Protocol Title: Circadian Rhythm as a Novel Therapeutic Target in the Intensive Care Unit
Brief Title: Feasibility Pilot of Bright Light in the Intensive Care Unit

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Excerpted from full IRB protocol for observational aims and described pilot study.

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STATEMENT OF PURPOSE: SPECIFIC AIMS

The overall objectives of this research project are to prospectively investigate ICU day-night light patterns and their association with circadian abnormalities; investigate the association between circadian abnormalities and the duration of delirium; and evaluate the feasibility of providing daytime bright light to treat circadian abnormalities among critically ill patients. Our central hypothesis is that exposure to abnormally high overnight light and abnormally low daytime light (non-circadian light patterns) disrupts the circadian master clock and causes circadian abnormalities in ICU patients. In turn, circadian abnormalities contribute to sleep disruption and ultimately ICU delirium. The rationale for the proposed project is that circadian abnormalities may constitute a novel therapeutic target for interventions to prevent or shorten delirium and improve ICU outcomes. This work builds upon our own work and published studies that describe circadian abnormalities in critically ill patients. Prior studies are limited by small numbers of subjects or by periods of observation that start many days after ICU admission.[17-23] We will use a melatonin metabolite, urinary 6-sulfatoxymelatonin (aMT6s), to measure circadian abnormalities; this measure has been successfully used in critically ill patients.[24] We plan to accomplish our overall objectives via the following specific aims:

Aim 1: Determine the association between ICU day-night light patterns and circadian abnormalities (i.e., circadian misalignment and decreased circadian amplitude).

Hypothesis 1: Non-circadian ICU light patterns (i.e., abnormally low daytime light levels and abnormally high overnight light levels) are associated with increased circadian misalignment and decreased circadian amplitude as measured by urinary aMT6s.

Aim 2: Determine the association between circadian abnormalities and the duration of delirium.

Hypothesis 2: Increased circadian misalignment and decreased circadian amplitude are associated with more days of delirium.

Aim 3: Evaluate the feasibility of providing daytime bright light in the ICU and examine the effect size of daytime bright light on circadian abnormalities in a pilot randomized controlled trial.

Hypothesis 3.1: Daytime bright light is acceptable and tolerable to patients and has high fidelity and sustainability as an intervention.

Hypothesis 3.2: Daytime bright light will be associated with decreased circadian misalignment and increased circadian amplitude (effect size).

BACKGROUND:

Overall Premise: This research project addresses intensive care unit (ICU) delirium which is a significant, modifiable source of ICU morbidity and mortality. Delirium affects 50-80% of patients admitted to the medical ICU (MICU).[1] Delirium is a syndrome of acute cerebral dysfunction with features of a change in baseline mental status, inattention and either disorganized thinking or an altered level of consciousness.[2] Patient risk factors for ICU delirium include older age, hypertension, dementia, alcohol abuse, and chronic benzodiazepine use.[2] Critical illness related risk factors for delirium include severity of illness, mechanical and non-invasive ventilation, and high doses of benzodiazepines during ICU admission.[2, 3] ICU delirium is associated with adverse outcomes such as longer hospital stay, impaired cognition, and increased mortality.[4-11] Additional days of delirium incrementally increase the risk of death and cognitive impairment at one year.[3, 4] Evidence for the use of any medications to treat delirium is limited. Non-pharmacologic treatments such as sleep promotion have shown promise and are recommended by expert guidelines.[12, 13] Currently sleep promotion efforts are focused on minimizing overnight sound, light, and care to provide patients with a sleep opportunity.[14] *However, there is a lack of attention to the potentially significant contribution of circadian abnormalities to the problem of ICU sleep disruption and consequent delirium.*

The circadian system is controlled by a central master clock and is a key determinant of sleep timing. The master clock is synchronized with the 24-hour day by external cues via a process called entrainment. Light is the most influential external entrainment cue. Under normal entrainment, the circadian system promotes arousal during the day and allows sleep during the night. Sleep quality and length are optimal when they occur during an individual's "biologic" or "circadian" night. Circadian abnormalities contribute to inappropriate sleep timing, impaired sleep quality and decreased sleep quantity. These three elements of sleep disruption have been clearly shown in critically ill patients,[15-17] and together with circadian abnormalities these elements form a vicious cycle. Circadian abnormalities are defined in this proposal as misalignment and decreased amplitude. *We assert that optimal sleep promotion and therefore optimal treatment and prevention of delirium requires the promotion of normal circadian entrainment. The proposed project supports this by investigating the influence of ICU day-night light patterns on circadian abnormalities, examining the association between circadian abnormalities and duration of delirium and piloting a daytime bright light intervention (Figure 1).*

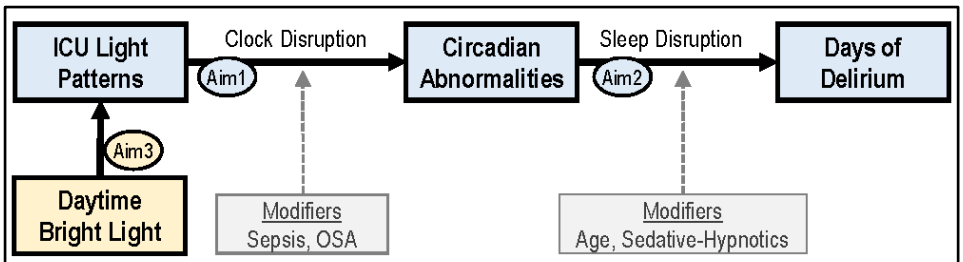


Figure 1: Hypothesized exposures, mechanisms and outcomes. "Clock" is master circadian clock; "OSA" is risk of pre-existing obstructive sleep apnea.

Premise for Aims 1 and 2: ICU day-night light patterns conflict with circadian entrainment and cause circadian abnormalities. External cues for entrainment include light, meal schedule, and physical activity. As noted above, light has by far the greatest biologic influence on entrainment.[18] The robustness of entrainment and vulnerability to disruption are determined by the timing, intensity (lux), and duration of a light dose.[19] Normal entrainment requires bright light exposure during the day (wake) period and dim or no light during the night (sleep) period. Daytime bright light interventions deliver at least 1,000 lux and more typically deliver 2,500 to 10,000 lux over 30 minutes to several hours.[20, 21] During the night, short bursts of bright light (e.g., 5 minutes) at relatively lower intensities (e.g., 100 or 250 lux) can cause circadian abnormalities.[19] Interventions aimed at ICU sleep promotion have focused on lowering overnight

light levels,[22] but have not addressed the significant problem of daytime light being too low for entrainment (See preliminary data). *It is our premise in Aim 1 that non-circadian day-night light patterns in the ICU cause circadian abnormalities.* **Circadian abnormalities are present in critical illness, associated with delirium, and feasible to study.** Studies of urinary 6-sulfatoxymelatonin (aMT6s), continuous heart rate, and actigraphic rest-activity have shown associations between critical illness and circadian abnormalities.[23-28] In these studies, roughly 75% of ICU patients studied have evidence of circadian abnormalities. One small study has shown that delirium is associated with circadian misalignment in patients weaning from mechanical ventilation.[29] These studies (Table 1) demonstrate the feasibility of studying circadian rhythms in the ICU but have been limited by small numbers (<30 patients), brief periods of observation (24 hours), or periods of observation that start days after ICU admission (>5 days post admission). *It is our premise in Aim 2 that circadian abnormalities are common in ICU patients and likely to be associated with duration of delirium. Delirium is at least partially mediated by sleep disruption, which is a proposed factor on the causal pathway between circadian abnormality and delirium.*

Table 1: Circadian Rhythm Measurements and Related ICU Studies

Variable	Strengths	ICU Studies Using this Variable
Urinary 6-aMT6s	**Gold Standard**	Septic patients (n=17) v. non-septic ICU (n=7) and healthy controls (n=21); enrollment 11 days post ICU admission; abnormal aMT6s patterns in septic patients but not controls.[27] Additional References: Gehlbach,[30] Frisk[24] Verceles[28]
Heart rate	Recorded as part of usual care; starts at ICU admission	Medical ICU sedated patients (N=11); time post ICU admission not listed; heart rate with circadian variability but misaligned.[31]
Actigraphy	Low cost for long-term monitoring; non-invasive	Neurologic ICU with traumatic brain injury patients (N=16); enrollment 18 days post injury; rest-activity consolidation associated with better recovery.[32]

Premise for Aim 3: Daytime bright light therapy in acute medical settings and nursing homes improves patient outcomes. Small studies of post-operative patients exposed to a bright light dose in the morning showed 40 to 42% reductions in delirium.[33-35] Increased exposure to sunlight in hospital rooms is associated with shorter lengths of stay and lower mortality (cardiac ICU).[36] The provision of daytime bright light to nursing home patients improves the circadian amplitude and reduces depression, cognitive decline, agitation, confusion, and anxiety.[37] To leverage the most influential circadian entrainment cue (light) and to take the first step towards a multi-modality entrainment intervention, the proposed project will investigate the feasibility and effect size (on circadian abnormalities) of a daytime bright light intervention. *It is our premise in Aim 3 that an intervention that improves circadian function via exposure to daytime bright light will improve circadian abnormalities and ultimately delirium.*

Significance of research contribution: We expect that the results of this study will improve understanding of circadian abnormalities in the ICU. We expect that pilot data from Aim 3 will inform the development of a large-scale entrainment intervention for the treatment of delirium. This contribution is expected to be significant because it is likely to provide evidence for a therapeutic target and intervention to shorten or prevent delirium. Prior work has established that additional days of delirium have a significant impact on mortality and cognition. Though the proposed project will focus on ICU light exposure, this line of investigation will also lead to a multi-modality intervention using multiple entrainment cues: (1) daytime bright light, (2) intermittent daytime feeding (e.g., meals or bolus enteral feeding), and (3) promotion of physical activity.

RESEARCH PLAN:

Overall Project Rationale

Optimal sleep promotion and therefore optimal treatment and prevention of delirium requires the promotion of normal circadian entrainment. The project supports this by investigating the influence of ICU light patterns on circadian abnormalities, examining the association between circadian abnormalities and delirium, and piloting a daytime bright light intervention. To study the most relevant patients, our inclusion/exclusion criteria will select patients at increased risk for delirium.

Project Overview

a. Setting: The study site is the medical intensive care unit (MICU) at Yale-New Haven Hospital (YNHH), York Street Campus and St. Raphael's Campus. Median ICU stay is 3 days. Predominant reasons for admission are sepsis and acute respiratory failure. MICU rooms are private. There is currently a unit-wide sleep promotion protocol which limits care activities from 00:00 to 04:00.

b. Design: Aim 1 and 2, prospective cohort study; Aim 3 pilot randomized controlled trial (RCT). Aim 3 which is not dependent on Aims 1 and 2 will be conducted first.

c. Cohort: We will enroll 100 subjects at risk for ICU delirium. In addition, we will enroll 16 subjects into the pilot randomize control trial.

d. Inclusion and exclusion criteria: This study will focus on adults at an increased risk for ICU delirium. We have selected age ≥50 years as an inclusion criteria to study middle-aged to older adults who are at increasing risk for delirium while not overly restricting our sample. We will not restrict patients based on admission severity of illness (APACHE II) because we think this is a critically important confounder and would like to study the effect of the full spectrum of severity of illness on our outcomes. We will exclude patients at significant risk for pre-existing circadian abnormalities (e.g. shift work). We will also exclude patients with co-morbid disease or medication use that makes measurement of urinary aMT6s or actigraphy unreliable. Table 2 lists inclusion and exclusion criteria.

Table 2: Inclusion Criteria	**Exclusion Criteria**
1. Hospital admission less than 30 hours as of noon on day of enrollment 2. Expected to say in the MICU ≥24 hours after enrollment 3. Expected to produce ≥250 mL urine / day 4. Age ≥50 years 5. Able to understand English.	**At significant risk for pre-existing circadian abnormalities:** – Severe chronic brain injury (Injury greater than 30 days ago resulting in the inability to live independently) OR Acute brain injury of any severity (Injury less than 30 days ago including acute intracranial bleed, traumatic brain injury, central nervous system infection, tumor, hepatic encephalopathy) – Documented circadian disorder (<1% population) or blind/disease of the optic nerve – Current history of substance abuse including alcohol (use in last 30 days) – Transferred from an outside hospital – Homeless **Unable to participate in study activities:** – History of bipolar disease (Bright light therapy possibly unsafe in this population). – Paralyzed (due to injury, disease or medications)

e. <u>Recruitment:</u> Patient recruitment will follow Yale University consent procedures, and we will obtain HIC approval before starting study activities. MICU admissions will be screened daily via the EMR. Eligible patients will be approached within 30 hours of hospital admission. Before consent, the patient will be assessed for delirium via the Confusion Assessment Method for the ICU (CAM-ICU). If not delirious and able to communicate, the patient can provide consent; otherwise, a legally authorized

representative (LAR) as delineated by Connecticut State Law can provide consent.

a. In cases which the LAR provides consent, assent from the patient will be attempted daily and obtained whenever possible via simple verbal explanation of the purpose, activities, risks and benefits of the study.
b. In the event a patient originally enrolled via LAR were to regain their capacity to consent themselves, trained study staff will follow the below protocol for re-consent.
    i. Study staff will introduce identify themselves as a member of the research team and clarify that they are not part of the primary ICU team.
    ii. The protocol will be described to the patient; this description will include an overview of student events they already completed, cover in detail the study intervention and any remaining/future study procedures/events, and cover the risks associated with participation.
    iii. We will assure study subjects that participation is voluntary and that the decision to continue their participation will have no impact on their current or future care.
    iv. A copy of the consent document will be provided to the patient.

f. <u>Timeline of Study Activities (Fig 2)</u>: Patients will be enrolled within 30 hours of hospital admission and before 12:00 on the day of enrollment which is designated "Study Day 1 (D1)." Actigraphy, delirium monitoring, and light measurement (part of feasibility) will start no later than 12:00 on D1. Actigraphy and light measurement will continue until D5 or MICU discharge whichever is longer. If the patient is discharged from the hospital prior to day 5, all study activities stop upon hospital discharge. Study activities will continue if/when the patient is transferred to the general medical floor if the patient completes at least D2 (13:00) in the MICU. Delirium monitoring will occur until D30 or hospital discharge.

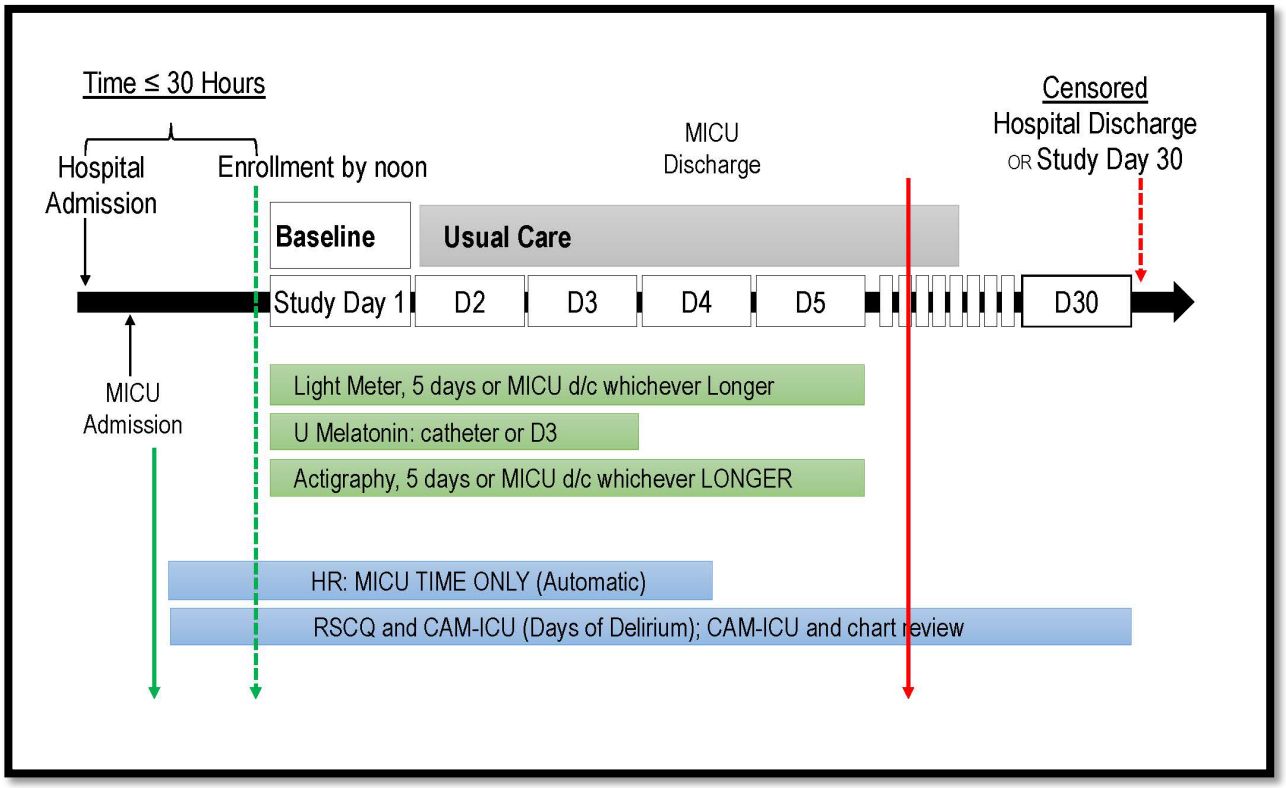


Figure 2: Study activities timeline.

APPROACH TO AIMS

Aim 1: Determine the association between ICU day-night light patterns and circadian abnormalities (i.e., circadian misalignment and decreased circadian amplitude).

Rationale: Aim 1 will test our hypothesis that non-circadian ICU light patterns are associated with increased circadian abnormalities as measured by urinary aMT6s. Our approach is to measure light levels (10-second intervals) and aMT6s (1-hour intervals, gold standard) for 72 hours following study enrollment; we will also collect exploratory measures of circadian rhythm, namely, actigraphy and heart rate. We will collect descriptive patient data to allow model adjustment during analysis. We define non-circadian ICU light patterns as abnormally low daytime light levels and abnormally high overnight light levels. We define circadian abnormalities as circadian misalignment and decreased circadian amplitude. The absence of circadian rhythm is an extreme decrease in amplitude (i.e., 100%). *This work will establish if non-circadian ICU light patterns are associated with the development of circadian abnormalities.*

Research Design: We will enroll 100 subjects at increased risk for ICU delirium; subjects will be screened and consented as above. We will collect the following measures:

a. **Room light levels** will be monitored from enrollment until Study D5 or until MICU discharge. We will set the light meter (HD450, Extech Instruments, New Hampshire) to read levels in lux at 10-second intervals. Meters will be placed in a standard location on the wall above the head of the bed as close as possible to eye level. Additional light measures will be taken adjacent to the patient's face (by holding the light meter next to their face for several seconds); these measures will be taken several times per day to assess light levels at or close to the eye.

b. **Urinary aMT6s (1-hour intervals)** is the primary circadian measure for this aim. Melatonin is normally released just before habitual sleep time, and peak levels occur during sleep midpoint; urinary aMT6s peaks 2 hours after sleep midpoint.[38] For the proposed study, urinary aMT6s will be collected for 72 hours or until MICU discharge whichever occurs first. Urinary aMT6s will not be collected after MICU discharge. A 10mL aliquot of pooled urine sample collected every 1 hour will be used for analysis; total volume of urine will be recorded to allow for calculation of total aMT6s excreted. Total aMT6s excreted can be measured and is valid in patients with acute kidney injury, patients receiving diuretics,[39] and patients with decompensated cirrhosis.[40] We have the support of MICU nurse champions and the agreement of nursing leadership for the bedside nurse to collect these samples. Samples are stable at room temperature for 24 hours, will be transported to the lab daily, and stored at -80°C in the Translational Research Core. Samples will be batched and subsequently analyzed using a highly sensitive, competitive ELISA kit (IBL Laboratories, Germany).

Figure 1: Actiwatch

c. **Secondary measures** of actigraphy, surface body temperature, and continuous heart rate monitoring will be used in an exploratory manner. We plan to examine correlation with urinary aMT6s for use in future studies.

i. Actigraphy (Fig 3) via the Actiwatch Spectrum™ (Philips Healthcare, Netherlands) set at 15-second epochs and placed on the patient's wrist will be used to measure rest-activity from enrollment until Study Day 5 or until MICU discharge. Actigraphy uses accelerometer technology mounted on a wristwatch-like device to characterizes rest versus activity of the wearer. This data device allows time series monitoring with a high sampling frequency and has been successfully used in the ICU

setting.[41, 42]

ii. Heart rate varies around the clock with peaks in the late morning and early evening and a nadir during the sleep midpoint in normal patients.[43] Heart rate (5-second intervals) will be recorded per MICU standard of care from MICU admission until MICU discharge; this extended period of monitoring will provide insight into circadian abnormalities before study enrollment and after melatonin monitoring has been completed.

d. Patient characteristics for calculation of sleep midpoint, confounders, and effect modifiers will include collection of age, gender, sleep habits and timing, medical history (including hypertension and risk of obstructive sleep apnea (OSA) based on STOP-Bang Score[46]), home medications, MICU admission diagnosis, sepsis presence and severity (as defined by the sepsis-3 criteria[47]), illness severity (APACHE II score elements), ventilator support, and MICU medication use (including sedative-hypnotic medications)**.** This data will be obtained via the EMR and via patient/surrogate interviews. Though the study is observational, melatonin, melatonin agonists, and non-benzodiazepine sleep aids (zolpidem, zopiclone, zaleplon) will not be given to study subjects while in the MICU. These agents are not part of usual care, and MICU leadership is agreeable to this restriction. ICU care events including phlebotomy, medication administration, transfusion, radiology studies, and procedures (e.g., line placement, intubation, endoscopy, catheterization, etc.) will be tracked by time of occurrence for the entire MICU admission. This process of obtaining timestamped care events has been automated via a collaboration with Yale ITS and requires minimal person-time.

Expected Outcomes: We expect that a low day/night dose ratio will be associated with increased misalignment and decreased amplitude of urinary aMT6s. We expect that this relationship will remain after controlling for listed confounders. We anticipate that we will see effect modification by sepsis and by OSA risk.

Aim 2: Determine the association between circadian abnormalities and the duration of delirium.

Rationale: Aim 2 will test our hypothesis that increased circadian misalignment and decreased amplitude are associated with more days of delirium. Our approach is to measure days of delirium in the same cohort of 100 patients that have been evaluated for circadian abnormalities in Aim 1. After enrollment, we will check patients twice daily for delirium until hospital discharge. We have selected days of delirium as our metric of delirium severity because it is standard in the field and because studies have shown that additional days of delirium convey additional risk for mortality and cognitive impairment.[4, 5] We will measure (and control for) total amount of sleep (sleep quantity) and overnight sleep efficiency (sleep quality) via actigraphy. We propose that these metrics of sleep disruption act as potential confounders and/or effect modifiers of the association between circadian abnormalities and delirium. For this project focused upon circadian patterns and sleep disruption rather than detailed sleep architecture (e.g., sleep stages), actigraphy, rather than polysomnography, is the sleep measure of choice. It is our expectation that circadian abnormalities will be associated with increased days of delirium. *This aim will be the basis for investigation of circadian entrainment as a means of treating ICU delirium.*

Research Design: The 100 subjects enrolled in Aim 1 will be examined for the outcome of days of delirium in Aim 2. We will collect the following measures: Circadian measures, actigraphy, and patient characteristics will be collected as described in Aim 1. Delirium: Research staff blinded to patient circadian

status and trained in the CAM-ICU will assess patients for delirium once daily from the time of MICU admission until hospital discharge or hospital day 30.[48] The CAM-ICU is a guideline recommended, validated delirium detection tool with a sensitivity >93% and a specificity >98%.[2, 48, 49] We are increasing sensitivity in our study by adding validated daily chart review for delirium.[50]

Expected Outcomes: For patients with circadian abnormalities, we predict more days of delirium. We expect this relationship will remain after controlling for age, gender, severity of illness and ventilator-free days. We expect that age, sedative-hypnotic medication dose and measures of sleep disruption will act as effect modifiers.

Aim 3: Evaluate the feasibility of providing daytime bright light in the ICU and examine the effect size of daytime bright light on circadian abnormalities in a pilot randomized controlled trial.

Rationale: Aim 3 will test our hypothesis that daytime bright light (hereafter bright light) is acceptable and tolerable to patients and has high fidelity and sustainability. Our approach to testing this hypothesis is a pilot RCT. We will randomize patients to usual care or to bright light daily while in the MICU. We will collect metrics of acceptability, tolerability, fidelity, and sustainability. The rationale for selecting bright light for this pilot intervention is that light is by far the dominant circadian entrainment cue.[51] The proposed method delivers light to the patient and does not require the patient to have their eyes open or look directly into the light.[52] In addition, brief light delivery early in the morning (e.g., 30 minutes of 10,000 lux directed at the patient), could cause undesirable circadian phase shifts in patient population who have circadian misalignment of the delayed type[30] It is our expectation that this intervention with be feasible to deliver in MICU patients. *We will use this Aim to calculate effect size for use in the anticipated large-scale circadian intervention to follow this pilot RCT.*

Research Design: For Aim 3, we will screen and enroll 16 patients using the same inclusion/exclusion criteria as Aims 1 and 2. We will collect room light levels, circadian measurements, patient characteristics, and ICU care events as before. Patients will be randomized via simple randomization with assignment via random number generator to either usual care (n=5 patients) or to bright light for 4 hours daily (n=5 patients) or to bright light for 8 hours daily (n=5 patients). The bright light intervention will be delivered from 09:00 to 13:00 daily (4 hour group) or 09:00 to 17:00 daily (8 hour group). The bright light will be delivered from study day 2 until study day 5. The bright light will continue if the patient is transferred to the floor. Bright light will be delivered by a free-standing apparatus that delivers 10,000 lux at a temperature 5000K. The device will be placed at the bedside within 36 inches of the patient's head and is expected to provide at least 1,250 lux at the angle of gaze.

To remain in the study, the patient must be in the ICU through D2 (e.g., the first day of potential intervention and the night following). After D2, bright light and other study activities will continue if the patient is transferred out of the ICU to the general medical floor. To maintain as much control of the environment as possible, study patients will be booked only to private rooms on the general medical floor.

If symptoms of eye strain, visual disturbance or headache occur, patients will not continue bright light exposure. These reversible symptoms of direct bright light therapy are unlikely, but they will be tracked as a metric of feasibility under the category of patient tolerance. Feasibility Metrics will include patient acceptance (percent of patients/surrogates who agree to bright light when described to them); patient tolerance (percent of days that patients continue with additional treatments once exposed to bright light); intervention fidelity (percent of time per day that device delivers the planned dose of light); and intervention sustainability (percent of intended intervention days that device is used).

Expected Outcomes: We expect that bright light exposure is feasible, will decrease circadian misalignment, and will increase circadian amplitude.

STATISTICAL CONSIDERATIONS

Aim 1 Analytical Approach: Individual sleep midpoint will be calculated as halfway between habitual bedtime and habitual waketime as indicated during patient/surrogate interview questionnaires. Light dose will be calculated as the sum of mean lux per hour for each hour between 08:00 and 17:00 (day dose) and 22:00 and 06:00 (overnight dose). A day/night dose ratio will then be calculated by dividing the daytime light dose by the overnight light dose. Light dose ratio will be treated as continuous exposure variables, with higher numbers indicating a more favorable (circadian) exposure and lower numbers indicating a less favorable (non-circadian) exposure. Circadian alignment and amplitude will be calculated using time series analysis of urinary aMT6s using smoothing techniques to examine characteristics of circadian rhythm: acrophase (maxima) and nadir (minima). Statistical measures will evaluate for serial correlation, seasonality (periodicity), and trend. Longitudinal cosinor techniques will be used to test for alignment of nadir and acrophase with normal circadian phase and amplitude (e.g., individual sleep midpoint and estimated normal peak aMT6s).[55] The degree of misalignment versus normal will be recorded in minutes. The amplitude of the cycle will be defined as one-half of the difference between the acrophase and nadir and will be recorded in nanograms (ng) per hour.[30] Normal values have been identified for aMT6s.[30, 56] The assessment of circadian abnormalities for association with light patterns will be solely based on aMT6s analysis. Heart rate, iButton gradient readings, and actigraphy activity counts will be evaluated via cosinor techniques analogous to the aMT6s analysis described above. Actigraphy activity counts will also be evaluated by visual inspection of normalized mean activity per hour (Fig 3) and as described by Duclos et al.[32] Confounder and effect modifier variables: Severity of illness will be calculated according to the APACHE II algorithm[57] and expressed as a continuous variable. Sepsis will be expressed as a categorical variable (absent, septic, septic shock) based on the sepsis-3 criteria.[47] The risk of OSA will be expressed as a categorical variable (low risk, high risk) based on the STOP-BANG algorithm.[46, 58] Overnight ICU care events per the timestamp data described above will be calculated as the number of ICU care events per hour between 22:00 and 06:00. Average daytime and overnight room temperature will be calculated as a continuous variable.

Testing for Associations: Because both measures of circadian abnormality (misalignment and decreased amplitude) are continuous and normally distributed, multivariable linear regression models will test for associations, with light dose ratio serving as the exposure. Linearity of the associations will be examined graphically, and higher order terms will be considered as necessary. Models will be adjusted for age, gender, severity of illness, sepsis, risk of OSA, ICU care events per hour, and room temperature variables. We will test for modification of the association between light dose ratio and the outcomes by sepsis and risk of OSA. Because of the non-trivial intra-correlation coefficient expected from the serial correlation of the repeated outcome measures over time, models will employ generalized estimating equations with an auto-regressive correlation structure. Model fit will be evaluated with residual analysis, and significance will be defined as a two-sided p-value ≤ 0.05. Power Calculations. For both continuous, normally distributed outcomes, power calculations assume a two-sided alpha of 0.05, power of 90%, a sample size of 100, and prevalence of covariates ranging from 20% to 50%. For minutes of misalignment, we further assume a mean of 180 minutes with a standard deviation of 95 and for amplitude a mean of 450 ng with standard deviation of 180.[30] Under these assumptions, our sample of 100 is sufficient to detect a range of minimal average shifts between 52-65 minutes of misalignment, and 98-123 ng of urinary aMT6 per

incremental change in the explanatory variables.

Aim 2 Analytic Approach: Circadian measures will be analyzed as in Aim 1. Sleep disruption will include two measures: (1) total amount of sleep, a continuous variable calculated as the number of sleep epochs in a 24 hour period and (2) overnight sleep efficiency, a continuous variable calculated as the percent of epochs scored as sleep between 22:00 and 06:00. Sleep will be based on standard Philips Actiwatch Software algorithms. Days of Delirium will be calculated as the sum of days on which the patient is delirious. Delirium will be considered present if either the CAM-ICU or the chart abstraction is positive for a given calendar day. Patients will be censored at day 30 or at hospital discharge.[59, 60] Confounder and effect mediator variables: Severity of illness, age, and gender will be treated as in Aim 1. Ventilator use will include invasive and noninvasive positive pressure ventilation and will be quantified as ventilator-free days based on published algorithms.[61] For sedative-hypnotic medications, equivalent daily doses of benzodiazepines and narcotics will be calculated using published algorithms.[62, 63] Propofol and dexmedetomidine total daily dose will be recorded and included in the models.

Testing for Associations: Multivariable Poisson models will assess the associations between circadian misalignment and amplitude and days of delirium. Models will be adjusted for age, severity of illness, ventilator-free days, dose of sedative medication, and measures of sleep disruption. We will test for modification of the associations between misalignment and amplitude and days of delirium by age, sedative-hypnotic medication dose and measures of sleep disruption. Linearity, serial correlation, and model fit will be addressed as in Aim 1. Power Calculation: Patients with delirium on the day of enrollment will be excluded, our effective sample size will be reduced by 20% to 80 participants. Assuming two-sided alpha of 0.05, 90% power, overdispersion of 20%, and a mean of 3 days of delirium,[4] our sample of 80 allows the detection of a minimal risk ratio of 1.12 for each 60 minutes of misalignment. Under the same assumptions, our sample of 80 will detect a minimal risk ratio of 1.08 for each change of 100ng of aMT6s.[64]

Aim 3 Analytical Approach: Feasibility: Based on qualitative analysis, we will judge the intervention as feasible if it achieves at least 70% in each of the feasibility metrics: acceptance, tolerance, fidelity, and sustainability. Effect Size: Circadian abnormalities will be assessed as described under Aim 1. Using multivariable logistic regression, we will test for associations between bright light exposure and decreases in circadian misalignment and increases in circadian amplitude. The estimated association will inform the effect size in the design of future interventional studies.

SUBJECT POPULATION

Patients admitted to the Medical ICU and who meet inclusion / exclusion criteria will be recruited into this study. Decisionally impaired persons, females of childbearing potential and pregnant women who are admitted to the MICU and who meet inclusion / exclusion criteria might be recruited into this study; however, they will not be specifically recruited and subjects will be ≥ 50 years old and severe chronic brain injury is an exclusion criteria.

Table 2 (repeated)

Inclusion Criteria	Exclusion Criteria
– Hospital admission less than 30 hours as of noon on day of enrollment – Expected to say in the MICU ≥24 hours after enrollment – Expected to produce ≥250 mL urine / day – Age ≥50 years – Able to understand English.	**At significant risk for pre-existing circadian abnormalities:** – Severe chronic brain injury (Injury greater than 30 days ago resulting in the inability to live independently) OR Acute brain injury of any severity (Injury less than 30 days ago including acute intracranial bleed, traumatic brain injury, central nervous system infection, tumor, hepatic encephalopathy) – Documented circadian disorder (<1% population) or blind/disease of the optic nerve – Current history of substance abuse including alcohol (use in last 30 days) – Transferred from an outside hospital – Homeless **Unable to participate in study activities:** – History of bipolar disease (Bright light therapy possibly unsafe in this population). – Paralyzed (due to injury, disease or medications)

RECRUITMENT PROCEDURES

Patients will be screened daily from an automated list generated from the YNHH EMR. Patients who opt out of research participation via MyChart (patient information portal) will be excluded from this list. Potential patients and/or their legally authorized representatives will be contacted in person or via the phone. Such contact will be conducted by Dr. Knauert or her trained research staff.

Prior to approaching patients for study recruitment, we will obtain permission from their attending physician. Physicians in the Medical ICU will either sign a MD permission form which will provide permission to approach any of their patients or, if the physician prefers, we will request permission on a case-by-case basis.

DETERMINATION OF ELIGIBILITY

Eligibility will be determined by study staff via review of the electronic medical record; staff will be appropriately trained in HIPAA, screening and consent and enrollment procedures. Currently this will be PI Melissa Knauert and other staff will be added to the protocol when identified and trained.

ASSESSMENT OF CURRENT HEALTH PROVIDER RELATIONSHIP FOR HIPAA CONSIDERATION

It is possible that some of the research subjects may be on the MICU service for which Dr. Knauert, Dr. Pisani or Dr. Yaggi are the attending. This will be a relatively rare event. Participation in the study will not alter usual MICU care (other than possible Daytime Bright Light for Aim 3 subjects randomized to this intervention).

REQUEST FOR WAIVER OF HIPPA AUTHORIZATION FOR RECRUITMENT/ SCREENING

This study was granted a waiver of HIPPA Authorization for recruitment and screening procedures.

PROCESS OF CONSENT/ASSENT

Patient and patient surrogates will be approached about enrolling their family member into this study. When appropriate, both the surrogate and patient will be approached together to explain the study and obtain consent. Patient's ability to make an informed decision will be assessed by multiple methods including speaking with the nurse and physician caring for the patient as well as the patient's family (legally authorized representative). An assessment for delirium will be performed to determine if the patient is delirious (CAM-ICU). Informed consent will be obtained from the surrogate when the patient is unable to provide consent and from the patient when they are deemed able to provide consent. If the patient is conscious and communicating with study staff, but unable to provide formal consent, we will ask them for assent regarding study activities. Specifically, if the patient refuses study related blood draws including before and during phlebotomy attempts, we will not continue. Blood draw attempts will be limited to two (2). Furthermore, if during the course of the study, the subject should become sufficiently cognitively capable of understanding the nature of his/her participation in the research study and is capable of communicating, consent will be obtained from the subject. If the subject does not give consent to continue study activities, study participation will stop. When the surrogate is not physically present at the hospital (i.e., COVID-19 visitor restrictions or other reasons). They will be contacted via phone. We will request permission to discuss the study and, if permitted, provide a summary of study activities. If the surrogate is interested, we will email consent paperwork and the study information sheet to the surrogate. We will then review the consent paperwork and answer any questions. If the surrogate gives consent, we will have them sign the consent paperwork and return it to us via our lab email (icustudy@yale.edu). Study activities will start only after signed consent is obtained. Alternatively, we may use the EPIC-based consent system to transmit and receive the signed consent. Use of the EPIC-based consent system will not alter communication over the phone with the surrogate.

Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Subject ability to consent will be assessed via standard delirium assessment (CAM-ICU) and agitation assessment (RASS). Barriers to communication between the patient and study staff (visual, hearing impairment) will also be assessed. In the case of delirium, agitation, or communication difficulty, formal surrogate consent will be obtained along with informal agreement from the patient (assent) when possible.

PROTECTION OF PARTICIPANT PRIVACY

All PHI and subject data will be collected and maintained electronically. Data management procedures will ensure accurate and efficient data collection and analysis; confidentiality and real-time, on-demand study monitoring reports. All data will be maintained in accordance with HIPAA guidelines for participant confidentiality and privacy. All data will reside on secure, HIPAA-compliant database and file-sharing resources managed by the Data Management and Informatics Core (DMIC) of the POA and by Yale ITS. Access to data resources will be strictly limited to research staff and investigators, and all such resources will reside on a local network not accessible outside the secure Yale environment. All study data will be managed using REDCap, a secure, web-based data collection and workflow management system developed at Vanderbilt University and supported by the national Clinical and Translational Science Award (CTSA) program. REDCap's authentication, security and auditing features comply with the FDA Title 21 CFR Part 11 guidelines for Electronic Records and Electronic Signatures. Yale's implementation of REDCap is managed jointly by POA/DMIC and by Yale ITS, and has been certified by Yale's Information Compliance Office as meeting HIPAA privacy and security guidelines.

METHODS FOR SECURITY OF STORAGE AND SHARING MATERIALS

Outcome data will be shared, along with associated demographic and clinical data including age, gender, race/ethnicity, evaluation of functional status, and medical conditions. To enable the widest dissemination of data, while also protecting the privacy of study participants and the utility of the data, we will de-identify and mask potentially sensitive data elements, consistent with HIPAA considerations and in full compliance with the NIH public data sharing policy (for further details, see http://grants.nih.gov/grants/policy/data_sharing). Data sets will be subjected to cleaning and quality control measures. Following these procedures, for experiment types such as RNAseq and metabolomics, the data will be deposited in relevant public databases (e.g., the Gene Expression Omnibus (GEO), the Sequence Read Archive (SRA), the database of Genotypes and Phenotypes (dbGaP) and the Metabolomics Workbench) as required by the NIH and by journals. We will comply with NIH expectations for data release specified in the Supplemental Information to the GDS Policy (as outlined at http://gds.nih.gov/pdf/supplemental_info_GDS_Policy.pdf). Data will be shared once the data have been cleaned and quality control procedures are completed. Generally speaking, these procedures should be completed by 3-6 months after data generation. As per the GDS policy, after submission begins, data will be held in an exchange area accessible only to the submitting investigators and collaborators for a six-month period, after which the data will be available for research access without restrictions on publication. Final analyses relating these data to specific biologic outcomes will be released with publication. The consent form provides consent for the data to be used for future research purposes and to be shared broadly through unrestricted-access databases.

STUDY RISKS

There is minimal risk to subjects. There are no changes to usual MICU care during the observational portion of this study (Aim 1 and 2). For all enrolled patients, there is minimal risk of breach of confidentiality. There is a risk of minor skin irritation caused by Actiwatch Spectrum device application. Urine collection will be from catheterized urine that would otherwise be discarded; patients will not be catheterized to collect urine for the study. Patients who are enrolled in Aim 3 regarding the feasibility and effect size of daytime bright light will also be exposed to a bright light device set to deliver 10,000 lux at the surface of the lamp; at the planned distance of 36 inches this will degrade to <1250 lux. Direct bright light exposure (i.e. during treatment for outpatient circadian disorders) has minor and reversible side effects of eye strain, visual disturbance, and headache. If symptoms develop, light therapy will be discontinued, and the side effect will be tracked as a metric of feasibility. Also, hypomania and mania in patients with a history of bipolar disease have also been reported as uncommon but serious side effects of overexposure to light therapy. Patients with a history of bipolar disease will be excluded from the study.

MINIMIZING RISKS

The above-mentioned risks will be minimized in the following manner: Risks regarding patient confidentiality are minimized via data management strategies which isolate all personal identifying data elements. Only users having project-specific access rights can view or modify personal identifying information or print reports that include patient names or other identifying information. This study will have no paper records other than the consent forms which are stored within a locked file cabinet in the PI's office. The office is locked when not occupied. All electronic data will be maintained on a secure, firewalled server.

Skin irritation from the Actiwatch Spectrum or iButton device can be mitigated by movement of device to a contralateral site. If skin irritation is severe, the Actiwatch Spectrum or iButton will be removed, and study participation will be discontinued. If symptoms (eye strain, visual disturbance or headache) develop, light therapy will be discontinued, and the side effect will be tracked as a metric of feasibility. In addition, hypomania and mania in patients with a history of bipolar disease have also been reported as uncommon but serious side effects of overexposure to light therapy. Patients with a history of bipolar disease will be excluded from the study.

DATA AND SAFETY MONITORING PLAN

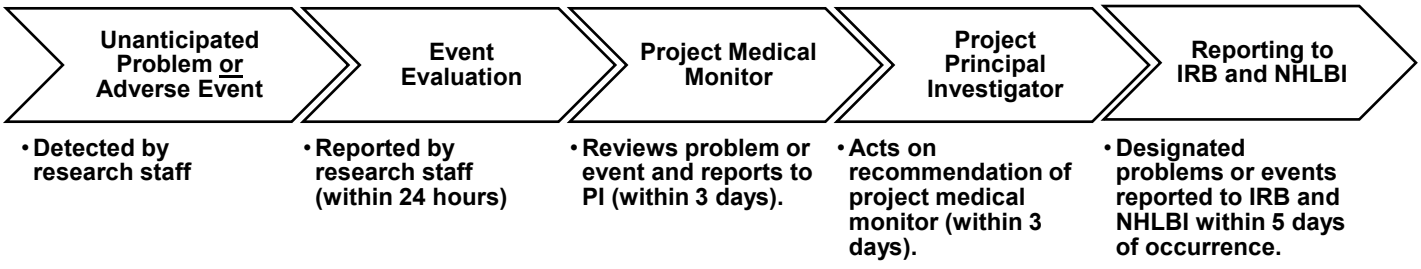
Data and Safety Monitoring for Clinical Trials: This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, the following Data and Safety Monitoring for Clinical Trials Plan will be followed.

Main Study DSMP

A **medical monitor** will oversee the proposed research project. **Dr. Shyoko Honiden**, Yale-New Haven Hospital MICU attending and board certified in critical care medicine, has agreed to serve as project medical monitor. She has no conflicts of interest with this role. Dr. Honiden will conduct interim monitoring of accumulated data from research activities to assure the continuing safety of participants and integrity of the accumulating data. The medical monitor is independent of the study investigative team and will report progress including safety concerns to the project principal investigator. Safety concerns will be also be reported to the IRB.

1. **Safety:** Safety will be monitored at intervals related to patient enrollment. Safety and device protocols will be reviewed by the medical monitor every twenty patients to assure uniform and safe application of project devices. Research staff will report skin irritation or bright light related symptoms as they occur via event evaluation forms. In addition, research staff will identify and immediately report unanticipated problems, unexpected adverse events and serious adverse events (defined below). Safety concerns will be also be reported to the IRB.
2. **Protocol Compliance:** The project medical monitor will check enrolled patients for compliance with IRB requirements, conformance with informed consent procedures, verification of source documents and investigator compliance. One in ten patients will be randomly selected for conformance.
3. **Event Evaluation:** Adverse event or unanticipated problem occurrence will prompt an event evaluation and a report to the project medical monitor. The adverse event report will NOT include identifying patient information but will otherwise provide a clinical summary of the study patient and the circumstances immediately associated with the adverse event / unanticipated problem including date of the event, type of event and a narrative event description.

Flow Diagram for Adverse Event / Unanticipated Problem Detection, Review and Reporting:



Unanticipated Problems are defined as any incident, experience, or outcome that meets all of the following criteria: 1) unexpected, 2) related or possibly related to participation in the research, and 3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Adverse Events: An **adverse event** will be defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). Adverse events that occur during study enrollment will be reported by research staff to the project medical monitor via an event evaluation.

A **serious adverse event** is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria (modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a)):

1. results in death or is life-threatening
2. requires prolongation of existing hospitalization
3. results in a persistent or significant disability/incapacity
4. results in a congenital anomaly/birth defect
5. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Response to Adverse Event: All study patients are (by definition) concurrently admitted to the MICU. The response to any adverse event will be appropriate medical care. Adverse event occurrence will prompt an event evaluation and report to the project medical monitor by research staff.

The project medical monitor will evaluate adverse events along the parameters of relationship, severity, and expectedness:

Relatedness:

1. Unrelated: Adverse event(s) clearly not related to the project
2. Unlikely: Adverse event(s) doubtfully related to the project
3. Possibly: Adverse events(s) may be related to the project; known to occur, but the temporal relationship is unclear; other causes are possible or biologically very plausible
4. Probably: Adverse event(s) likely associated with the project; known to occur and temporal relationship is appropriate; other causes are unlikely
5. Definitely: Adverse event(s) clearly associated with the project

Severity: The following scale will be used to grade the severity of adverse events noted during the study:

1. Mild adverse event: Did not interfere with normal activity, minimal symptoms, no intervention required
2. Moderate adverse event: Interfered with normal activity to some extent, moderate symptoms, minimal or local intervention required
3. Severe adverse event: Prolonged hospitalization with need for intervention to prevent escalation of condition
4. Life-threatening / disabling adverse event: Event that puts the patient at risk of death at the time of the event if immediate intervention is not undertaken
5. Fatal adverse event

Expectedness: An unexpected adverse event is any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents such as the IRB-approved research protocol and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

The **principal investigator (Knauert)** will have overall responsibility for adverse event reporting to Yale University's IRB and NHLBI. Unanticipated problems, unexpected adverse events or serious adverse events will be reviewed by the medical monitor. **The principal investigator will provide reporting of any of the following to the IRB and NHLBI within 5 days of occurrence:**

1. Unanticipated problems, unexpected adverse events or serious adverse events that are possibly, probably or definitely related to study protocols.
2. IRB approved revisions to the project which change participant risk.
3. Notice of any actions taken by the Yale University IRB regarding the project and any responses to these actions.

POTENTIAL BENEFITS

This research has the potential to benefit future patients admitted to the MICU via improved circadian entrainment. There is minimal risk involved in this study, and appropriate precautions to guard against risk have been taken. This protocol is intended for broad distribution following the research study. The findings of this research will be generalizable to a significant portion of MICU patients and thus provide potential future benefit to many critically ill patients, especially those at greatest risk for delirium (older age, history of hypertension).

RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative is to not participate and to receive usual care in the Medical ICU.

2. **Payments for Participation (Economic Considerations):**
   Study subjects will receive a $100 pre-paid gift card upon completion of study day 5 as compensation for their time and any minor inconveniences they may have experienced while participating in the study. In order to be eligible for study payment, subjects must complete through day 5 of the study protocol unless they are discharged from hospital prior to day 5. If a subject is discharged from the hospital prior to study day 5 but after study day 2, they will receive payment for their participation. In the event a study subject wishes to discontinue study participation before the end of study day 5 for any reason other than listed above, they will no longer be eligible for payment.

Study payment will be given directly to the subject at the end of study day 5 in the form of a physical gift card. Gift cards will be provided to the patient in a marked envelope. In the event a patient lacks the capacity to accept study payment at the time of study day 5, payment for participation will be included in the patient's secured personal belongings or provided to the patient's surrogate contact to hold for the patient.

3. **Costs for Participation (Economic Considerations):** No cost

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