Methodology Issues in a Tailored Light Treatment for Persons with Dementia - Investigating the Impact of Duration and Amount of Light on the Circadian System Response – Aim 1
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Mount Sinai	Protocol Name:	Methodology Issues in a Tailored Light Treatment for Persons with Dementia - Investigating the Impact of Duration and Amount of Light on the Circadian System Response – Aim 1
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1.1 Purpose/Specific Aims

Investigate the minimum effective circadian stimulus (CS) dose (amount) needed to promote better sleep, cognition, mood, and behavior in Alzheimer's disease/Alzheimer's disease-related dementias (AD/ADRD) patients living in controlled environments.

A. Objectives

In a randomized, within-subjects, placebo-controlled study, extend the grant activities to investigate the minimum effective CS dose needed to promote better sleep, cognition, mood, and behavior in AD/ADRD patients living in controlled environments. Using the circadian stimulus (CS) dose response function, we will test 3 doses, delivered for 1 h per day between 7-9 am: (1) below threshold (CS=0.05, control), (2) half saturation (CS=0.3), and (3) close to saturation (CS=0.6). Following the short-term protocol completed in the current grant (preliminary studies), these exposures will be followed by a 4-week washout period and crossover to experience the other lighting conditions.

B. Hypotheses / Research Question(s)

Light therapy has shown great promise as a nonpharmacological treatment to help regulate sleep in AD/ADRD patients and to improve cognition. Studies have demonstrated that daytime light exposure can consolidate and increase nighttime sleep efficiency, while increasing daytime wakefulness and reducing evening agitation. More importantly, light exposure during the day has been shown to improve memory in AD/ADRD patients. A study showed that light can not only improve sleep but also improve cognition1. Longer and better sleep during the night should diminish disruptive behaviors in people with ADRD during the day and, by extension, have a positive impact on caregivers, both in institutions and at home. The sleep-wake cycle responds to very specific spectra of light. Human melatonin suppression (a marker of the circadian clock) has a peak sensitivity to light close to 460 nm 2,3. Light sources typically used in elder care facilities do not necessarily provide efficacious stimulation to the circadian system. Our research team has shown, however, that 470-nm (blue) light treatment presented for 1 h in the early evening can consolidate and increase sleep efficiency in nursing home residents diagnosed with mild to moderate AD/ADRD symptoms. New data from our R01 also indicated that high correlated color temperature (CCT) polychromatic light sources (bluish-white light) decreased depression scores in those with AD/ADRD living at home. The same lighting improved sleep scores and reduced agitation and depression in those with ADRD living in nursing homes. For this within-subjects, crossover design, we will recruit 45 participants who will experience all 3 experimental conditions, placebo control of CS = 0.05, moderate CS at 0.3, or full CS at 0.6. It is hypothesized that there will be a strong association between dose and improvement in outcome measures (cognitive status, sleep disturbances, depression, and agitation): the greater the amount, the greater the response.

1.2 Research Significance

The proposed study proceeds from our data showing that light that is carefully designed and delivered so that it maximally affects the circadian system can improve sleep (measured with sleep questionnaire and actigraphy), mood, and behavior in older adults and AD/ADRD patients living at home and in controlled environments. Our premise is that AD/ADRD patients living in nursing homes are in continuous dim light and that a tailored lighting intervention (TLI) that can passively deliver the light that can have a significant impact on sleep, mood and behavior in this population. The next steps for more widely

adoption of light as a non-pharmacological intervention to improve sleep, mood, and behavior is to better understand the appropriate dose (amount and duration) of light needed to be effective. In our studies to date, we used a "catch-all" approach to demonstrate the effect. In this renewal, we are starting to "zoom in" the details of this intervention, so that a more precise dose can be then implemented in larger clinical trials. In summary, the aims proposed in this study are needed for the next big step in this area.

1.3 Preliminary Data

Summary of Accomplishments – Parent Grant

Publications: 13 peer-reviewed papers (plus 1 in review) and numerous technical conferences.

Tailored Light Treatment Development: We have developed and tested the tailored lighting intervention in previous research studies. All previous studies were conducted by Dr. Figueiro at the Lighting Research Center at Rensselaer Polytechnic Institute, Troy, NY.

Study 1. Circadian entrainment. As reported in Figueiro et al, ADRD patients living at home exhibit much greater circadian disruption that age-matched healthy older adults (Figure 1, Table 1). The LRC/RPI team, together with collaborators at CWRU collected data from 16 healthy older adults and 21 AD/ADRD patients (MMSE range 16-24). Two measures of circadian entrainment were determined. Relative activity (RA) is a "contrast" calculation based upon the most active and least active periods in a day; a higher value suggests more consolidation and less circadian disruption. The continuous 10-h block with the highest mean activity level (M10) and the continuous 5-h block with the lowest mean activity level (L5) were determined. The RA for each participant was calculated by the following ratio: RA = (M10-L5)/(M10+L5). Phasor analysis, where the resonance between the 24-h light-dark pattern and rest-activity pattern is calculated; the higher the resonance, measured by the phasor magnitude, the greater the circadian entrainment. Phasor angles were determined, indicating the phase relationship between the light-dark and rest-activity patterns. Entrained individuals typically have positive phasor angles of about 1 to 2 h; they are usually active in bright light after rising in the morning and continue to be active throughout the day and into the dim evening light. AD/ADRD patients were found to have significantly more circadian disruption, significantly less activity during waking hours, and significantly lower

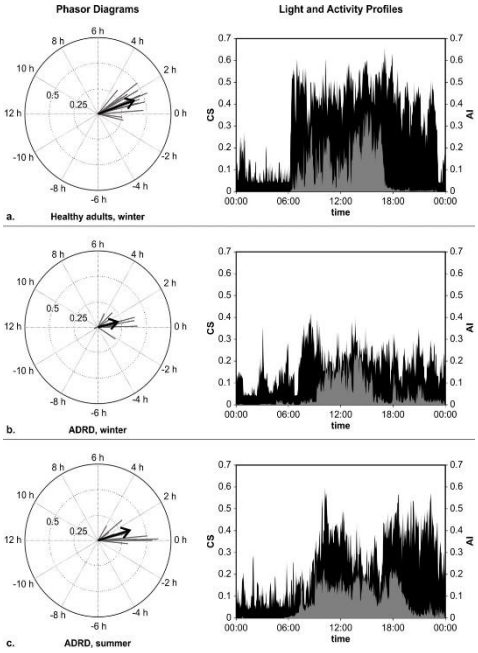


Figure 1. Phasor diagrams with light and activity profiles for each of the 3 groups, (a) healthy adult subjects studied during winter, (b) a group of subjects with AD/ADRD studied during winter, and (c) another group of AD/ADRD subjects studied during summer. Representative 5-day average light (CS, gray) and activity index (AI, black) profiles shown on right.

relative activity amplitude. Circadian light exposures experienced by both groups were not, however, significantly different. As expected, those with ADRD had greater levels of circadian disruption than healthy older adults, especially in winter months.

Table 1. Light and activity data for each of the 3 groups

Group	Phasor Magnitude*+	Phasor Angle	RA*	M_{10}*	L_5	CS_{10}*+
Healthy adults	0.40 ±0.02	1.31 ±0.26	0.68 ±0.02	0.47 ±0.01	0.09 ±0.01	0.15 ±0.02
ADRD, Winter	0.22 ±0.04	0.98 ±0.57	0.50 ±0.05	0.34 ±0.02	0.11 ±0.01	0.09 ±0.02
ADRD, Summer	0.35 ±0.05	1.13 ±0.44	0.51 ±0.06	0.36 ±0.03	0.12 ±0.02	0.17 ±0.03

* A significant difference ($p < 0.05$) between the Healthy adults, Winter and the ADRD, Winter groups

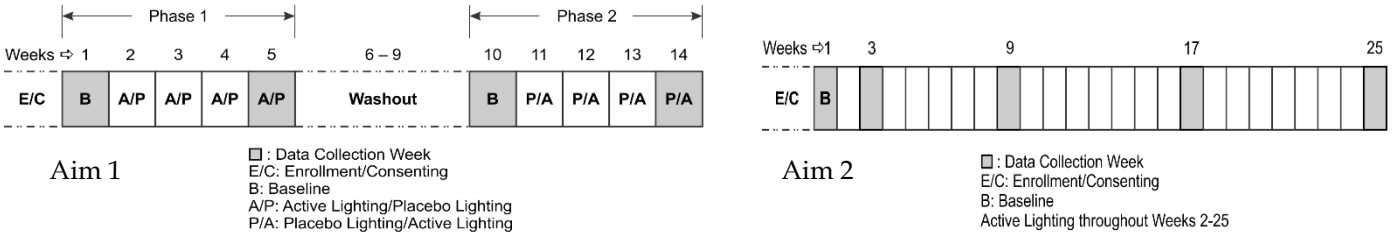
+ A significant difference ($p < 0.05$) between the ADRD, Summer and ADRD, Winter groups

Study 2. Tailored lighting intervention (TLI) in the home. Together with Case Western University, we collected data for a 10-week intervention in which we installed experimental lighting and measured its effects on sleep-wake rhythms for AD/ADRD persons and their live-in caregivers across three 7-day data collection periods: under participants' usual home lighting [baseline], intervention lighting, and after return to usual home lighting [post]. In this study22 we investigated the effects of a TLI on sleep and behavior in dyads (older adults with AD/ADRD and their caregivers) living at home. Our results from 35 older adults with AD/ADRD and 34 caregivers demonstrated that circadian entrainment and sleep efficiency was significantly ($p <0.05$) increased and depression scores from the Geriatric Depression Scale (GDS)23 were significantly decreased with TLI.

Study 3: Tailored lighting intervention (TLI) in controlled environments. In this study24 we investigated the effects of a TLI on sleep and behavior of 14 older adults with AD/ADRD living in nursing homes and assisted living facilities. The lighting intervention significantly ($p <0.05$, Cohen's d range from = 0.4 to 1.1) decreased global sleep scores from the Pittsburgh Sleep Quality Index (PSQI)5 and increased total sleep time and sleep efficiency, as measured by actigraphy. Phasor magnitude, a measure of the 24-hour resonance between light-dark and activity-rest patterns, also increased, suggesting an increase in circadian entrainment. The lighting intervention significantly ($p <0.05$) reduced depression scores from the Cornell Scale for Depression in Dementia (CSDD)8 and agitation scores from the Cohen-Mansfield Agitation Inventory (CMAI).9 At the completion of this study, the investigators hypothesized that a longer exposure time (i.e., more than 4 weeks) could have been beneficial (see study 5 for results). We have also demonstrated that a light table, delivering strong circadian stimulation to AD patients during the day, increases sleep and reduces depression and agitation.25

Parent Grant Competing Renewal (May 2014-April 2019) Specific Aims. In the competing renewal, which was awarded in May 2014, we proposed to extend the work in the parent grant to investigate, in a crossover, randomized, placebo-controlled design, the short-term effect of the TLI on sleep, mood and

behavior in AD/ADRD patients. A control light delivered low circadian stimulus was used as placebo. Each lighting intervention was delivered for 4 weeks, separated by a 4-week washout period. Data were collected just prior to (baseline) and 4 weeks after intervention was in place. In a second aim, we set out to investigate the long-term impact (6 months) active lighting intervention on sleep, behavior and mood in AD/ADRD patients living in nursing homes. Data were collected periodically (baseline and in weeks 3, 9, 17 and 25), as shown below.



Study 4: Short-term effects of the TLI on sleep and behavior of older adults with AD/ADRD. The PI completed recruiting, under the current R01 grant. Sixty nursing home participants who met the study's inclusion and exclusion criteria were enrolled and 46 (30 females, 16 males; mean age 85.1 years [SD 7.1]) completed in the study. All had been diagnosed with moderate or late stage AD/ADRD. As shown in Figure 3a, the active intervention (blue bar) represents mean PSQI scores after 4 weeks of the lighting intervention, which are significantly reduced ($p<0.05$, Cohen's $d = 0.5$) compared to baseline (gray bar). While the placebo (or control) condition was also significantly reduced compared to baseline, the reduction observed for the active intervention was significantly greater than that for the control intervention. Similar results ($p < 0.05$, Cohen's $d = 0.3$) were observed with the depression scores (CSDD) and the agitation scores (CMAI) ($p < 0.05$, Cohen's $d = 0.4$). The results of this study were recently published 46.

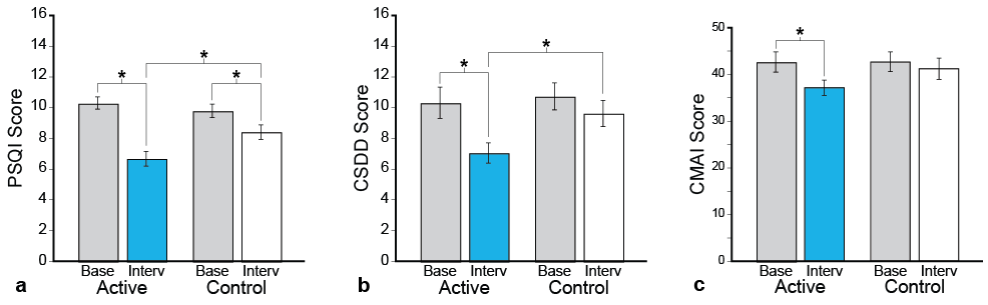


Figure 3. Effects of the short-term TLI on subjective measures of sleep (a), depression (b), and agitation (c). (* represents p <0.05).

Study 5: Long-term effects of the TLI on sleep and behavior of older adults with AD/ADRD. We have successfully recruited 53 participants (43 have completed the study) into this long-term phase of the project. For the long-term study, as shown in Figure 4, PSQI, CSDD and CMAI scores also show a significant ($p < 0.05$) continuous decline with treatment over the course of the study. The results of this study are in press in the Journal of Alzheimer's Disease Reports.

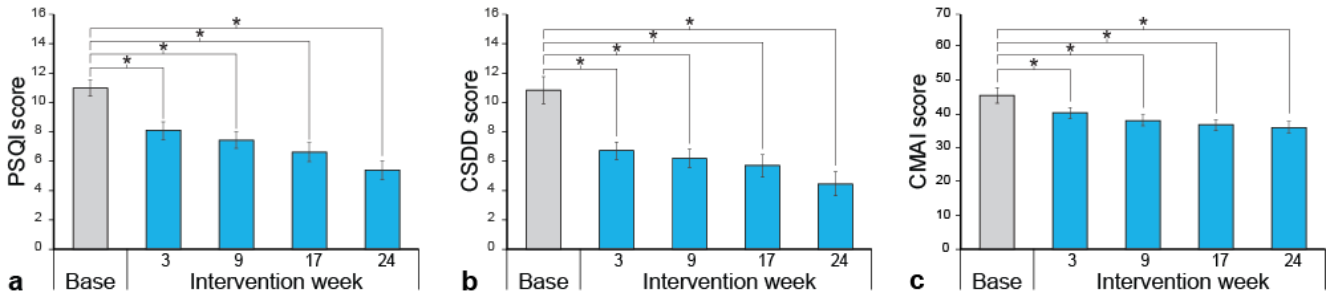


Figure 4. Effects of the long-term TLI on subjective measures of sleep (a), depression (b), and agitation (c). (represents p <0.05).*

1. Setting of the Human Research:

Data collection will occur at long-term care facilities and assisted living facilities in the NYC area and in St. Peters Health Partners long term care and assisted living facilities in the Albany and Troy, New York area.

2. Resources Available to Conduct the Human Research:

Mariana Figueiro is a Professor of Medicine in the Department of Population Health Science and Policy at the Icahn School of Medicine. She specializes in human circadian responses to light. She is currently a PI on an R01 investigating the impact of light on sleep efficiency of older adults with ADRD living in nursing homes (Study 3, above). Her team will lead data collection and analysis. Dr. Figueiro has demonstrated the ability to recruit older adults, including those with Alzheimer's disease and their caregivers, in 3 recent NIH-funded trials. Collaborating physicians have access to a large number of eligible participants.

3. Study Design:

A. Research Procedures

AIM 1

For this within-subjects, crossover design, we will recruit 45 participants who will experience all 3 experimental conditions. (1) Recruitment/Enrollment. Pre-selection diagnosis according to the following

pre-selection criteria: Participants must be diagnosed with moderate to severe AD/ADRD, as defined by a Mini Mental Score Examination (MMSE) between 0 and 19, and have a score >5 on the PSQI. Participants will be living in controlled environments (e.g., memory care, nursing homes, long-term care). Once a potential participant has been identified, the facility personnel will contact the family member, who will be invited to participate in the screening. If the screen is positive and consent is obtained from the family member (and participant, if appropriate), the research assistant (RA) will identify and measure the room where the TLI would be installed. (2) Baseline measurements and lighting intervention planning. Once screening and informed consent are completed, the research team will obtain baseline light measurements and calculate the configuration of lamps needed to provide the study light levels. A member of the research staff will either be in the facility or be in touch with the caregiver daily to assure compliance to the protocol. (3) Administration of study conditions and outcome data collection. For Aim 1, given its within-subjects nature, a 4-week washout period between each CS dose exposure will be included. Conditions will be counterbalanced within subjects. The lowest CS dose (CS=0.05) will be used as the control, non-active condition. Assessments outlined below under "Data Points" will be made during a baseline week prior to exposure to each CS dose and at the end of each 4-week exposure to each CS dose. CS doses will be counterbalanced across participants, who will be randomly assigned to start the study with a specific CS dose. Participants will be exposed to each lighting condition for 1 hour each day at wake time – typically between the hours of 7:00 AM and 9:00 AM.

Data Points

Each of the 3 CS doses will be administered for a period of 4 weeks, with a washout period of 4 weeks between conditions. The below data points will be collected at the end of each baseline week (weeks 1, 10, and 19) and the end of each 4-week intervention (weeks 5, 14, and 23).

Questionnaires

Cognitive status using the MoCA -

Sleep disturbance using the PSQI: The PSQI is a tool that can be used to measure sleep quality in clinical populations, composed of 19 items that generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction).18 The sum of the 7 component scores yields a single global score. A global score >5 is considered to indicate sleep disturbances. We will include those who have scores >5.

Depression screening using the CSDD: The CSDD8 is a 19-item tool designed to rate symptoms of depression in patients with dementia. This tool evaluates the presence and extent of mood-related signs (anxiety, sadness, irritability); behavioral disturbances (agitation, loss of interest); physical signs (loss of appetite, weight loss); cyclic functions (mood variation, sleep quality); and ideational disturbances (suicidal thoughts, poor self-esteem). This scale has a high inter-rater reliability (kappa = 0.67), internal consistency (alpha = 0.84), and validity (correlation of 0.83) with depressive symptoms.8 It uses a comprehensive interviewing approach that derives information from the patient and the informant

(caregiver, in general). The final CSDD ratings represent the rater's clinical impression. Raters will be blind to the experimental condition. Scores ≥9 indicate depression.

Agitation will be measured using the CMAI: The purpose of the CMAI is to assess the frequency of manifestations of agitated behaviors in elderly persons. The CMAI is a caregivers' rating questionnaire consisting of 29 agitated behaviors, each rated on a 7-point scale of frequency.

Sleep burden using The Sleep Disorders Inventory (SDI). The SDI is an expanded version of one item of the Neuropsychiatric Inventory (NPI). It describes the frequency, severity, and caregiver burden of sleep-disturbed behaviors. The SDI is a simple and short instrument that can be administered multiple times during a study protocol. Validity of using the sleep questions of the NPI as an independent instrument (i.e. the SDI) in sleep research requiring a caregiver's report of
sleep symptoms by showing good correlation, but not redundancy, with quantitative sleep measurements was shown.

Field Monitoring Assessments

Daysimeters: The participant will be given the Daysimeter and asked to wear it as a pendant during all times while awake for each seven day assessment week. The facility staff and the research assistant will help ensure adherence to the measurement protocol. We have shown through our grant work that light measurements from Daysimeters used as pendants are the closest to light measurements at eye level.

Wrist actigraph: Participants will be asked to wear the actigraphs for 7 days during the assessment weeks. Actigraphic monitoring employs an accelerometer the size of a small which will be worn on the nondominant wrist of each participant. Actigraphy has been demonstrated in prior studies to be well tolerated by older adults with AD/ADRD and strongly correlates with polysomnography (PSG) and sleep logs. A member of the research team will perform site visits to deliver devices and assist the participant in application and any necessary adjustments of the instrument placement.

C. Study Duration for AIM 1 – 23 weeks for each participant.

Tailored Lighting Intervention (TLI) – General Overview. Combining spectrum and light level, the TLI will allow us to: (1) use a light source that will stimulate the circadian system according to model predictions and (2) provide the participants with options as to how the light treatment will be delivered. Instead of having to sit in front of a light box, table and floor lamps can be used to deliver the TLI, which are inexpensive and easy to install and much more feasible in this population. TLI quantities for each aim will be based on calculations made using the mathematical model developed by Rea et al., which provides a method for determining the CS for any light source and light level. Older people are slightly less sensitive to short wavelengths than young observers for any source of light, but the differential effect is

small. The optical density of a normal, older person's crystalline lens is about 0.2 times greater in this region of the spectrum than it is for a young observer (≈ 63%). This age-dependent differential density of the lens at short wavelengths is comparable to having a given participant see the same light source at 2 distances, one being 25% greater than the other. The model calculations will correct light levels to account for these changes. Motion sensors will control all the table and floor light fixtures, so that lights are not on when no one is in the room. These lights use light emitting diodes (LEDs) and are very energy efficient. The research assistant will be instructed to ensure that the lights are not turned off when patients are immobile but awake in the room. A manual override switch will be provided for emergencies and unanticipated contingencies. Neither system will compromise ocular safety nor limit evening activities. The levels meet the Illuminating Engineering Society (IES) recommendations.39

TLI for Aim 1. Amount and Spectrum: Three CS doses will be used to test the impact of amount on the outcome measures described above. The first will deliver a CS of 0.05 (below threshold for activation of the circadian system and will serve as the control condition), one half way (CS=0.3), which has been used in our previous studies, and one close to saturation (CS=0.6). Figure 5b shows the CS calculations for the light levels that will be tested in the study. CS values at the eye can be achieved by manipulating light levels and spectrum (color of light). The higher CS values will use higher light levels (300 lux at the eye for CS of 0.3 and 1000 lux at the eye for CS of 0.6) bluish-white light sources (correlated color temperature (CCT) of 5000 K and shown as "daylight" in Figure 5b) and the lower CS will use low levels (< 30 lux at the eye) of yellow-white light sources (CCT of 2700 K and shown as incandescent in Figure 5b). The combination of light level and spectra to achieve each of the CS values are based on the Rea et al model described above. Note that, by manipulating spectrum to make it more or less tuned to the circadian system, we can use lower light levels than those generally used by light boxes sold for seasonal affective disorder. Also note that the CS of 0.3 has been shown in our studies to be effective for improving sleep, mood, and behavior in persons with ADRD, as detailed in the preliminary studies above. To avoid expectation, we will tell the caregivers we are evaluating which type of light is more effective for improving sleep. We will also collect expectancy questionnaires at start of data collection.

Distribution: The lighting interventions will provide diffuse ambient illumination throughout the room where the study participant spends the most time (usually a bedroom or common area). This will be done via adding table or floor lamps to the space. If participants stay in common areas sitting around tables, a "tray light", currently being used in our studies, will be placed on top of the table. This tray light is calibrated to account for objects being placed on top of it and it can deliver the desired CS at the eye level.

Duration and Timing: For Aim 1, the TLI will be provided for 1 h per day between 7-9 am, with each participant maintaining the same start time throughout each 4-week trial. Based on our experience, patients are generally awake before 8 am, so this schedule should be doable for everyone. An RA will be staying with participants to assure that the lighting is being delivered accordingly. To sample light exposures outside the intervention period, a Daysimeter will be worn by the patient during the assessment weeks.

Administration of TLI: Each of the 3 CS doses will be administered for a period of 4 weeks, with a washout period between conditions. The lowest CS dose (CS=0.05) will be used as the control, non-active condition. Assessments will be made during a baseline week prior to exposure to each CS dose and at the end of each 4-week exposure to each CS dose. CS doses will be counterbalanced across participants, who will be randomly assigned to start the study with a specific CS dose.

Data Analysis:
Analyses will include: (1) evaluation to determine data quality, (2) creation of constructed variables and determination of variable distributions, (3) testing of parametric statistical assumptions wherever appropriate, (4) preliminary (generally bivariate) testing of hypotheses, (5) consideration of potential covariates to build into the statistical models to assess treatment effects, and (6) development and elaboration of multivariate models. In evaluating outcomes of the intervention, we will first determine whether the TLI significantly affected the outcome measures listed below. As initial analyses, we will perform a within-subjects analyses of variance (ANOVA) using the change in scores between baseline and active and between baseline and comparison. Paired t-tests will be used to compare scores for the TLI and comparison lighting. Sidak correction will be used, when needed, on all post hoc 2-tailed t-tests. In addition to these standard analytical approaches to evaluate the endpoints of our study, more-focused analyses will be used to investigate the endpoints pertaining to the specific aims. In Aims 1 and 2, for example, we will also investigate dose-response curves to determine minimum effective CS dose to promote better outcome measures of interest (e.g. sleep quantity and quality). The cutoff values will be investigated and confirmed for their optimality using ROC curve methodology. Further, using various regression tools, we will investigate the optimum TLI duration on agitation, cognition, and nighttime sleep measures in ADRD patients. For Aim 3, we will then employ generalized linear mixed-effects models with outcomes listed below as dependent variable (depending on the nature of the outcome variable, we will use an appropriate link function), a random effect for study participant, and a fixed effect for treatment (i.e., a dummy variable for the experimental condition, with the comparison control condition and the baseline condition as the reference categories). These analyses allow for different numbers of observations for different participants (e.g., if there are dropouts). Furthermore, we can explicitly test for a week effect by including a dummy variable in the linear mixed model, with baseline or comparison light as the reference. These models will allow explicit assessment of time-varying and time-static effects as well as potential interactions on the outcome while incorporating distinct sources of variations. We will inform the functional nature of the relationship between time and outcome by first employing model-free LOESS smoothing techniques. In addition to mixed-effects, we will also assess significance under marginal models using generalized estimating equations with robust standard error computation method to address potential misspecification of the variance structure in linear mixed-effects models and between-subject ANOVA. As sample size and its associated degrees of freedom allow, we will also adjust for covariates that may be associated with outcome measures, such as season, gender, cognitive status, functional status, baseline sleep disturbance, and antidepressant medication load. It is possible that the treatment effect will have greater impact on sleep scores in the winter, when daylight

availability is less. Within the limits of the sample, we will explore treatment-covariate interactions for each participant-level covariate. If strong interactions are observed, it will suggest that a future study could possibly be stratified on the given factor. We will also assess significance of random subject-to-subject variation by testing the relevant variance component using a mixture chi-square test. Finally, because we will be assessing actigraphy for multiple 7-day periods in each lighting intervention condition, we can model the treatment effect as a function of time within each treatment period, to test, for example, whether the treatment benefit increases over time or is maximally achieved at a certain number of weeks. This will also allow efficient use of the data should a resident drop out within a treatment period. The nature of dropout will be investigated to assess any selection bias influencing our inferential process. We will analyze which characteristics are associated with drop out.

a) Recruitment Methods (see PPHS policy):

Participants will be recruited from long-term care and independent living facilities in the Capital District area as well as sites in the metro NYC surrounding area.

Recruitment methods will include: 1) directly contact providers of pts that take care of pts with AD or MCI, 2) flyers placed in participating sites or advertising in the community, 3) Institute websites, 4) clinicaltrial.gov, 5) Alzheimer's Association and other related websites

b) Inclusion and Exclusion Criteria:

Subject Screening
Subject screening will be performed by the research coordinator or study RN and will done by a survey of medical chart and medication list and by interview with facility staff such as the unit manager. Potential participants would be screened by the study nurse or clinical coordinator at the site. Subjects and family members will be given as much time as needed to ask questions and consider the research project. The study nurse will be in contact with the social worker at the participating care facilities.

Inclusion Criteria:

- Over the age of 60 years old with a diagnosis of mild to moderate dementia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV or V) criteria
- History of sleep disturbances as determined by a PSQI score ≥5.
- Subjects taking anti-depressants will be included, but type of medicine and dosage intake will be monitored.
- Comprehension of and ability to read and write English.

Exclusion Criteria:

- There will be no exclusion based on gender, race, or ethnicity.
- Obstructing cataracts, macular degeneration, and blindness.
- Use of sleep medication
- Severe sleep apnea or restless leg syndrome (RLS). Apnea will be screened for using the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ), a 12-item scale yielding scores between 0 and 60. The study will use a score of 29 as a cutoff for men (sensitivity 75%, specificity 65% for sleep apnea), and a cutoff of 26 for women (sensitivity 80%, specificity 67%). RLS will be screened for using the International Restless Legs Scale (IRLS), a 10-item scale that yields scores between 0 and 40. The study will use a cutoff of >11 (indicating the presence of symptoms that are at least moderate) as a positive screen for RLS.
- Potential participants will also be screened by interview with primary caregivers, physicians, or family members for history of severe photosensitivity dermatitis, severe progressive retinal disease (e.g., macular degeneration), or a permanently dilated pupil (e.g., after certain types of cataract surgery), manic depressive disorder, or migraines. While there is no supportive evidence that these conditions are associated with adverse responses to bright light therapy, they are theoretical risks.

c) Number of Subjects:

Aim 1
We will recruit 45 participants who will experience all 3 experimental conditions.

d) Study Timelines:

Participation length for each subject:
Aim 1: 23 week participation

Each aim will be completed in order before recruitment will begin for the next aim. We anticipate that each aim will take approximately one year to complete. The entire study duration including data analysis is 5 years.

Consent Process:

Consent process will take place in clinic offices or for participants living in long-term care, at the participants care facility. Researchers will be in contact with participants or surrogates and caregivers weekly between study visits. Participants and or family members will have an opportunity at these times to ask any questions that may have arisen since consent was obtained. Participants and family members will also be able to contact the researchers at any time by phone or email with questions or concerns.

Research coordinators, research nurse or Principal Investigators will be obtaining consent. Primary physicians will identify patients who might qualify for the study. They will then refer these patients to the research coordinators, who will complete the consent process. The consent process should take 20 to 30 minutes but participants will be allow as much time as necessary to ensure understanding of the protocol. Copies of the consent form can be taken home and brought back if necessary.

Emphasis will be placed on the voluntary nature of the research study. Participants will be reminded at each study visit that they can stop taking part in this research study at any time without any penalty and withdrawal will not affect their ability to receive medical care.

Subject Understanding

Participants or surrogate/family members will be asked to summarize their understanding of what will take place during the research study by use of Teach-Back questions (see below). If they are unable to provide this summary, details of the study will be reviewed again until they are able. Only participants and families who can read and understand English will be recruited.

Teach-Back Questions –

We have gone over a lot of information. I would like to ask you a few questions to make sure I have done a good job explaining the study to you.

1. In your own words, please answer these questions about this study:
2. Why are we doing this study (what are we trying to learn)?
3. What things (including tests and procedures) will you have to do in this study?
3. What are some of the risks of being in this study?
5. What is the benefit of being in this study?
6. How will being in this study be different than usual medical care?
7. How long will you be in this study?
8. Taking part in this study is voluntary. What does that mean to you?
9. If you don't want to be in this study, what are your other choices?
10. What will happen if you chose not to be in this study?
11. What will we do to make sure your information remains confidential?
12. What other questions do you have about this study?

Cognitively Impaired Adults

Capacity to consent will be determined by the participant's personal physician based on cognitive testing or the physician at the care facility. The majority of residents in long term memory care facilities have capacity determined at admission. Capacity is determined by the personal or

facility physician through the use of cognitive testing such as the Mini Mental State Exam (MMSE). The maximum MMSE score is 30 points. A score of 20 to 24 suggests mild dementia, 13 to 20 suggests moderate dementia, and less than 12 indicates severe dementia. The inclusion criteria for this study is moderate to severe dementia with an MMSE score of 0 to 19. While we will be tracking cognition using the MMSE, we will rely on physician or facility recommendation and documentation for participant's ability to consent for themselves. Potential participant's medical record will be checked prior to the consent process to assess if capacity has already been determined. When participants are deemed unable to provide their own consent by their physician or physician at the care facility, family member/legal guardian/power of attorney will be contacted by the research coordinator to obtain surrogate consent. Participant assent will also be obtained when the participant is able to assent. If the participant's physician determines that there has been a change in cognition over the course of the study and the participant is now able to provide their own consent, the consent process will repeated.

Tailored Lighting intervention (TLI). The TLI will provide high circadian stimulation during the day produced by light sources that provide moderate light levels of spectra that are tuned to the sensitivity of the circadian system. For Aim 1, a comparison lighting intervention will also be used. The TLI and comparison lighting interventions will remain in place and will be delivered to participants for 8 weeks each in a counterbalanced manner. Combining spectrum and light level, TLI will allow us to: (a) use a light source that will stimulate the circadian system, and (b) provide the participants with options as to how the light treatment will be delivered. Instead of a light box, the intervention will use table and floor lamps, which are inexpensive and easy to install. TLI quantities will be similar to those previously used by the PI and are based on calculations made using the mathematical model developed by Rea et al., 11 which provides a method for determining the circadian stimulus (CS) for any light source and light level. For the daytime lighting solution, a light source that strongly affects the circadian system (bluish-white light) will be used in new plug-in, floor-standing, or table light fixtures added to the rooms of the selected participants. The new light fixtures will be placed on timers and will be programmed to be automatically turned on at preferred times chosen by the participant (or caregiver). The bluish-white lights will remain on during the day starting at the preferred time (but no later than 9 am) and will switch off automatically. A motion sensor will control all the table and floor light fixtures, so that lights are not on when the room is unoccupied or the patient is asleep (when no effective lights are entering their eyes). Hobo data loggers will be used to monitor lights on/off and lighting patterns of each device, giving us a good reading of the room occupancy/effective light at the eye. A manual override switch will be provided for emergencies and unanticipated contingencies. Neither system will compromise ocular safety nor limit evening activities. It is expected that the existing pre-intervention light fixtures will be used to provide the evening light, since most fixtures use warm color light bulbs; if new fixtures are needed, they will be supplied with a warm color light bulb. An assessment will be made to determine the CS provided by the existing lighting. In addition to the prescribed change in the intervention light source spectrum, the daytime intervention lighting, which uses the bluish-white light, will produce light

levels at least 10 times higher than the yellowish-white light during the evening, which is the same as the one used for the comparison control lighting, ensuring a high circadian light-entrainment contrast between day and night during the active lighting intervention but not during the control lighting intervention. The model predicts that approximately 30 lux at the eye of an incandescent lamp is needed for 30 minutes to reach threshold activation of the circadian system with saturation of circadian response at about 1000 lux. According to the Illuminating Engineering Society Lighting Handbook, light levels required for general illumination in residences should be between 50 to 100 lux on the horizontal plane. We will deliver at least 300-400 lux at the eye of the bluish-white light during the day (CS of 0.4 or greater) and about 50 lux at the eye during the evening hours (CS of less than 0.1) and when the control lighting intervention is used. About 300-400 lux at the eye of the bluish-white light should result in at least 40% melatonin suppression for a 1-hour exposure.166 Although it is not known whether CS for circadian entrainment is the same as CS for acute melatonin suppression, the literature suggests that these responses to light are similar. Older adults are slightly less sensitive to short wavelengths than young observers for any source of light but the differential effect is small. The optical density of a normal older person's crystalline lens is about 0.2 times greater in this region of the spectrum than it is for a young observer (≈ 63%). This age-dependent differential density of the lens at short wavelengths is comparable to having a given participant see the same light source at two distances, one distance 25% greater than the other. The calculations will correct for these changes.