of PHI will expire upon completion of all data analysis directly related to the study.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

Lisa M. Wu, Ph.D.
Northwestern University Feinberg School of Medicine
Department of Medical Social Sciences
633 North St. Clair, Office 19-073
Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

This consent expires on 4/30/2021. After this date, Northwestern University may not gather new information about you, use or disclose your personal health information collected in this study for any purpose other than the research study described in this consent unless it obtains permission to do so from you."

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by informing the study team.

I agree	I disagree	
_____	_____	The researcher may audio record the neuropsychological testing portion only of each session so that the study team can score the tests accurately after those sessions. Note: Your name would not be on the audio files. They would only be identified by your unique study ID number.
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies.

Your signature documents your permission to take part in this research.

Signature of participant	Date
Printed name of participant	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.