


# Treatment of Post-TBI Fatigue with Light Therapy

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	Protocol Name:	Management of post-TBI fatigue with light exposure
	Principal Investigator:	Wayne Gordon, Ph.D., ABPP/Cn
	Primary Contact Name/Contact Info:	Lauren Nelson, <a href="mailto:lauren.nelson@mountsinai.org">lauren.nelson@mountsinai.org</a> , x45190
	Date Revised:	3/9/2016
	Study Number:	IF1813452

**PROTOCOL TEMPLATE INSTRUCTIONS HRP-503**


- These instructions accompany the MSSM “Template Protocol” document and are intended to assist you in developing a human research protocol.
- Using the MSSM “Template Protocol” document, prepare a document with the following sections.
- Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section “N/A”. Do not delete any sections.
- **For any items below that are already described in the sponsor’s protocol, the investigator’s protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document.. Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.**
- When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.

**Header:**

- **Protocol Title**  
Treatment of Post-TBI Fatigue with Light Therapy
- **Investigator**  
Wayne Gordon, PhD, ABPP/Cn
- **Date Revised**  
3/9/16
- **Study Number**  
GCO# 12-1256(0001)(01) RM  
Project 2

**Brief Summary of Research (250-400 words):**

Fatigue is experienced much more frequently by individuals with traumatic brain injury (TBI) than in the general population and is relatively stable and persistent within one to two years of injury. The effects of post-TBI fatigue are considerable. Fatigue after TBI is strongly associated with depression, pain, sleep quality, self-reported neurobehavioral function (cognitive, motor, somatic), health related quality of life, and overall quality of life. Moreover there is evidence to suggest that post-TBI fatigue commonly goes untreated, due in part to the lack of validated treatment options.

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There are no empirically supported treatments for post-TBI fatigue although medications are routinely used in its treatment. Promising research from other disorders (e.g., cancer, chronic fatigue syndrome) and pilot research that we have conducted in individuals with TBI suggests that non-pharmacological approaches might be promising areas of study. Exposure to bright white light has been shown to reduce or prevent fatigue in women with breast cancer, people with seasonal affective disorder, and shift workers. It is a low cost treatment with minimal associated risks.

## 1) Objectives

- Aim 1: Evaluate the efficacy of 4 weeks of daily BWL exposure in reducing PTBIF immediately post-treatment and at one-month follow-up.
  - H1: Individuals receiving 4 weeks of daily BWL treatment will report significant reductions in fatigue compared to those receiving DRL
  - H2: Treatment effects will be maintained one month after treatment completion
- Aim 2: Explore potential effects of BWL exposure on mood, sleepiness, sleep quality, circadian rhythms, anxiety, cognition and life satisfaction.
  - H3: Individuals receiving 4 weeks of daily BWL treatment will report significant reductions in daytime sleepiness and depressed mood as well as improvements in sleep quality and circadian rhythms, compared to those receiving DRL
  - RQ1: Is treatment with BWL associated with improvements in anxiety, cognition and life satisfaction?
- Aim 3: Investigate potential mechanisms for effects of BWL exposure on fatigue, including changes in mood, sleepiness, sleep quality and circadian rhythms.
  - RQ2: Are treatment-related changes in fatigue mediated or moderated by mood, sleepiness, sleep quality and circadian rhythms?
- Aim 4: Determine whether individual characteristics are associated with treatment outcomes.
  - RQ3: Are demographic or other patient characteristics associated with positive treatment outcomes?

## 2) Background

Fatigue is a common problem after TBI that is related to, but distinct from, sleepiness, sleep difficulties and depressed mood. Fatigue affects up to 80% of individuals with TBI (far more than the general population) and is relatively stable and persistent after the first year post-injury.<sup>25-32</sup> Post-TBI Fatigue (PTBIF) is strongly associated with depression, pain, poor sleep quality, neurobehavioral dysfunction and poor quality of life (QOL).<sup>27,32-35</sup>

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To date, little evidence has been generated in support of treatments of PTBIF.<sup>36</sup> Many medications including neurostimulants, dopaminergics, antidepressants and atomoxetine, as well as caffeine and herbal preparations, are used to manage fatigue or promote wakefulness, often with undesirable side effects. Only two controlled studies examining the efficacy of a pharmacological agent for PTBIF have been published. In a double blind, placebo-controlled crossover trial, Jha et al. randomized 53 individuals with TBI who complained of disabling fatigue and/or sleepiness to receive up to 400 mg of modafinil or placebo. Modafinil was not superior to placebo in treating either fatigue or sleepiness. Kaiser and colleagues conducted a double blind, placebo-controlled pilot study with 20 individuals with TBI and found that modafinil reduced daytime sleepiness, but did not reduce fatigue.

Behavioral management techniques, such as cognitive behavioral therapy (CBT), seek to reduce fatigue's effects through use of compensatory strategies, economizing energy use and improving sleep hygiene. These techniques are well-supported in conditions such as cancer and multiple sclerosis but have received little attention in the TBI literature, although Ouellet and Morin did demonstrate that CBT for post-TBI insomnia also improved fatigue. One randomized controlled study (RCT) of patients with TBI or stroke demonstrated significant improvements in mental fatigue and cognitive performance after 8 weeks of mindfulness-based stress reduction.<sup>45</sup> Because data for the TBI group (n=11) were not analyzed separately, the effectiveness of this approach with TBI is not known.

Substantial evidence exists that aerobic exercise and other forms of physical activity reduce fatigue in individuals with cancer, multiple sclerosis and other conditions. Although there are studies currently underway at the NY-TBI-MS and elsewhere on the benefits of exercise after TBI, no research has yet been published.

Regular exposure to bright white light (BWL) is a new potential treatment for PTBIF. BWL treatment involves daily exposure to light (typically 30 minutes) using a small light box. Systematic reviews have shown that BWL is effective in reducing depression and in treating circadian rhythm disturbances and other sleep-related disorders. BWL has also been shown effective in treating sleep disorders in individuals with dementia and to reduce daytime sleepiness and improve cognitive performance in healthy adults without disabilities.

Although fatigue is commonly found in many medical disorders, the effect of BWL on fatigue in these populations has received little attention, with the exception of cancer-related fatigue (CRF). Liu et al. examined the relationship between ambient light exposure and CRF in 63 women with stage I-III breast cancer prior to and during chemotherapy. Fatigue was assessed using self-report, and light exposure was recorded with a wrist Actigraph (a watch-like device to monitor movement, activity and light levels). More light exposure was associated with less fatigue; changes in light


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exposure and in fatigue were also correlated.

Ancoli-Israel and colleagues reported on an RCT investigating the effects on CRF of daily exposure to BWL in 39 women diagnosed with breast cancer undergoing chemotherapy.<sup>55</sup> Patients were assigned to receive either BWL or dim red light (DRL) for 30 minutes every morning throughout the first 4 cycles of chemotherapy (8-12 weeks) using a commercially available light box (Litebook®). In those receiving DRL, CRF increased significantly from baseline to the end of the last chemotherapy cycle. In contrast, subjects receiving BWL experienced no increase in fatigue. The DRL group also showed significant desynchronization of circadian rhythms compared to the BWL recipients. No adverse effects were reported in either group. This research suggests that BWL holds promise as a treatment for fatigue in other medical disorders, including TBI. Since TBI is associated with increased sleepiness, mood disturbance, poor sleep quality and disruptions of circadian rhythms, BWL therapy may also have beneficial effects in these domains and consequently result in improved cognition and life satisfaction.

While the mechanism by which light therapy affects fatigue is not well understood, it is thought to involve non-visual photoreception; i.e., action of light on the nervous system via the eye that is unrelated to vision. Rods and cones in the retina that convey visual information to the brain are most sensitive to green/green-yellow light (506 to 555 nanometers [nms]). Light-sensitive retinal ganglion cells<sup>62</sup> produce melanopsin, a photopigment that is most sensitive to shorter wavelengths of light such as blue light (480 nms) but also responds to longer wavelengths. These ganglion cells project into various non-visual areas of the brain, including the suprachiasmatic nuclei in the hypothalamus, which regulate circadian rhythms and function as the body's internal clock. These cells also stimulate the pineal gland, which controls melatonin production. Via these channels, light exerts crucial alerting effects on the human brain, increasing serotonin levels and reducing melatonin production. Thus, several biological action mechanisms for light therapy on fatigue are possible, including increasing alertness and decreasing sleepiness, improving mood and sleep quality, and regulating circadian rhythms.

We have also conducted an *Intervention Development* study to examine the feasibility and safety of BWL treatment in individuals with PTBIF, to estimate effect size and assess sensitivity of measures. We randomized 13 individuals with PTBIF to receive 28 days of treatment with BWL or DRL. DRL is widely used as a placebo in light therapy studies because it is relatively inactive biologically, and is known to induce positive treatment expectations comparable to those of BWL, even though it is visibly different from BWL. Treatment involved sitting in front of the light box for 30 minutes per day within 30 minutes of waking. Actigraphy data and sleep diaries were collected for 3 days before and after treatment. Participants completed measures of fatigue, sleepiness, sleep quality, mood, treatment satisfaction, treatment credibility and outcome expectancy, before and directly after treatment and again one month after treatment.

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*Safety, feasibility and treatment compliance.* Side effects and adverse events were monitored weekly for all participants: none were reported in either treatment condition. All participants were able to use the light box independently at home. Some requested additional telephone guidance on the use and positioning of the light box; 8 of 12 reported “no difficulty” using the box and 4 experienced minor initial difficulties (e.g., angling it correctly). Daily reminders helped participants remember to complete their sleep diaries. Ten participants reported missing no treatment sessions; the other 2 reported missing 2 and 4 sessions each. One subject dropped out after one week of treatment saying that light box use conflicted with her schedule.

*Treatment credibility and satisfaction.* Treatment credibility measures were administered 1-2 weeks after starting treatment. Both treatments were found to be credible and subjects in both groups reported that they expected substantial symptom improvement. Satisfaction with treatment outcome was somewhat better in the BWL group.

*Treatment effects.* Change scores were used for between-group comparisons to remove effects of any baseline differences between groups. Robust effect sizes in Cohen’s “medium” and “large” ranges were seen for BWL both between and within groups (0.32-1.56) on fatigue measures (see Appendix VI for all effect sizes). In most cases, effects were somewhat decreased at follow up but were generally in the medium range. This is unexpected, as past research indicates that treatment effects dissipate after treatment is discontinued. Medium or larger effect sizes were also noted for BWL on measures of daytime sleepiness, sleep quality and mood. Effect sizes for DRL were generally small.

Actigraphy findings indicated improvements in sleep in both groups but with larger effect sizes for BWL. Circadian rhythm data were more ambiguous, with modest changes in phase and rhythmicity in both groups. These findings suggest that BWL and DRL therapy are safe, feasible and credible for use with individuals with TBI, that the measures selected were sensitive to treatment effects and that BWL may be a promising treatment for PTBIF, with potential benefits for daytime sleepiness, mood, circadian rhythms and sleep as well. Indeed, daytime sleepiness, mood, circadian rhythms, and sleep quality may actually function as mediators or moderators of BWL treatment effects on PTBIF, given their documented responsiveness to light exposure. Because of the promising initial findings in our small pilot study and the need for empirically validated PTBIF treatment, an *Intervention Efficacy* trial investigating the effect of BWL on PTBIF is warranted. Based on: 1] the literature on alerting effects and cognitive benefits of BWL and the connection between PTBIF and cognition; 2] our own unpublished research suggesting the important role of anxiety in PTBIF and sleep disturbance; and 3] potential improvements in life satisfaction resulting from BWL effects on function, we will evaluate cognition, anxiety and life satisfaction as potential secondary effects of treatment.

To date, no trials of BWL treatment have been conducted in individuals with TBI. However,

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research is under way in Australia examining the effects of blue light, with some positive preliminary results. We have chosen to examine the benefits of BWL rather than blue light in the proposed study for two reasons. First, evidence suggests that extended exposure to blue light may have harmful effects on the retina in older adults. Second, there is strong evidence that as people age, their circadian photoreception decreases, particularly for blue light. Using full spectrum BWL (400nm to 740nm) maximizes the potential benefits of light therapy in adults over 50, who represent a large and growing proportion of people with TBI. In the proposed study, we will examine the effects of age on therapy outcomes. Light therapy also has potential for PTBIF because of its low cost (less than \$200 for a Litebook), apparent lack of side effects and ease of access (it can be easily used at home without supervision), making it safer and more attractive for treating fatigue than pharmacological treatments.

### 3) Setting of the Human Research


All research procedures will be conducted in the Brain Injury Research Center at the Mount Sinai Medical Center at 5 East 98<sup>th</sup> Street and at the Centre for Neuro Skills facilities (all sites). Light box treatment will be self-administered in participants' homes.

### 4) Resources Available to Conduct the Human Research

This research capitalizes upon the existing infrastructure of the Mount Sinai Brain Injury Research Center (MS-BIRC) and the New York TBI Model System (NY-TBI-MS, #02-0677 P1) as it builds on a successful set of standard operating procedures for identifying and enrolling individuals with TBI into research projects, collecting clinical data and prospectively following patients with TBI. Our research team (which consists of four senior PhD level investigators, a PhD level statistician, one Masters level clinical research coordinator, and three research assistants with Bachelor's degrees in related fields, in addition to four postdoctoral research fellows with PhD or PsyD degrees in clinical psychology) has also developed expertise and standardized methods for collecting data from informants of patients who are enrolled in prospective longitudinal studies. Our research team collectively has conducted over a dozen clinical trials, published over 200 peer-reviewed manuscripts, and made presentations at over 100 national and international professional meetings. The research team for this particular study will be trained in the protocol and closely supervised by Dr. Gordon, an established researcher and licensed clinical neuropsychologist. Staff at the BIRC-MS will train the co-investigator and research coordinator at the Centre for Neuro Skills via conference calls, voice and video over internet protocols (such as Skype and Go To Meeting), and in-person meetings at either the Centre for Neuroskills or the BIRC-MS.

Dr. Lisa Kreber, Ph.D. is co-investigator and lead for the project at all Centre for Neuroskills sites involved (Bakersfield, CA, Los Angeles, CA, and in Dallas, TX) with the help of the onsite research coordinators. She is the Senior Neuroscientist/Research Coordinator at the Centre for Neuro Skills in Bakersfield, CA as of 2005. She has worked in TBI research for twelve years dating back to her



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Master’s thesis, with multiple journal publications and presentations. BIRC-MS Faculty, particularly Dr. Gordon, will provide consultation and oversight for this project as needed.

Clinical Research Coordinators will complete screening evaluations and consenting, as well as all assessments, training in use of light boxes, treatment adherence activities and basic data management. CRCs will be at minimum Bachelor’s level prepared, with experience in conducting clinical research and in working with individuals with brain injuries or related disabilities. The study PI will train CRCs to administer the assessments. CRC Level II will assist CRCs as needed, to ensure sufficient personnel for blinded outcome assessment and will train them for data management.

**5) Study Design**

**a) Recruitment Methods**

We will use recruitment techniques that have proved successful in our research, including flyers and discussions with our patients with PTBIF. We will distribute recruitment materials to individuals who participate in other studies or who attend support groups at our center, at consumer conferences and to previous research participants who have expressed willingness to be contacted for future studies. We will post information about the study on the MSMC and Mount Sinai Brain Injury Research Center websites and Facebook page, on Brain Injury Association websites and on clinicaltrials.gov. We will also contact patients seen by our collaborating physiatrists using post mail. Additionally we will distribute recruitment materials at other medical centers serving patients with TBI, such as NYU Langone Medical Center, through collaborating psychologists with patients appropriate for research. Our prior recruitment experience suggests that the sample will be diverse in terms of demographics and injury-based characteristics.


Additionally, we have added the Centre for Neuro Skills facilities, post-acute rehabilitation centers in Bakersfield, CA, Los Angeles, CA, and Dallas, TX as external sites for this project. The site expects to add 30-40 participants per year to the protocol. Patients undergoing post-acute rehabilitation at the Centre for Neuro Skills will be approached for participation in the study.

**b) Inclusion and Exclusion Criteria**

Inclusion Criteria:

1. Documented TBI of any severity
2. At least 12 months post injury (PTBIF typically stabilizes by 12 months<sup>76,77</sup>)
3. Presence of clinically significant fatigue, operationalized as a score of 22 or more on the Multidimensional Assessment of Fatigue (an empirically based cut point previously used for clinical fatigue in TBI);<sup>32,70,71,78</sup>



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4. Age 18 or older
5. English speaking

Exclusion Criteria:

1. Neurological disease other than TBI
2. Pregnancy (because of pregnancy fatigue)
3. Medical illness causing fatigue, such as anemia, hypothyroidism, HIV, renal failure, cirrhosis or cancer treatment in the past year
4. Current major depressive episode or substance abuse
5. Diagnosed sleep disorder or high risk for sleep apnea
6. History of bipolar disorder or manic or hypomanic episodes
7. Current chronic, severe headaches
8. Sensitivity to bright light
9. History of retinal damage or disease.

**6) (NOTE: You may not include members of vulnerable populations as subjects in your research unless you indicate this in your inclusion criteria.)**

**a) Number of Subjects**

To obtain the necessary sample size of 80 study completers with 40 in each treatment arm, we conservatively estimate that we will need to screen 136 individuals (30% negative screens) and enroll 95 of them (15% attrition).

**b) Study Timelines**

Subjects' participation in the study will last approximately two months. Assessments will be conducted at three points: T1 (baseline), T2 (end-of-treatment) and T3 (follow-up at one month post treatment). Actigraph data will be collected for 3 days at T1 (prior to the initiation of treatment). Participants will use the light box for 4 weeks and then return at T2 for repeat administration of the measures and Actigraphy for 3 more days. T3 will take place 4 weeks after light box treatment is completed and will not involve the Actigraph.


**c) Endpoints**

The primary study outcome will be fatigue. Secondary outcomes will include sleepiness, circadian rhythms, mood, satisfaction with life, cognition, anxiety and sleep quality.

**d) Procedures Involved in the Human Research**

Overview of Treatment/Assessments

Subjects' participation in the study will last approximately two months. Assessments will be conducted at three points: T1 (baseline), T2 (end-of-treatment) and T3 (follow-up at one month

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post treatment). Actigraph data will be collected for 3 days at T1 (prior to the initiation of treatment). Participants will use the light box for 4 weeks and then return at T2 for repeat administration of the measures and Actigraphy for 3 more days. T3 will take place 4 weeks after light box treatment is completed and will not involve the Actigraph. Subjects will be paid \$20 for completion of each study assessment (including \$10 for a screening assessment prior to T1).

### Enrollment and Assessments


Potential participants who contact the research team and express interest in the study will undergo the informed consent procedure followed by a screening assessment to assess eligibility. We will obtain consent in accordance with federal and MSSM regulations. Participants who qualify for the study will complete the remaining items from the T1 battery at this point. To document the presence of TBI, they will be asked to provide detailed information about their injury (mechanism, date, severity) and provide medical records or sign releases allowing us to access medical records documenting their TBI.

After completing the baseline battery, we will give participants an Actigraph. They will wear the Actigraph for 72 hours before starting the intervention. They will also complete a sleep diary on which they will record time to bed and time awake. After these three days, they will return to the research center, and we will download their Actigraph data. We will then train participants to use the light box. Consistent with American Academy of Neurology criteria for intervention studies<sup>79</sup> we will then randomly assign subjects to receive either BWL or DRL using a predetermined, random sequence in blocks of randomly determined size between 6 and 10. A staff member of the BIRC who has no contact with the study participants and is not otherwise involved in the project will do the randomization. He or she will provide the research assistant with a case containing the appropriate light box (note that the BWL and DRL light boxes are indistinguishable). Participants will be asked to record their use of the light boxes and their fatigue on a daily basis. A week after treatment begins participants will be called and asked to complete an assessment of treatment credibility and outcome expectancy.

After one month of light treatment (T2), we will re-administer the baseline battery along with satisfaction and user experience questionnaires and 3 more days of Actigraphy. One month after T2, we will administer the assessment battery a third and final time (T3). Research team members who conduct outcome assessments will be blind to participants' treatment allocations. They will enter the data only after the participants have completed all study assessments (i.e. after T3) to avoid bias. Participants will be asked not to reveal treatment allocation to research team members. Participants will also be asked to refrain from light treatment in the month intervening between T2 and T3. Upon completion of follow-up, interested participants will be offered a discount coupon to purchase their own light box if they wish to do so.

### Intervention

Participants will self-administer light daily using a Litebook® (The Litebook Company Ltd.). The

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Litebook is a small (6" x 5" x 1") and lightweight (8 oz.) box. Users are instructed to place it about 18" from their face and within 45° of the visual field for 30 minutes within half an hour of waking each morning, for 4 weeks. The participant may eat, read, watch TV, etc. while sitting in front of the box. The Litebook utilizes light-emitting diodes (LED) to provide a full spectrum that mimics the visible spectrum of sunlight. Although they are white lights, they are blue light "enriched", peaking at 460nm in the blue spectrum, allowing recipients to experience benefits of larger doses of blue light than are present in normal white light, as well as potential benefits of full-spectrum light exposure. Ultraviolet light is filtered out to prevent retinal damage. A device that appears identical but that uses red LEDs emitting DRL, peaking between 625 and 650nm, will be used for the comparison group. Prior to randomization a member of the research team will train participants to use the light box and instruct them to call the research team if they have questions about its use.

**Study Monitoring and Safety**

Bright light therapy has an excellent safety profile and has been shown to be well tolerated by most patients.<sup>48</sup> Side effects are infrequent; the most common ones are mild headache, eyestrain, nausea and agitation. Side effects generally remit spontaneously. Study exclusion criteria were chosen to maximize safety. We will ask subjects to inform us of any new or intensified symptoms or health problems that they experience while using the light box. If significant adverse effects are experienced, the participant will be directed to discontinue treatment temporarily and consult their physician. Subjects will be withdrawn from the study if they experience any clinically significant side effects beyond those anticipated or if side effects are severe. We will ask participants not to alter medication use during the study unless it is medically necessary, and to notify the research team if alterations are made.


**e) Specimen Banking**

N/A

**f) Data Management and Confidentiality**

All data obtained from subjects will be treated confidentially. Only the principal investigators and research assistants will have access to information about subjects that is identifiable. Hard copy data at Mount Sinai and the Centre for Neuro Skills will be stored in a locked file cabinet in the research staff office, with identifying information stored separately. Hard copy data will not be transmitted between Mount Sinai and the Centre for Neuro Skills as it will not be necessary for analysis.

At Mount Sinai and the Centre for Neuro Skills, research data will be stored on secure networked drives with access limited to the research team and collected on secure, encrypted laptops. REDCap (Research Electronic Data Capture- a secure web-based data capture tool supported by Mount Sinai) will be used as a database management system for project data at Mount Sinai.

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REDCap is a secure web-based data capture tool developed by Vanderbilt University and supported by Mount Sinai's Research Information Technology Department. It ensures database designs meet institutional and sponsor standards for security and compatibility. Project data managed by REDCap will have research numbers only, no names or other identifying information. Since Mount Sinai is a partner institution of REDCap, project data will remain on Mount Sinai's secure servers and not be transmitted elsewhere by REDCap. All project data captured in REDCap will not have any identifiers other than the unique research identification numbers, and remain stored on Mount Sinai's secure servers.

Data collected through websites (Assessment Center for Neuro-QOL measures and CNS Vital Signs for cognitive assessment) will be stored securely on those sites without any identifiers other than the unique research identification numbers (see below). Medical records received will be stored in hard copy or scanned into encrypted files. Subjects will be given unique research identification numbers (codes) that will be used for analyses and reports. The link between identifying information and subjects' unique research codes will be stored in an encrypted file. The computer will be kept in a locked room in the research staff office. Access to the link will be limited to the principal investigator, the project coordinator, and the research assistants. Clinical information, if any, included in the research data is protected by the rules on medical record confidentiality of the Mount Sinai Medical Center and HIPAA. Identifying data will be kept separately to ensure participants' confidentiality. Data will be stored for the time period required by Mount Sinai regulations.

All visits completed remotely (via videoconferencing methods such as videochat or Skype) will be completed in a private room so that only the research team will be able to see and hear the research subject.

Data from the actigraphs and light boxes will be sent to Dr. Ancoli-Israel in a password protected, encrypted electronic database by Dr. Spielman, the project statistician or one of the research coordinators. All identifiers will be removed other than study ID numbers.

Data analyses are described in detail in the study protocol.

**g) Provisions to Monitor the Data to Ensure the Safety of Subjects**

**Part I: Elements of a Data and Safety Monitoring Plan**


**MSSM Principal Monitor:**

The principal monitor will be the PI

Last Name: Gordon

First Name: Wayne

Academic Title: Jack Nash Professor, Vice Chair

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Bright light therapy has an excellent safety profile and has been shown to be well tolerated by most patients. Most of the risks of the intervention are relatively minor. Side effects are infrequent; the most common ones are mild headache, eyestrain, nausea and agitation. Side effects generally remit spontaneously. Study exclusion criteria (listed above) were chosen to maximize safety. Steps will be taken to exclude those at greater risk (e.g., individuals with depression, mania, chronic headache). Subjects will be asked to document any new or intensified symptoms or health problems that they experience while using the light box and to notify the research team of any. If significant adverse effects are experienced, the participant will be directed to discontinue treatment temporarily and consult their physician. Subjects will be withdrawn from the study if they experience any clinically significant side effects beyond those anticipated or if side effects are severe. Participants will be asked not to alter medication use during the study unless it is medically necessary to do so; they will be asked to notify the research team if they do so. Adverse events (including accumulated adverse events) will be monitored weekly by the PI (local monitor).

**Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)**


The study’s safety will be monitored by the PI and PPHS in keeping with National Institute of Neurological Disorders and Stroke guidelines for monitoring clinical trials.<sup>80</sup> He will monitor safety, adverse events, data quality, completeness and timeliness; compliance with goals for recruitment and retention; protocol violations; and scientific developments external to the study that may impact participant safety or the ethics of the study. All adverse events and safety issues will be reported to the PPHS and sponsor in concordance with Mount Sinai PPHS regulations.

**h) Withdrawal of Subjects**

Subjects may withdraw their participation at any time. We ask them to notify us in writing if they decide to withdraw. In addition, subjects will be withdrawn from the study if they experience any clinically significant side effects beyond those anticipated or if side effects are severe.

**7) Risks to Subjects**

Bright light therapy has an excellent safety profile and has been shown to be well tolerated by most patients.<sup>48</sup> Side effects are infrequent; the most common ones are mild headache,

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eyestrain, nausea and agitation. Side effects generally remit spontaneously. Study exclusion criteria were chosen to maximize safety. Subjects entering the study are screened by the research coordinator using the Mini International Neuropsychiatric Interview (MINI) for any history of bipolar disorder or manic episodes. Those who endorse any past history of bipolar disorder or manic episodes are immediately disqualified from the study. Those who do qualify are contacted bi-weekly during the light therapy phase of the study to check in for any symptoms of mania, adverse events or other health concerns. Qualified subjects are also explicitly instructed to contact the PI and research team of any health problems they sustain while in the light treatment phase of the study. Other risks in the study are related to loss of private information and emotional discomfort or distress from personal questions asked during interviews and assessment screenings. These issues will be monitored for safety.

### 8) Provisions for Research Related Harm/Injury

We will ask subjects to inform us of any new or intensified symptoms or health problems that they experience while using the light box. If significant adverse effects are experienced, the participant will be directed to discontinue treatment temporarily and consult their physician. Subjects will be withdrawn from the study if they experience any clinically significant side effects beyond those anticipated or if side effects are severe. We will ask participants not to alter medication use during the study unless it is medically necessary, and to notify the research team if alterations are made.


It is possible that some of the questions asked during interviews may make the participant feel uncomfortable. However, answering these questions isn't mandated. Also, there always exists the potential for loss of private information; however, there are procedures in place to minimize this risk. These procedures include (but are not limited to) keeping paper documents in locked cabinets and using passwords to protect electronic files.

### 9) Potential Benefits to Subjects

Participants may experience improvements in fatigue, mood, or sleepiness. They may also experience no benefits. There is much discussion in the literature on the most effective wavelength for treating sleep and depression. DRL may still have an effect on mood and sleep but it is rarely significant. Thus, it is one of the traditionally used controls for BWL (31, 32). We expect benefits to occur in the bright white group only.

### 10) Provisions to Protect the Privacy Interests of Subjects

Participants' privacy interests will be protected by ensuring that all communication of sensitive or personal information is done in private conversations with project CRC's. CRC's are trained to

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interview subjects respectfully and with sensitivity to privacy concerns, particularly when discussing potentially sensitive topics relating to personal function and behavior (e.g., regarding personal care or emotional distress). They are trained to listen attentively and empathically but without inappropriate familiarity. Participants are given the option of not responding to questions that they do not want to respond to. When attempting follow up with participants, telephone messages that maybe left do not identify the individual as a research subject and include no personal information about their medical condition.

### 11) Economic Impact on Subjects

It is not expected that participants will incur any costs by participating in the research.

### 12) Payments to Subjects


Subjects will be paid \$20 by check for completion of each study assessment (including \$10 for a screening assessment prior to T1). Upon completion of follow-up, interested participants will be offered a discount coupon to purchase their own light box if they wish to do so. In order to issue checks, the Mount Sinai Department of Finance may need to collect private health information from participants, such as social security number, for tax reporting purposes. If participants do not wish to disclose their social security number, they can waive their compensation during their first visit by telling the research staff that they do not wish to receive payment.

### 13) Consent Process

The consent process will take place in a private testing room at the BIRC.

Before the subject has signed the consent form, agreeing to participate in the study, the research coordinator will determine if the subject has capacity to provide informed consent. Verbal feedback will be solicited from potential subjects in order to judge their capacity to consent, according to the University Of California San Diego Brief Assessment Of Capacity to Consent (UBACC). They will be asked to state in their own words what the purpose of the study is, what they are expected to do, and what the risks and benefits are. If they fail to provide correct answers, they will receive the explanation of the study again. If they fail again to provide correct answers to any questions, they will not be accepted in the study. If necessary, a mental status examination will be administered. Subjects will be encouraged to contact the principal investigator if they have questions about the protocol.



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If the patient is deemed capable of consenting, the consent process will proceed according to SOP HRP-090 Informed Consent Process for Research.

**14) Process to Document Consent in Writing**

Consent will be documented using the standard PPHS consent template.

**15) Vulnerable Populations**

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

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

This research involves cognitively impaired adults. In order for the subject to participate in research, he/she must demonstrate the capacity to give informed consent by attaining a score of 20 on the UBACC, as described in “Consent Process” above. Subjects who do not attain a score of 20 will be excluded from the study.

**16) Multi-Site Human Research (Coordinating Center)**


Mount Sinai will be the coordinating and main research center. Data from all sites (Centre for Neuro Skills and Mount Sinai) will be stored on the same electronically encrypted databases initially created at Mount Sinai. Centre for Neuro Skills research staff will be given access to these databases to enter their research data.

**17) Community-Based Participatory Research**

N/A

**18) Sharing of Results with Subjects**

There are no plans to share data with subjects although data will be provided to research subjects or their providers on request.


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**19) External IRB Review History**

N/A

**20) Control of Drugs, Biologics, or Devices**

Light boxes and actigraphs will be stored in locked cabinets in the Brain Injury Research Center.

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## 6. Analyses and Statistical Plan

### a. Data Processing

We will follow all relevant federal regulations regarding confidentiality and data security in research. We will review forms for completeness and accuracy prior to data entry. The database for the project will be established in REDCap, a web-based data management system. REDCap minimizes data entry errors by using menu-driven modules designed to accept only the valid range of values for each variable. Double-entry will reduce the chance of other errors

Dr. Lianqi Liu will carry out Actigraphy data analyses on a de-identified encrypted database. The Actiware 5 software calculates sleep/wake statistics based on night intervals marked by the scorer, i.e., it provides these statistics for each interval (night), as well as a mean of all intervals (nights). Once the night intervals are correctly marked, the software scores each epoch (minute) as sleep or wake, based on a specific internal algorithm and provides analysis of data, including sleep onset latency, sleep efficiency, sleep time, wake time, % sleep, % wake, naps, resting and normal night time sleep. The Actigraphy software does not provide circadian activity rhythms analysis. Dr. Lianqi Liu will export edited epoch-by-epoch activity data to SAS programs to perform standard circadian activity analysis including calculation of Amplitude, Acrophase, Mesor, and the F-statistic. The activity level per epoch (minute) is used to estimate circadian activity rhythms. Circadian activity rhythms are analyzed by fitting each subject's activity data to a 5-parameter extended cosine model.<sup>117</sup>


### b. Data Analyses: Overview

We will calculate descriptive statistics for all measures. We will examine distributions and address substantial non-normality using data transformations, as necessary. If we detect a significant baseline group imbalance on a demographic or clinical variable, we will include that variable as a covariate in subsequent analyses. Dropouts and treatment completers will be compared on baseline variables. We will examine associations among demographic characteristics and outcome measures to identify necessary covariates for subsequent analyses.

We will fit random effects models to test the primary hypotheses, examining the effects of treatment over time. This model is a preferable alternative to traditional repeated measures ANOVA or ANCOVA, in that it takes into account the correlated nature of repeated measurement within an individual. The model allows us to examine the influence of demographic and injury characteristics prior to the inclusion of the treatment effect. We will conduct analyses on the full Intent-To-Treat sample (all subjects randomized) using full maximum likelihood estimation. We will determine model fit using Akaike's Information Criteria.

### c. Hypothesis Testing

*H1: Individuals receiving daily BWL treatment will report significant reductions in fatigue from baseline compared to those receiving DRL.* The primary outcome measure, GFI, will be the dependent variable in the multi-level regression. We will enter time into the model first and examine fit. We will add any demographic or study measures identified as potential confounders in the preliminary analyses, and examine improvement of fit. Finally, we will add the treatment effect to the model and examine differences in fit to determine the presence and strength of the treatment effect over time. The same analyses will be conducted using our secondary fatigue outcome measure, the TBI-QOL Fatigue.

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*H2: Individuals receiving daily BWL treatment will report significant reductions in daytime sleepiness and depressed mood as well as improvements in sleep quality and circadian rhythms from baseline compared to those receiving DRL.* Testing of this hypothesis will be identical to that for H1, with ESS (sleepiness), Neuro-QOL Depression (mood), NeuroQol Sleep (sleep quality) and circadian rhythm measures (from Actigraphy) as the dependent variables.

*H3: Treatment effects will be maintained one month after treatment completion.* Pilot data suggests that the positive effects of BWL persist beyond termination of active treatment. To address whether treatment effects are indeed maintained one month after treatment completion, we will extend the multilevel analysis for H1 to include data from the T3 follow-up assessment. One advantage of a third assessment is that the possibility of time as a non-linear effect can be explored. Model fit for a linear versus non-linear time effect will be compared to determine best fit. As in H1, any demographic or study measures identified in the preliminary analyses will be added, with examination of improvement of fit. Finally, we will add the treatment effect to the model to examine the persistence of the treatment effect over time.

d. Research Questions


*RQ1: We will assess whether treatment with BWL is associated with changes in circadian rhythms and improvements in anxiety, cognition and life satisfaction using the analyses described for H1, with Neuro-QOL Anxiety, CNS Vital Signs Neurocognitive Index and CFQ (cognition), and SWLS (life satisfaction) as the respective dependent variables.*

*RQ2: As it is not clear whether BWL's effects on PTBIF are direct effects or secondary to changes in other domains, we will examine whether PTBIF scores are mediated or moderated by mood, sleepiness, sleep quality and circadian rhythms. These analyses will focus on the magnitude of the effect, as recommended by Kraemer et al.<sup>118</sup> We will use a fixed-effects approach in which the dependent variable is the GFI pre-post change. We will compare the between treatment group effect sizes for those with and without the respective potential mediator or moderator. An effect will be considered present if a substantial difference in effect size is observed. Results from these exploratory analyses could be used to guide the design of future RCTs that would focus on those subjects most likely to respond to BWL.*

*RQ3: Because current research suggests that age, gender and injury severity may be associated with treatment outcome,<sup>33,65,119,120</sup> we will examine these individual characteristics and any others that the literature suggests may be relevant at the time of analysis. We will add these variables to the multilevel model one at a time and test to determine if the variable improves fit. Continuous variables that improve the fit will be examined further by determining the correlation between them and GFI separately for the two treatment groups, and comparing the strength of the correlations.*

e. Statistical Power

[The sample size for this study will provide adequate power to test the primary hypothesis. We will recruit enough subjects to fill the Treatment (DRL-BWL)-by-Time (pre-post) repeated measures design (40 subjects per treatment group, total N = 80). This design achieves 90% power to test the treatment effect using a Geisser-Greenhouse Corrected F Test with a 5% significance level, based on an effect size of 0.37, and achieves 81% power to test the Treatment-by-Time interaction using a Geisser-Greenhouse

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Corrected F Test with a 5% significance level, based on an effect size of 0.32. Effect sizes (Appendix VI) were chosen based on the pilot findings, and then reduced by 20% to correct for possible inflation given the small sample size. []