TWILIGHT Study: Treatment with Light Therapy

Effect of light exposure during acute rehabilitation on sleep after traumatic brain injury

Protocol Version 1.2

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Confidentiality Statement

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I. Background and Significance:

Sleep disturbance is a common clinical problem after Traumatic Brain Injury (TBI). Disrupted sleep exacerbates other symptoms after TBI such as fatigue and can impede overall recovery after TBI (Castriotta RJ W. M., June 15, 2007) (Mathias JL, 2012;13). Trouble falling or staying asleep (insomnia) and reversal of sleep/wake cycles (circadian rhythm disorders) are two categories of sleep disturbance occurring frequently after TBI. Insomnia affects roughly one-third of TBI survivors and reports of overall sleep disturbances are as high as 70% (Mathias JL, 2012;13). In a study by Ayalon et al. (Ayalon L, 2007), 36% of individuals with TBI who reported suffering from insomnia met the diagnostic criteria for a circadian rhythm sleep disorder. Sleep disturbances are also common during inpatient rehabilitation. Makley et al. (Makley MJ E. J., 2008) found that 68% of patients with a closed head injury demonstrated disturbed sleep during inpatient rehabilitation. The clinical utility of diagnosing sleep disorders using criteria from the Diagnostic and Statistical Manual or International Classification of Sleep Disorders is limited in clinical situations such as the first weeks of recovery after TBI as these diagnostic criteria require the presence of symptoms for at least a month, rely heavily on subjective report and can be confusing given the frequency of co-occurring medical and psychiatric disorders (Ohayon MM, 2009). In these clinical situations, other tools for assessing sleep quality may be especially useful. These tools include sleep logs, measurements of movement with actigraphy and overall clinical assessment of sleep patterns.

Most studies looking at treatment of sleep disturbances and wakefulness after TBI have focused on pharmacologic interventions and have reported limited efficacy in improving sleep. The sedative-hypnotic medications typically used in the treatment of sleep disorders in the general population are often not appropriate for use after TBI given concerns about cognitive and behavioral side effects (Flanagan SR, 2007) (Larson EB, 2010). There are case reports of improved sleep in the chronic phase of TBI recovery with cognitive behavioral therapy (Ouellet MC M. C., 2007) and light exposure (Carter KA, 2010) (Chesson AL, 1999) but these treatments have not been studied in the acute rehabilitation phase. BWL exposure is considered an appropriate option for some sleep disorders in a variety of clinical populations including those with dementia (Mishima K, 1994) (Riemersma-van der Lek RF, 2008). The proposed study will help elucidate both the effects of BWL exposure after TBI in the inpatient rehabilitation setting as well as clinical feasibility of delivering light exposure in this case setting.

Sleep disturbance may hinder the rehabilitation process. Clinically significant sleep disturbances after TBI correlate with higher rates of depression, anxiety, pain (Fogelberg DJ, 2012) and fatigue (Englander J, 2010), all conditions which could deter full engagement in rehabilitation. Even in a healthy population a moderate reduction in the amount of quality sleep over time can negatively impact cognitive functions such as behavioral alertness and working memory (Banks S, 2007). BWL exposure has been shown to be effective in both reducing agitated behavior and improving cognition in older adults with dementia (Mishima K, 1994) (Riemersma-van der Lek RF, 2008) (Forbes D, 2011). After TBI, there is an association of sleep problems with more functional limitations, higher reliance on other people for care, and diminished satisfaction with quality of life at one year after injury (Fogelberg DJ, 2012). Improved sleep in the acute recovery phase after TBI may positively impact other rehabilitation outcomes. In the study by Makley, et al. (Makley MJ J.-G. L., 2009) sleep disturbance was associated with longer average length of stay for both acute trauma center (22 days vs. 9 days) and inpatient rehabilitation (37 days vs. 21 days). In non-TBI populations BWL exposure has shown efficacy in the treatment of mood symptoms and improving alertness even with small doses and durations of treatment, such as a single one-hour session (Reeves GM, 2012) (Riemersma-van der Lek RF, 2008) (Revell VL, Jan 2006) (Chang AM, 2012) (Terman M, 2005) (Wirz-Justice A, 2012) (Friedman L, May 2012)

(Neikrug AB, 2012). These additional effects of BWL exposure may provide clinical benefit beyond improved sleep in persons recovering from TBI and will be assessed in the proposed study.

Research and clinical evaluation of sleep often employ actigraphy, which allows for the evaluation of subject movement over time and can be extrapolated to wake/rest cycles (Morgenthaler TI, 2007). Use of actigraphy for sleep evaluation with subjects after brain injury has been successful in both inpatient (Zollman FS C. C., 2010) and outpatient settings (Ayalon L, 2007). Additionally, considerations regarding movements and sleep specific to TBI and actigraph placement, including spasticity and paresis (Zollman FS C. C., 2010), are important and will be considered in the execution of this study.

Our study group has extensive experience with the inpatient Rehabilitation brain injured population, research experience in regards to sleep after brain injury, and demonstrated use of light therapy and actigraphy in individuals with TBI (Fogelberg DJ, 2012) (Watson NF, 2007) . The University of Washington investigators have current IRB permission to conduct a pilot study of BWL exposure on the acute rehabilitation unit to allow for the current study protocol to be refined early in the research process and demonstrate logistics and feasibility to collaborating TBIMS centers. In the current health care climate, low cost treatments with low staff burden are valued and we will evaluate these factors in this study (Wood RL, 1999) (Whitmore RG, 2012).

II. Target Population:

Individuals aged 18-70 years with moderate to severe traumatic brain injury (TBI), 30 days or less out from TBI hospitalized on acute inpatient rehabilitation. Moderate to severe TBI will be determined using the TBI Model System (TBIMS) case definition (Traumatic Brain Injury Model Systems, 2013): damage to brain tissue caused by an external mechanical force, post-traumatic amnesia (PTA) greater than 24 hours, or loss of consciousness greater than 30 minutes or Glasgow Coma Scale (GCS) score in the Emergency Department of 3-12, or intracranial abnormalities on imaging (Cuthbert JP, 2012).

Exclusion parameters for age and time since injury are needed in this study since sleep patterns and light effects change with aging and the focus of this study is in the early recovery phase of TBI. Potential subjects will be excluded from the study if they have a past medical history of bipolar disorder (Terman M, 2005); retinal pathology, complete blindness, or light sensitivity; absence of eye opening; tetraplegia with less than antigravity strength in all myotomes caudal to C6 level given the limitations on measuring movements with; or confirmed or suspected diagnosis of obstructive sleep apnea (Zollman FS C. C., 2010). BWL exposure is unlikely to change the underlying pathology for obstructed sleep and therefore potential subjects with a known history of sleep apnea treated with continuous positive pressure device, a body mass index > 40 kg/m2 at eligibility assessment, or who are classified as being "high risk" for sleep apnea based on the Berlin questionnaire (Netzer NC, 1999) will be excluded from the study. The Berlin questionnaire evaluates risks factors for sleep apnea including snoring, breathing pauses and daytime sleepiness. We are utilizing multiple criteria for exclusion for obstructive sleep apnea given the potential limitations of subjective questionnaires in subjects with TBI.

III. Potential benefit to this population:

Bright White Light (BWL) exposure has potential to clinically impact care for persons with Traumatic Brain Injury, especially given the prevalence of co-occurring conditions such as sleep and mood disorders. Investigations into the use and tolerance of Bright White Light exposure in this population are limited, especially in the acute recovery phase and in the inpatient setting. This study will improve our understanding of therapeutic and functional effects of light therapy and the relationship

with sleep efficiency. There is interest in non-pharmacologic treatment options for complications arising from patients experiencing a Traumatic Brain Injury (TBI), and this study investigates a treatment option and feasibility of integrating into usual care in the inpatient rehabilitation unit setting. If our hypothesis is correct, and there is clinically significant benefit from Bright White Light exposure, some study participants may have direct benefit from this study.

IV. Research Hypothesis's and Specific Aims

Specific Aims:

Aim 1: In persons with TBI, prospectively compare overnight sleep efficiency in a cohort exposed to morning Bright White Light with a comparison group exposed to Red Light in an acute inpatient rehabilitation setting.

Aim 2: Explore the relationship between Bright White Light exposure during inpatient rehabilitation after TBI and mood, therapy participation, attention, rate of functional recovery and length of stay.

Aim 3: Develop and describe sleep study procedures on the inpatient rehabilitation unit for persons with TBI to support optimal and feasible design of future studies in this important area.

Research Hypothesis:

In persons with TBI, prospectively compare overnight sleep in a cohort exposed to morning Bright White Light with a comparison group exposed to Red Light in an acute inpatient rehabilitation setting.

Hypothesis 1: Individuals exposed to Bright White Light for 30 minutes each morning will have better sleep compared to the Red Light exposure group, as measured by sleep efficiency.

Hypothesis 2: Individuals with daily morning Bright White Light exposure will have better mood (as measured by the Positive and Negative Affective Schedule, PANAS), therapy participation (as measured by a 0-100 therapist rating) and attention (as measured by the Symbol Digit Modalities Test) at 10 days compared to individuals with daily Red Light exposure. The group exposed to Bright White Light will also have less daytime sleepiness and fatigue (as measured by the Karolinska Sleepiness Scale (KSS) and the Barrow Neurological Institute Fatigue Scale (BNI-FS), a faster rate of functional recovery as measured by FIM^{TM} efficiency for the rehabilitation stay and a shorter length of stay compared to those in the Red Light group

Hypothesis 3a: Bright White Light exposure will be rated as a reasonable addition to clinical care by staff using Likert scale ratings. Categorize and quantify rates of any side effects of Bright White Light and Red Light exposure in persons with TBI during inpatient rehabilitation.

Hypothesis 3b: Bright White Light and Red Light exposure will be generally well tolerated with side effect profiles and rates similar to those observed in previous studies with other populations.

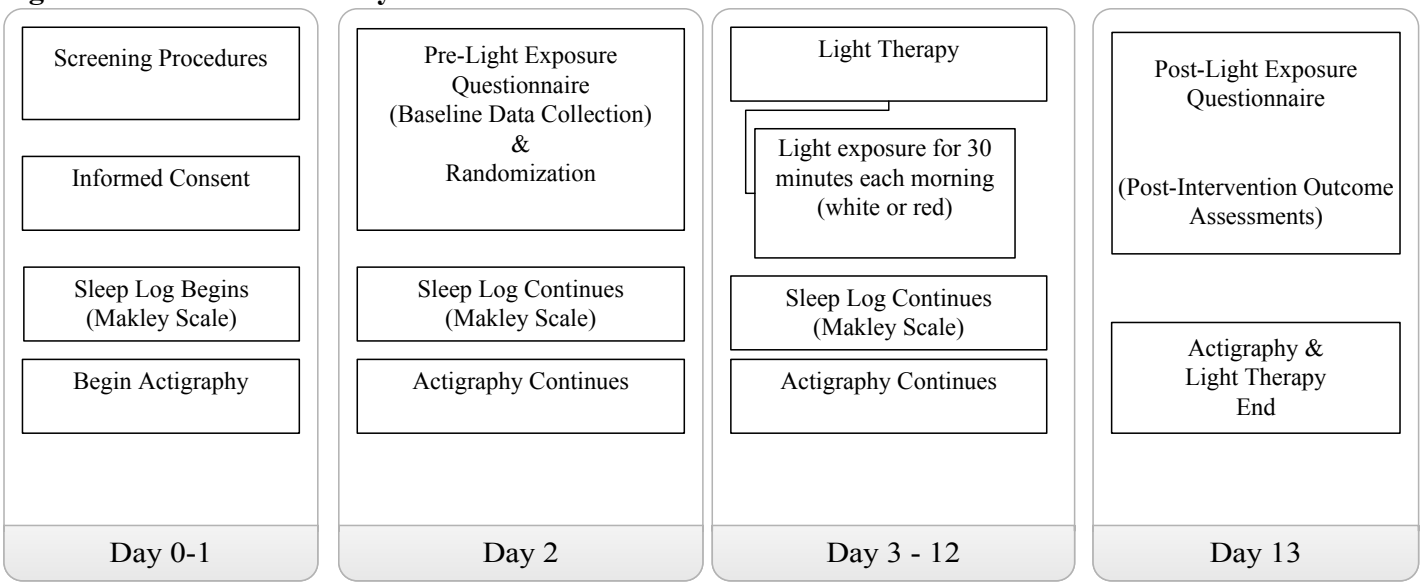
See Appendix for Flowchart on Specific Aims of this study

V. Study Description

We propose to recruit a prospective cohort of persons with TBI to compare effects of Bright White Light exposure to Red Light (RL) exposure. Light therapy treatments will be given daily in the morning for up to 10 days, and an Actiwatch will be worn that records movements for the entirety of the study. We will utilize objective assessments of sleep quality, subjective mood report, rate sleepiness and fatigue and complete measures of attention and participation in rehabilitation therapies to explore the

effects of light exposure in the acute inpatient rehabilitation setting. We will also evaluate the anticipated device costs and staff burden involved in utilizing light therapy exposure in the inpatient rehabilitation clinical setting. An overview of study procedures with timeline is described in Figure 1 below with further details in the sections that follow.

Figure 1. **Overview of Study Procedures for TWILIGHT**



VI. Screening for Eligibility:

Although subjects will be screened for this study concurrent with screening for eligibility for enrollment into the Traumatic Brain Injury Model System (TBIMS) study (Traumatic Brain Injury Model Systems, 2013), these are independent studies and subjects will have the choice to enroll in both, neither, or either one. The TBI Model Systems program, sponsored by the National Institute on Disability and Rehabilitation Research (NIDRR), is the largest longitudinal study of TBI in the nation. NIDRR awards 5 year grant awards to institutions that are national leaders in medical research and patient care and these. Institutions which receive this distinction are collectively termed, the TBI Model Systems. As part of the TBI Model Systems, the University of Washington TBI Model Systems research team is recognized as providing the highest level of comprehensive specialty services from the point of injury through chronic care stages, including re-entry into full community life. The current grant cycle is for the 2012-2017 time period, and one of the areas of interest for the UW TBI Model Systems research team is the treatment of sleep difficulties after TBI.

The screening process will begin will reviewing the medical charts for patients that are on the inpatient rehabilitation unit at Harborview Medical Center. If a patient meets the inclusion criteria, research staff will approach the patient to determine whether the patient is cognitively capable of giving their consent for the study by administering the Galveston Orientation and Amnesia Test. The study will then be explained to the patient; or if the patient is experiencing post traumatic amnesia, the study will be explained to the patient's legally authorized representative. Consent will be obtained either from the patient or, if he or she is unable to provide informed consent, the patient's legally authorized representative.

VII. Study Sample:

Study participants will be recruited from acute inpatient rehabilitation at three participating TBI Model Systems institutions (University of Washington, Mount Sinai, Baylor). Eligible participants will be within three months of sustaining a moderate to severe TBI (as defined by the TBI Model Systems (Traumatic Brain Injury Model Systems, 2013)), admitted to acute inpatient rehabilitation, English speaking, and aged 18-70 years. Exclusionary medical factors will be identified in the medical record and through interview during screening/baseline assessment. In a pilot study comparing the effects of BWL and RL exposure in a sample of subjects with chronic TBI, Cantor et al. (Cantor, et al., 2012) reported an effect size of 0.63 for sleep duration. Because this pilot study involved subjects in the chronic phase of TBI, who were living at home rather than in an institution, and underwent a longer course of treatment (28 days in that study vs. 10 days in this study), we chose to take a conservative approach to calculating the required sample size. Based on an estimated effect size of 0.5 and 80% power, 128 subjects would be required to complete this study (64 per group). We anticipate recruitment over three years at three sites. Historical TBIMS and associated trial enrollment totals from the participating sites supports this study enrollment goal.

VIII. Inclusion Criteria:

1. Within three months of moderate to severe TBI
2. Admitted to acute inpatient rehabilitation
3. Ages 18-70
4. English speaking

VIII. Exclusion Criteria:

1. Complete blindness
2. Absence of eye opening or disorders of consciousness (Rancho level of 1-3)
3. Past medical history of retinal pathology
4. Past medical history of light sensitivity
5. Past medical history of narcolepsy
6. Past medical history of bipolar disorder
7. Past medical history of obstructive sleep apnea (OSA)
8. Sleep disturbance defined as having a "0" rating by research staff (using all sources available). If rated a "0" for no sleep disturbance, they must also NOT be receiving sleep medications in the last 72 hours
9. Suspected diagnosis of obstructive sleep apnea (determined by the Berlin Questionnaire)
10. Tetraplegia with less than antigravity strength in all myotomes caudal to C6 level given the limitations on measuring movements with actigraphy in this population (i.e. cannot reliably detect upper extremity or lower extremity movement with this level of paralysis).
11. Current medical orders indicated for night time sleep disruption (e.g. chest PT, MIE q2 hours of meds that disrupt sleep). *May be re-approached if the medical orders are no longer in place.

IX. Rationale for Study Population

The study population of interest is TBI in the setting of acute inpatient rehabilitation, which is typically moderate to severe TBI. Persons less than 18 years of age or greater than 70 years are being excluded from the study because of baseline sleep physiology differences seen in younger and advanced ages. We wish to enroll those with sleep disturbances; those with normal sleep will not be enrolled. We are excluding those who would not benefit from light exposure due to eye abnormalities or those with other pathology that will interfere with sleep and cannot be affected by light exposure. Additionally, since actigraphy relies on limb movement for recording, those with tetraplegia would be excluded.

X. Data Collection and Measures

Screening of subjects will need to occur to determine eligibility of subjects, including review of medical chart. If patients are not eligible or are excluded based on exclusion criteria, no identifiable data is retained. Once consented into the study, the exclusion criteria will be reviewed with the patient and/or their legal representative. Data collection measures, areas assessed, and the timing of when this data is collected is shown in Table 1.

Table 1: Data Collection Measures and Areas Assessed

Measure	Area to be Assessed	Screening and Baseline (Day 0-2)	Intervention (Days 3-12)	Outcome (Day 13)
Demographics	Characteristics (age, education, gender)	X		
Injury characteristics	Cause of injury, date of injury, lowest GCS, PTA/GOAT	X		
Medical History	Diagnoses, medications at enrollment, symptoms, associated injuries (ICD-9 codes), vital signs	X		
Berlin questionnaire	Sleep apnea	X		
Clinician Rating: Delirium Rating Scale Revised 98 Item 1	Sleep disturbance	X		
Makley scale	Sleep disturbance	X	X	
Actigraphy	Sleep parameters	X	X	
Light Therapy Time	Light exposure time		X	
Medication categories	Potential confounders (see data sheet)	X		X
FIM™ Scores and Efficiency	Functional score	X		X
Hospitalization	Acute LOS, Rehab LOS	X		X
Symbol Digit Modalities Test	Attention	X		X
PANAS	Mood	X		X
Therapy participation	Function	X		X
Karolinska Sleepiness Scale	Daytime sleepiness	X		X
Barrow Neurological Institute Fatigue Scale	Daytime fatigue	X		X

A. Screening Measures:

The following data will be used as descriptive characteristics of the subjects upon study completion. Initially this data will be used during the screening process to ensure appropriate patients are approached for participation:

- **Demographics**: Age, gender, race/ethnicity, weight (kg), height (cm), BMI (calculated).

- **Injury Characteristics:** Time since injury, Post-resuscitation GCS score, duration of PTA as measured by TBIMS procedures using the Galveston Orientation and Amnesia Test (GOAT), associated injuries including ICD codes.
- **Medical History:** Current diagnoses, past diagnoses, medications (at enrollment, during treatment and at outcome measure), vital signs.
- **Berlin Questionnaire** (Netzer NC, 1999): The 10-item questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

B. Randomization Measure:

Randomization will occur by research staff member assessing the patient for sleep disturbance, using all sources available, in the first item question from the *Clinician Rating: Delirium Rating Scale – Revised 98* (DelRS-R98) (Trzepacz PT, 2001). Our recent prevalence work showed that 86% of acute TBI admissions have sleep abnormalities using clinician ratings, specifically the DelRS-R98 (Nakase-Richardson R S. M., Prospective evaluation of the nature, course, and impact of acute sleep abnormality following TBI , 2013). Sleep disturbance questions will be asked of the clinical staff whom were involved in caring for the patient during Day 1 of study participation, significant other (if available), and directly of the patient (if possible). The rating will be used as a sleep disturbance severity marker which will be utilized by the statistician during randomization to help control for sleep disturbance severity (Sjösten N, July 2009).

C. Primary Outcome Measure:

Sleep efficiency scores derived from actigraphy data will be the primary outcome, and analysis will be done by Donald Fogelberg, Ph.D at the University of Washington. An Actiwatch 2 (Philips/Respironics, Bend, OR) will be used for study purposes to facilitate consistent measurement across sites. We will set the Actiwatch to record activity data in 60-second intervals. Actigraphy data will be automatically scored with Actiware software (Respironics, Philips Healthcare), which uses validated algorithms to determine whether an epoch of activity is "sleep" or "wake" (Cole RJ, 1992). Typically there is a lack of a consistent sleep/wake cycle in the study population, therefore we will be using sleep efficiency and total sleep time scores obtained during a set night-time interval (2200 to 0600) as the primary index of sleep function, as has been used in previous publications[39, 40]. We will be comparing average between group differences between the BWL and RL groups at baseline and after 10 days of light exposure.

D. Secondary Outcome Measures:

- Makley Scale: The Makley scale is a 4-point ordinal scale which allows staff to score sleep as follows: 0 = asleep; 1 = drowsy/falling asleep; 2 = drowsy/waking up; 3 = awake. An hourly sleep log on each patient will be filled out every two hours by the unit nursing staff from 2200 to 0600 hours starting at baseline and through the duration of the study.[41]]
- [42] Functional Independence Measure (FIM) is the most widely accepted functional assessment measure in use in the rehabilitation community. The FIM^{TM} is an 18-item ordinal scale, used with all diagnoses within a rehabilitation population. It is viewed as most practical for assessment of progress during inpatient rehabilitation (State University of New York at Buffalo, 1997) and is assessed as part of normal rehabilitation care at admission and discharge from the rehabilitation unit. FIM^{TM} efficiency is simply the change in FIM^{TM} score divided by the length of rehabilitation stay and is used as marker of relative speed of functional change. We will evaluate for effects on both FIM^{TM} motor and FIM^{TM} cognitive scores.
- Symbol Digit Modalities Test[43]: The SDMT is a pencil and paper test for attention that takes approximately five minutes to administer and is frequently used in evaluations after TBI (DeMonte,

2009)) (Kalmar K, 2008) (Hanks R, 2008). The SDMT will be administered at enrollment and after intervention. The Interagency Workgroup on TBI Outcomes selected the Symbol Digit Modalities Test as CORE common data elements in TBI outcomes research.

- Positive and Negative Affect Schedule: The 20-item Positive and Negative Affect Schedule (PANAS), developed with a sample of undergraduate students and validated with adult populations, comprises two mood scales, one measuring positive affect and the other measuring negative affect. Each item is rated on a 5-point scale ranging from 1 = very slightly or not at all to 5 = extremely to indicate the extent to which the respondent has felt this way in the indicated time frame. This scale is used to measure affect over a range of times including: at this moment, today, the past few days, the past week, the past few weeks, the past year, and generally (on average). Watson et al. (Watson, 1988) reported Cronbach's alpha coefficients for the various time reference periods ranging from .86 to .90 for the Positive Affect scale and .84 to .87 for the Negative Affect scale. For the general period, alpha was.88 for Positive Affect and .87 for Negative Affect. Test-retest correlations for an 8-week period ranged from .47 to .68 for Positive Affect, .39 to .71 for Negative Affect (for the general time period, Positive Affect stability = .68, Negative Affect Stability = .71[44]).
- Therapy Participation: Participation in rehabilitation therapies will be evaluated at enrollment and again after light therapy (day 13) by the subject's therapist using a 0-100 scale of cooperation with therapy that has been previously utilized in this population.[45]
- Karolinska Sleepiness Scale (KSS): The KSS is a well-validated, widely used single question survey that examines current sleepiness.
- Barrow Neurological Institute Fatigue Scale (BNI-FS): The BNI-FS is a scale that was designed to examine fatigue during acute recovery from TBI. It has good internal consistency and appears to specifically examine a single psychometric construct of fatigue in patients with TBI (Wäljas M, 2012).
- Clinician Feasibility Survey: This is a likert scale survey to assess phototherapy intervention for ease of use, perceived relevance to rehabilitation care, and impression of effectiveness. This survey will be available in paper and electronic versions.

XI. Study Procedures:

Screening and Enrollment:

Patients' medical records will be screened for inclusion/exclusion criteria. Informed consent will be obtained from the subjects after they have been determined to be cognitively capable to consent for the study. A subject will be considered unable to give independent consent if they are still in PTA (as measured by the Galveston Orientation & Amnesia Test (GOAT), with a score <76) or their medical record at the time of enrollment specifies that they are unable for other reasons to independently consent. If a subject is unable to consider consent independently, proxy consent will be obtained from the legally authorized representative (LAR). This process is part of obtaining informed consent for the TBI Model System study. In addition, clinical staff and research staff have established communication lines to approach patients at appropriate times that do not interfere with patient clinical care.

Baseline and Randomization:

Day 0-1 (2 days): After determining eligibility, the participant will be fitted with an Actiwatch (actigraphy) for continuous monitoring of activity levels both during the day and night (American Sleep Disorders Associatio, 1995). The Actiwatch will be worn continuously (with removal as needed for hygiene, shower or other clinical care) from enrollment to outcome measurement. Actiwatches will be fully charged and cleared of all previous data before being provided to a subject. Units will be set to record activity data in 60-second epochs. Actiwatches have sufficient built-in memory capacity and battery life to be used for approximately 30 days without recharging. Additionally, sleep logs that rate patient sleep are filled out every hour, between the hours of 2200-0600, this information is then obtained

as completion of the Makley scale. A complete review of symptoms and medical history will be obtained from the subject, LAR, and medical records.

Day 2: Baseline data collection is obtained (See Appendix for Baseline Data Collection Forms). Measures collected include: Symbol Digit Modalities Test, Positive and Negative Affect Schedule (PANAS), Barrow Neurological Fatigue Scale. Clinical Staff, will be asked if there was sleep difficulties and therapist will be asked to rate therapy participation for that day.

Day 2: Randomization. After baseline testing is completed, subjects will be randomized (50:50) using a 2-level stratification design based on two pieces of information:

1) Center (U. Washington-Seattle, Baylor-Dallas, Mount Sinai-New York) and
2) Severity of Sleep Disturbance using Delirium Rating Scale-Revised 98 Item 1

The rating for the Delirium Rating Scale Item 1 are: 1=Mild, 2=Moderate, 3=Severe
(Nakase-Richardson R S. M., Prospective evaluation of the nature, course, and impact of acute sleep abnormality following TBI , 2013)
Using an Access Database, developed by Jason Barber at the University of Washington, centers will randomize the participant into either the Bright White Light Group or the Dim Red Light Group. [46]

Light Therapy:

Days 3-13: Each morning for 10 days, the research and/or nursing staff will set up the Litebook® device in the marked out area of the bedside table. The light will be between 12 and 24 inches from the subject, allowing light to reach the subject's eyes. The subject will be in front of the device for 30 minutes, eating or otherwise doing relaxing activities and will have the eyes open. Both BWL and RL will be delivered using a Litebook® (The Litebook Company Ltd; Medicine Hat, Alberta, Canada). The Litebook® is a small (6 inch x 5 inch x 1 inch) unit with an attached stand that is placed 12-24 inches from the user's face and within 45 degrees of the visual field per manufacture guidance. Both the BWL and RL devices contain a data log to track the times at which the light box is turned off and on allowing the total time of exposure to be calculated. The cases for the BWL and RL units are visually identical. Research Staff will setup the Litebook ® on the bedside/over bed table as part of the subjects' morning/breakfast daily routine. The research staff will check in with nursing staff and the patient/LAR regarding adverse effects each day. Study medical staff will also be available for study questions or problems at other times and the patient's primary medical service will also be following for their overall medical care per routine. Nursing staff will be trained regarding the light exposure protocol as part of preparation for the study and the individualized setup for each subject will be reviewed and diagrammed in their room on enrollment. Subjects will receive 10 morning sessions of their assigned light therapy (BWL vs. RL).

Additional Data Collected

1) Sleep Logs: Sleep logs will be integrated with overnight nursing rounds. Trained nursing staff will perform regular ratings every hour of sleep/wakefulness between 2200-0600 using the Makley Scale, a 4-point ordinal scale ranging from 0 (asleep) to 3 (awake). This paper sleep log will be collected daily by the research study staff. This is part of routine rehabilitation care and will not add any sleep disruption for study participants. Sleep logs will be used as one tool to help interpret overall actigraphy data patterns during analysis.
2) Therapy Participation: The physical therapist will be asked by the research staff to rate at both baseline days and on the final two days outcome assessment time points.
3) Clinical Staff feedback: phototherapy intervention will rated using a likert scale on the following categories:

a. Ease of use
b. Perceived relevance to rehabilitation care
c. Impression of effectiveness.

Post Light Therapy Outcome Assessment

Day 13: At the conclusion of the light therapy sessions (and prior to discharge from rehabilitation),a blinded Outcomes Examiner will complete the post therapy outcome assessment. This assessment will include the following:

- Symbol Digit Modalities Test
- Positive and Negative Affect Schedule (PANAS)
- Barrow Neurological Fatigue Scale

XII. Data Analysis

The primary outcome is the between-group difference (BWL vs. RL exposure) in average sleep efficiency at baseline compared to after 10 days of light treatment. ANOVA will be used to compare groups controlling for demographics, injury severity, and use of medications.

Secondary outcomes (mood, therapy participation, attention, daytime sleepiness/fatigue) between groups assessed at baseline and after 10 days of light therapy will be compared using repeated measures ANOVA. FIM™ efficiency and inpatient rehabilitation length of stay will also be compared between groups using ANOVA controlling for the same variables as the primary outcome. Descriptive analysis will summarize responses to the nursing burden questions including estimated staff time for the intervention.

Initial scoring of the data will be done by each participating site with Actiware 5, a computer program which uses validated algorithms to determine whether an epoch of activity is "sleep" or "wake". The Actiware 5 software calculates sleep/wake statistics based on night intervals and provides these statistics for each interval (night), as well as a mean of all intervals (nights).Using a set interval of sleep, 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. The raw, de-identified actigraphy data will be transmitted in an encrypted zip file via email to the NDSC and stored on a secure server for further analyses. Dr. Fogelberg 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.

XIII. Data Management

Table 2. Performance measures.

Performance Area	Goal	Review Schedule	Evaluation Method	Accountability*
Pre Enrollment Activities				
Manual of Procedures			Ready for IRB	Glorieux, Bell, Hoffman
IRB Submission			IRB approval	Glorieux, Hoffman, Dubiel
Database complete			Trial data entry	Glorieux, Barber, NDSC
Actigraphic data handling plan complete			Protocol	Fogelberg
Research Assistant trained			Observation of test administration and scoring, physical set-up	Glorieux, Zumsteg, Dubiel
Study Binders				Wasmund
Investigator Communication				Wasmund, Glorieux, Zumsteg, Hoffman
Post-Enrollment Activities				
Enrollment per month			Enrollment report	Glorieux
Completion of baseline assessments		Monthly	Review by PI, Data Report	Wasmund, Site Coordinators
Completion of intervention		Monthly	Review by PI, Data Report	Wasmund, Site Coordinators
Completion of outcome assessments		Quarterly	Review by PI, Data Report	Glorieux, Site Coordinators
Data Safety Monitoring	100%	Quarterly and as needed	Review by PI, Quarterly report to Medical Monitor	Olson, Hoffman, Zumsteg
Data audit	95% agreement	Quarterly	Rescoring and coding of 5% of assessments	Glorieux
Data Analysis/Dissemination				
Complete Data Analysis				Hoffman, Dubiel, Zumsteg, Fogelberg
Complete primary report of study			Submission of manuscript for review	Hoffman et al
Design next study			Submission of	Investigators

			grant proposal	

Identifiers
Each study site will have specific site ID numbers; subjects will be assigned a unique number in consecutive order with site identification. These numbers will be assigned locally using the TWILIGHT Study Access Database. Study number, rather than name or medical record, will be on data collection forms. Consent forms with identifying information and contact forms will be filed separately from other study material and will be kept in a secure location (locked file or secure, password protected file on secure server, also with password protection). The link between study and identifying data will be destroyed as specified in the site's IRB documents.

Confidentiality
Hard copies of study files will be kept in a locked cabinet or a secure location accessible only to individuals who have signed institutional confidentiality agreements. Study number will be on data collection forms (other than the locator form with contact information). Data in electronic form will be encrypted and stored on a University of Washington or NIDRR server only accessible by authorized personnel. Identified information such as name, address, medical record number or phone numbers needed to initially identify participants or their LAR will be kept in separate files from the study data.

Only study personnel as well as representatives of the human protection offices, and representatives of the funding agency will have access to study records. The study will not intentionally collect any data that would need to be shared with state or local authorities. If the participant responds to assessment items or volunteers information about an intent to harm themselves or others (such as in review of systems questions), a standard IRB approved protocol (identical to the TBI Model System protocol) will be executed to manage such disclosures to ensure participant or others' safety and the subject's inpatient rehabilitation resident or attending physician will be informed verbally immediately.

Disposition of data
At each study site hard copy data will be stored in locked file cabinets or a secure location while the study is ongoing. When the study is complete, the data will be sent to a secure institutional records management location at each site similar to those used to store archived medical records as required by local and other regulations as applicable to each site. Washington State law requires clinical trial data be retained for 25 years. Electronic data will be entered into a database developed by the National Data and Statistical Center using an ACCESS database that will be kept behind secure firewall on servers accessible to site data managers with password-protected access. At the end of the study, each investigator will get a copy of the de-identified data. At the end of the study, all local copies of the contact information files will be destroyed.

ACG data: De-identified actigraphic data will be transmitted in an encrypted ZIP file via UW secure and government email to the NDSC and stored on a secure, password-protected server accessible only to site data managers and PIs.

Demographic, Injury Characterization, Traumatic Brain Injury Model System (TBIMS)
Outcomes: Data will be recorded on paper or directly into database developed by the National Data and Statistical Center at Craig Hospital using an ACCESS database that will be kept behind secure firewall on servers accessible to site data managers with password-protected access. Hard copies of the data will be stored in locked file cabinets or a secure location while the study is ongoing. Only de-identified data is released from the NDSC.

Paper and Pencil Tests, Cognitive Tests, Interviews: Data will be recorded on paper. All subjective questionnaires and cognitive testing scores will be entered into the secure database developed by the TBIMS NDSC at Craig Hospital using an ACCESS database that will be kept behind secure firewall on servers accessible to site data managers with password-protected access. Hard copies of the data will be stored in locked file cabinets or a secure location while the study is ongoing.

Sharing study results

Treatment conducted as part of this study may be of benefit to an individual participant (e.g. progress on cognitive testing over time). The main sharing of study results, however, will be with the general public and medical community which may benefit from our study outcome. We plan to report our findings in published material and at medical conferences. Data sharing will follow the TBIMS protocol.

XIV. Safety and Adverse Events

Each subject will be followed medically daily by their rehabilitation resident and attending physicians and have 24 hour monitoring by rehabilitation nursing. The research assistant at each site will check in with the patient/LAR and nursing staff daily Monday through Friday to elicit any concerns. Jared Olson, M.D. a physiatrist in the University of Washington's Department of Rehabilitation Medicine has expertise in TBI treatment and research procedures and has agreed to be the Data Safety Monitor (DSM). He will receive a quarterly summary of all Adverse Events for review and will be contacted by the study team within 24 hours of any Serious Adverse Event to review with the study physician. Any serious adverse event will be reported to the Human Subjects Division as well immediately. At quarterly intervals after subject enrollment begins, the DSM will review and evaluate the studies' clinical efficacy and safety data. The DSM will monitor study progress, examine adverse events (AEs) and serious adverse events (SAEs), and recommend the continuation without change, suspension, or termination of a study.

XV. Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality results in study withdrawal, is associated with a serious adverse event, is associated with clinical signs or symptoms, or is considered by the investigator to be of clinical significance.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is: fatal, life-threatening, prolongs hospital stay, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event.
All adverse events that do not meet any of the criteria for serious should be regarded as **non- serious adverse event.**

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 2 days following the last study treatment (Day 15).

Hospitalization
Subjects will be hospitalized patients receiving care for their recent traumatic brain injury. Therefore, hospitalization is a requirement to be a part of this study, and will not be included as an adverse event for this study.

XVI. Recording of Adverse Events

At each contact with the subject, the study staff must seek information on adverse events by specific questioning. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.
Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study, action taken, and outcome.

Evaluating Adverse Events
Assessment should include the intensity (severity) of the event and the relationship to Study Intervention(s).
Severity of AEs will be graded by the Investigator using the following criteria as guidelines:
1) ***Mild***: Nuisance, barely noticeable.
2) ***Moderate:*** Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
3) ***Severe:*** Symptoms significantly interfere with daily activities or sleep.

The relationship of the AE to the study treatment should be specified by the Investigator, using the following definitions:
1) ***Not Related***: Concomitant illness, accident or event with no reasonable association with treatment.

2) ***Unlikely***: The reaction has little or no temporal sequence from administration of the study treatment, and/or a more likely alternative etiology exists.
3) ***Possibly Related***: The reaction follows a reasonably temporal sequence from administration of the treatment and follows a known response pattern to the suspected treatment; the reaction could have been produced by the study treatment or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.
4) ***Probably Related***: The reaction follows a reasonable temporal sequence from administration of study treatment; is confirmed by discontinuation of the study treatment or by rechallenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state.
5) ***Definitely Related***: The reaction follows a reasonable temporal sequence from administration of study treatment; that follows a known or expected response pattern to the study treatment; and that is confirmed by improvement on stopping or reducing the dosage of the study treatment, and reappearance of the reaction on repeated exposure.

Notifying the Principal Investigator
Any study-related unanticipated problem posing risk of harm to subjects or others that are not Adverse Events should be reported on the "*Unanticipated Problems Form*". Any type of serious adverse event, must be reported to the site Principal Investigator or designee within 1 business day of the event. Within the following 48 hours, the investigators must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event.

Notifying the Local IRB
At the University of Washington, Dr. Jeanne Hoffman or Dr. Jennifer Zumsteg will be responsible for safety reporting to the IRB and complying with their reporting requirements. The other sites for this project will have an investigator who is responsible for safety reporting to their local IRBs. Copies of each report and documentation of IRB notification and receipt will be kept in the locked secured study file.

Notifying the Data Safety Monitor
Unanticipated problems posing risks to subjects or others and serious adverse events associated with the research will be forwarded to the Data Safety Monitor of the study at the University of Washington, within 24 hours.

Stopping Rules
There are no planned interim or futility analyses. The Data Safety Monitor may recommend stopping for safety based on overall study review.

Independent Data Safety Monitor
The Data Safety Monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report. At a minimum the Data Safety Monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The Data Safety Monitor should also indicate whether he concurs with the details of the report provided by the study investigator.

XVII. Ethical Considerations/Protection of Human Subjects

Ethical Conduct of the Study

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Institutional Review Board (IRB)

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

Subject Information and Informed Consent

This study will be conducted in compliance with Title 45 Part 46 of the CFR pertaining to informed consent. At the first visit, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, and potential benefits. Informed consent is a process that is initiated prior to the individual's or proxy's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families. Consent forms describing in detail the Study Agent(s)/Intervention(s) study procedures and risks are given to the participant/proxy and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the participant/proxy will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant/proxy and answer any questions that may arise. The participants/proxies should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants/proxies may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants/proxies for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Sample Characteristics that Raise Special Concerns

Participants may not be sufficiently able to independently provide informed consent. We will have proxy consent forms for the subject and the Legally Authorized Representative (LAR) in this case. Decision making capacity assessment is described in the above study procedure narrative. We do not anticipate re-consenting subjects as the study duration is only 10 days of intervention.

XVIII. Potential Risks, Potential Benefits, Intent to Benefit, and Risk/Benefit Ratio

Potential risks

Subjects may experience an adverse reaction to the active or comparison treatment; significant adverse reactions are unlikely given literature on these light therapy interventions in a variety of populations. The intervention involves exposure to light, which can be bright and which some participants may find bothersome. Side effects of the bright white light are generally mild and subside but can include hypomania, irritability, headache, nausea, eye strain or vision changes and sleep changes (Chang AM, 2012). Other side effects are not anticipated given the study target population and the study team's experience with sleep changes after TBI and light therapy. Other study procedures including the questions about cognition such as memory may be uncomfortable either physically or emotionally and will be approached respectfully and confidentially. The placement of the Actiwatch on the wrist will result in contact with the skin, and like any watch, could result in contact dermatitis. Contact Dermatitis is readily treated with skin lotion and may involve repositioning the device. Prior studies have not reported this as a problem.

As with any study, there is also a remote chance that an outside party may discover a participant's identity and participation in the study. Risk of physical harm or injury is unlikely given the mild nature of reported side effects in the literature regarding light exposure and the non-invasive nature of actigraphy. No risk to study personnel is anticipated.

Alternative common treatments for insomnia include sedative drugs / sleep medications, behavioral interventions and environmental modifications. These other interventions will be recorded and will not be blocked during this study.

Protection Against Risk

1. We will have a Data Safety Monitor who is independent of the study to review regular reports of any reported related or unrelated adverse events as noted above. All serious adverse events will be reported within 24 hours to him as well as to the IRB, Dr. Hoffman and site PIs. Our DSM will be able to halt recruitment until any adverse events are thoroughly explored. A summary of all adverse events will be generated quarterly.

2. Subjects will be interviewed in private settings, will be counseled that they may refuse to answer any question, and will be reassured that the information they provide is confidential.

3. We will take all the usual steps to protect the confidentiality of personal information, including but not limited to dissociating identifying information from research data; using unique alpha-number coding systems that permit linkages to identifying data only via files that are stored separately; storage of data on password protected servers or computers; storage of paper data forms in locked files within locked rooms with access limited to approved research staff. All investigators and research staff are required to undergo HIPAA training and to sign a confidentiality agreement under the authority of the Human Subjects Division of the University of Washington and participating sites.

Risk Management

Loss of Confidentiality: All of the paper-based assessments will be kept in locked file cabinets at the study site. All data will be identified by a subject number. The link between participant identities and subject number will be kept separately from the study data. All personnel will receive HIPAA training as required by the University of Washington's Human Subjects Division.

XIX. Importance of Knowledge to be Gained

At the completion of this study, we will have evidence on whether Bright White Light Therapy improves sleep after TBI. If this study is successful, we will have an **immediately available, effective, non-invasive** way of improving sleep for patients who have experienced a TBI that will enhance not only sleep timing but also thinking abilities and possibly long-term recovery after TBI.

XX. Study Finances

Funding Source

This study is financed through TBI Model System Grant for the 2012-2017 Grant Cycle. This a module multi-site project that will be conducted at three locations. All participating sites have received funding from the National Institute on Disability and Rehabilitation Research.

Subject Stipends or Payments

There is no compensation planned for subjects who choose to participate in this study.

XXI. Overall Project Evaluation

Overall study data completeness, timeliness, and quality will be monitored by the study investigators. Automated data reports will be generated monthly, displaying information relevant to the milestones described in the previous section. For example, cumulative subject accrual rates, subject retention rates, inter-rater reliability, and data accuracy reports will be generated routinely to monitor progress toward goals. Progress toward study milestone will be discussed at the project meetings. Quarterly reports will be filed with the NIDRR project officer. Quarterly safety reports will be submitted to Dr. Olson. Annual reports will be filed with the TBIMS Annual Reports.

Investigators and key study personnel will meet by telephone bi-weekly prior to the initiation of the intervention to discuss progress. Investigators will meet twice yearly at the TBIMS Project Directors meeting. Site teams will meet weekly during the intervention period to discuss progress and barriers.
If problems arise or tasks are not progressing as planned, Dr. Hoffman will work with the research team to devise an action plan. Plans will be put in writing with a timeline to correct the problem. Ms. Glorieux will track and follow-up on these plans. Any significant problems that would affect overall project outcomes will be reviewed with the NIDRR project officer to obtain additional assistance in developing an action plan.

Table 3: Timeline of Research Activities

	2013		2014		2015		2016		2017	
Pre-Enrollment Activities										
Complete feasibility study	X									
Manual of Procedures	X									
Primary site IRB	X									
Collaborator sites IRB		X								
Research Assistant Training		X								
Rehab Staff Training		X								
Post-Enrollment Activities										
Cumulative Enrollment Target				43		86		128		
Data collection			X	X	X	X	X	X		
Actigraphy interpretation			X	X	X	X	X	X		
Data Analysis/Dissemination										
Primary study report									X	
Manuscript preparation									X	X

Figure 2. Project Staff Flow Chart

List of Acronyms and Abbreviations

- **ACG** = Actigraphy
- **AE**= adverse event
- **BMI** = body mass index
- **BNI-FS** = Barrow Neurological Institute Fatigue Scale
- **BWL** = Bright white light (experimental treatment condition in this study)
- **DSM** = Data safety monitor
- **GCS** = Glasgow Coma Scale
- **GOAT** = Galveston Orientation and Amnesia Test
- **KSS** = Karolinska Sleepiness Scale
- **LAR** = Legally authorized representative
- **NDSC** = National Data and Statistical Center for the Traumatic Brain Injury Model S
- **NIDRR** = National Institute on Disability and Rehabilitation Research
- **PANAS** = Positive and Negative Affective Schedule
- **PTA** = Post-traumatic amnesia
- **RL** = Dim red light (comparison treatment condition in this study)
- **SAE** = Serious adverse event
- **SDMT** = Symbol Digit Modalities Test
- **TBI** = Traumatic brain injury
- **TBIMS** = Traumatic brain injury Model System

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Appendix

- Inclusion/Exclusion Checklist
- Makley Sleep Scale Form
- Berlin Questionnaire
- Del-R-98, Question 1 Form
- Functional Independence Measure (FIM)™
- PANAS
- Karolinska Sleepiness Scale
- Barrow Neurological Institute Fatigue Scale
- Quarterly Staff Survey (a.k.a. Clinician Feasibility Survey)
- Overview of Study Figure

TWILIGHT Study Inclusion and Exclusion Checklist

Inclusion Criteria
Must meet all of the criteria below

- ☐ Have experienced a moderate to severe TBI. Defined by any of the following:
  1) Loss of Consciousness greater than 30 minutes.
  2) Emergency Room admission with a Glasgow Coma Scale of 12 or below.
  3) Intracranial abnormalities on imaging.
  4) Post-traumatic amnesia that lasts more than 24 hours.

- ☐ Admitted to acute inpatient rehabilitation unit at Harborview Medical Center within 3 months of their Traumatic Brain Injury.

- ☐ Able to communicate in English.

- ☐ Between the ages of 18 and 70 years old

Exclusion Criteria
Unable to enroll if any of the following are true

- ☐ Complete blindness

- ☐ Absence of eye opening or disorders of consciousness (Rancho level 1-3)

- ☐ Does not have sleep disturbance (rating of "0" on item one of the *DelRS-R98.* If has a rating of "0", but if taking sleep medication in the last 72 hours, then include)

- ☐ Tetraplegia with less than antigravity strength in all myotomes caudal to C6 level given the limitations on measuring movements with actigraphy in this population (i.e. cannot reliably detect upper extremity or lower extremity movement with this level of paralysis).

- ☐ Past medical history of retinal pathology

- ☐ Past medical history of light sensitivity

- ☐ Past medical history of narcolepsy

- ☐ Past medical history of bipolar disorder

- ☐ Past medical history of obstructive sleep apnea

- ☐ Suspected sleep apnea. (Determined by administering the Berlin questionnaire)

- ☐ Current medical orders indicated for night time sleep disruption (e.g. chest PT, MIE q2 hours of meds that disrupt sleep)". For these subjects, may re-approached if the medical orders are no longer in place.

TWILIGHT STUDY

☐ **Was watch verified as on?** **Staff Initials** _____

Date: _____

Makley Sleep Scale Form
Clinician rating

Time	**Rounding Initials**	**Sleep Rating Given Observation in the Last Hour** (circle)			
2200		**0**	**1**	**2**	**3**
2300		**0**	**1**	**2**	**3**
0000		**0**	**1**	**2**	**3**
0100		**0**	**1**	**2**	**3**
0200		**0**	**1**	**2**	**3**
0300		**0**	**1**	**2**	**3**
0400		**0**	**1**	**2**	**3**
0500		**0**	**1**	**2**	**3**
0600		**0**	**1**	**2**	**3**
Ratings:		**Asleep**	**Drowsy/falling asleep**	**Drowsy/waking up**	**awake**

Where there any adverse events or effects?
☐Yes ☐ No Source:_____

If yes, please explain_____

Makley Sleep Log guidelines and FAQ's

Data collection

1. The sleep log can by collected by nurses or MA staff
2. Clinical staff will do data collection rounding on an hourly basis and rate the patient accordingly with a 0,1,2 or 3
3. The rating for each hour is the clinical staffs best assessment of observed sleep/non-sleep state based on how they were found, not what was being done clinically, if anything
4. Hourly ratings may be collected on paper or electronically
5. Sleep log for the first night, along with any and all information about the participant's sleep over the last 3 nights will be used to randomize. Information about the participant's sleep will be asked of any family or friends' present, clinical staff, medical chart review, and nursing notes. Please look to see if the participant has or is on any sleep medications in the past 72 hours.
6. Once the research staff has all information, they will rate the participant using the DelRS-98 item #1 to score their severity of sleep
7. Data may need to be used to reconcile actigraphy data if there are questions
8. Research staff should collect the sleep logs on a daily basis and place a copy in the participants file (de-identified)

FAQ's

1. Clinically what's the difference between 1 (falling asleep) and 2 (waking up) in the setting of night time rounds? Can we tell? **Answer**: Make your best clinically assessment. If patient is fully asleep then score = 0, if patient is fully awake then score = 3.

2. What do we do with missing hours on a sleep log? **Answer**: note it as missing data; follow-up with staff training/study education.

3. What do we do when a sleep log is entirely missing? **Answer**: keep looking to see if it can be found; include notation in case notes; follow-up with staff training/study education.

4. Staff says a patient slept fine but family notes the patient was restless overnight, what data do we take for rating of sleep disturbance in the study? **Answer**: Clinically we know that patients/subjects will be observed at different time points and that the type and quality of observations will be variable. Research staff should collect all available data and make their best summary of presence/absence of ANY sleep changes and if present the rating of severity (using the Del-RS-R 98 item 1) considering that this type of data is generally additive to describe what's happened overnight and not necessarily either/or. To score a subject as having no sleep disturbance there should be no clinical data that says the patient didn't sleep perfectly well (i.e. patient/caregiver/family report is all that sleep was fine, no medications given).

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**

a. Yes b. No c. Don't know

If you snore:

2. **Your snoring is:**

a. Slightly louder than breathing
b. As loud as talking
c. Louder than talking
d. Very loud – can be heard in adjacent rooms

3. **How often do you snore**

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

4. **Has your snoring ever bothered other people?**

a. Yes
b. No
c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**

a. Yes
b. No

If yes:

9. **How often does this occur?**

a. Nearly every day
b. 3-4 times a week
c. 1-2 times a week
d. 1-2 times a month
e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**

a. Yes
b. No
c. Don't know

Rating Sleep-Wake cycle disturbance:

Question 1 is utilized in this study

DELIRIUM RATING SCALE-R-98 (DRS-R-98)

This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 SEVERITY SCALE

1. Sleep-wake cycle disturbance

Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present
1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations

Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and "complex" if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present
1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2. Illusions present
3. Hallucinations present

3. Delusions

Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present
1. Mildly suspicious, hypervigilant, or preoccupied
2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3. Delusional

4. Lability of affect

Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present
1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language

Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language
1. Mild impairment including word-finding difficulty or problems with naming or fluency
2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

FIM- Functional Independence Measure

SELF CARE ITEMS:	ADMISSION	DISCHARGE
1. Feeding		
2. Grooming		
3. Bathing		
4. Dressing Upper Body		
5. Dressing Lower Body		
6. Toileting		
SPHINCTER CONTROL:		
8. Bladder Management		
a. Level of assistance		
b. Frequency of accidents		
9. Bowel Management		
a. Level of assistance		
b. Frequency of accidents		
MOBILITY ITEMS:		
Transfer Technique		
10. Bed, Chair, Wheelchair		
11. Toilet		
12. Tub or Shower		
Locomotion		
14a. Walking on admission		
14b. Wheelchair on admission		
14. Walking/Wheelchair-discharge (w/c/9)		
15. Stairs		
COMMUNICATIONS:		
17. Comprehension ...(a/v/b/9)		
18. Expression ..... (v/n/b/9)		
PSYCHOSOCIAL ADJUSTMENT ITEMS:		
22. Social Interaction		
COGNITIVE FUNCTION:		
26. Problem Solving		
27. Memory		

7=Complete Independence (Timely, safely)
6=Modified Independence (Extra time, device)
5=Supervision (pt does 100%)
4=Minimal Assistance (pt ≥75% of task)
3=Moderate Assistance (pt 50-74% of task)
2=Maximum Assistance (pt 25-49% of task)
1=Total Assistance (pt<25% of task)
0=Activity does not occur. (Use only at admission and only for #1-6,10-15; else use code "9".)
8=N/A, pt walking/not using wheelchair. (only for item #14b)
9=Unknown / assessed at >72 hours / activity does not occur (see instructions in code "0", above).
66=Data not available with new (1/1/02) scoring. (Use only at admission and only for #1-8a, 9, 9a, 10-15)

Use with 8b and 9b
7=No accidents
6=No accidents; uses device (catheter, ostomy)
5=One accident in the past 7 days
4=Two accidents in the past 7 days
3=Three accidents in the past 7 days
2=Four accidents in the past 7 days
1=Five or more accidents in the past 7 days
9= Unknown / assessed at >72 hours
66=Variable did not exist

PANAS Questionnaire

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment *OR* indicate the extent you have felt this way over the past week (circle the instructions you followed when taking this measure)**

1	2	3	4	5
Very Slightly or Not at All	A Little	Moderately	Quite a Bit	Extremely

_____ 1. Interested	_____ 11. Irritable
_____ 2. Distressed	_____ 12. Alert
_____ 3. Excited	_____ 13. Ashamed
_____ 4. Upset	_____ 14. Inspired
_____ 5. Strong	_____ 15. Nervous
_____ 6. Guilty	_____ 16. Determined
_____ 7. Scared	_____ 17. Attentive
_____ 8. Hostile	_____ 18. Jittery
_____ 9. Enthusiastic	_____ 19. Active
_____ 10. Proud	_____ 20. Afraid

Scoring Instructions:

Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect. Mean Scores: Momentary = 29.7 (*SD* = 7.9); Weekly = 33.3 (*SD* = *7.2)*

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect. Mean Score: Momentary = 14.8 (*SD* = 5.4); Weekly = 17.4 (*SD* = 6.2)

BASELINE **Pt. not able to report ☐**

Sleepiness Scale: (Karolinska Sleepiness Scale)

Here are some descriptors about how alert or sleepy you might be feeling right now. Which one corresponds to the statement describing how you feel at this moment?

i. Extremely alert
ii. Very alert
iii. Alert
iv. Rather Alert
v. Neither alert nor sleepy
vi. Some signs of sleepiness
vii. Sleepy, but no difficulty remaining awake
viii. Sleepy, some effort to keep alert

Pre Light Treatment

Date: _____ Score: _____

BASELINE

Barrow Neurological Institute Fatigue Scale

Pt. not able to report ☐

Please rate the extent to which each of the items below has been a problem for you since your injury. You should choose only ONE number from 0-7 on the scale below when making your response.

0	1	2	3	4	5	6	7
Rarely a problem		Occasional problem but not frequent		A Frequent Problem		A problem most of the time	

1. **How difficult is it for me to maintain my energy throughout the day?** _____
2. **How difficult is it for me to participate in activities because of fatigue?** _____
3. **How difficult is it for me to stay awake during the day?** _____
4. **How difficult is it for me to complete a task without becoming tired?** _____
5. **How difficult is it for me to stay alert during activities?** _____
6. **How difficult is it for me to build my energy level once I wake up in the morning?** _____
7. **How difficult is it for me to stay out of my bed during the day?** _____
8. **How difficult is it for me to stay alert when I am not involved in something?** _____
9. **How difficult is it for me to attend to something without becoming sleepy?** _____
10. **How difficult is it for me to last the day without taking a nap?** _____

11. **Please circle your OVERALL level of fatigue since your injury:**

0	1	2	3	4	5	6	7	8	9	10
No problem										Severe Problem

Quarterly Staff Survey

If you have been involved in the care of a patient enrolled in the TWILIGHT Study in the past three months please answer the questions below.

Date:_____

Please check one:

- ☐ **Rehabilitation Nurse**
- ☐ **Rehabilitation Therapist (PT, OT, SLP, TR)**
- ☐ **Other**

Please indicate whether you agree or disagree with the following statements:

Q1: It was easy to integrate light therapy into patient care.

1	2	3	4	5
Strongly Disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly Agree**

Q2: Light therapy did not increase my work load.

1	2	3	4	5
Strongly Disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly Agree**

Q3: Light therapy should be offered as a routine treatment option in in-patient rehabilitation.

1	2	3	4	5
Strongly Disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly Agree**

Comments?

Overview for Study Participants