BRIGHT LIGHT TREATMENT AT HOME TO IMPROVE SYMPTOM MANAGEMENT OF FIBROMYALGIA SYNDROME

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NCT03794908

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NIH Behavioral and Social Clinical Trial Protocol Template

Amendments

Date	Version	Section(s)	Changes
03Oct2018	2.0	All	Converted V1 to NIH template
03Dec2018	3.0	1.3	Added Seasonality Questionnaires to SOA @ V2
		2.2 & 10.2	Wording change only: [redacted], clarified that Specific Aim 2 outcomes are exploratory (i.e. not primary or secondary)
		6.2	Added two exclusion criteria: disability and plastic allergy
		6.5.2	Split pre-screening into 2 pieces: online survey and telephone interview
		9.1.8	Updated survey list with Seasonality Q; Pain intensity from 1-item to 3-item; updated Treatment Expectations Q; replaced PROMIS depression w/PHQ; added Sleep-related impairment
12Dec2018	4.0	29.1	Added Complex Medical Symptom Index and Multidimensional Inventory of Subjective Cognitive Impairment
		10-1.1	Updated consent form to state 7 lab visits instead of 8 lab visits, and now include the $10 travel stipend for each lab visit.
24Jan2019	5.0	1.3	Added Apple Watch & follow-up questionnaire to SOA, and updated footnote with FM fatigue survey
		5.1	Added a paragraph indicating that a sub-study is being added to protocol, and to refer to the appendix (section 13)
		9.18	Updated survey list to include PROMIS FM fatigue profile and follow-up questionnaire & health history questionnaire and For Females Questionnaire
		11.4	Listed members of safety monitoring committee
		13	New section: sub-study on using Apple Watch to identify changes in circadian phase across study period
15Apr2019	6.0	13.1	As per IRB request, the aims of the study were updated to indicate data will be collected from the Applewatch and app.
29May2019	7.0	5.1	Clarified enrollment plans for seasonal time changes
		5.2	Deleted stratified by age and replaced with stratified by sex
27 Aug2019	8.0	1.3	Added blood pressure measurement to schedule of activities
		6.2	Updated two exclusion criteria: removed disability and added text to no longer exclude for self-reported hypertension
		6.4	Added blood pressure ≥140/90 as screen failure
		6.5.1	Added recruitment efforts in Detroit and Ypsilanti communities
		9.1.3	Added procedure for blood pressure measurement
28 Oct 2020	9.0	6.5.1	Added Data Direct & EMERSE as recruitment options
		11.2.1.1	Specified data retention plan for data obtained from the EMR (used for recruitment)
17 Feb 2021	10.0	6.2	Modified exclusion criteria 'Previous experience with light treatment' to 'Any light treatment in the past year'

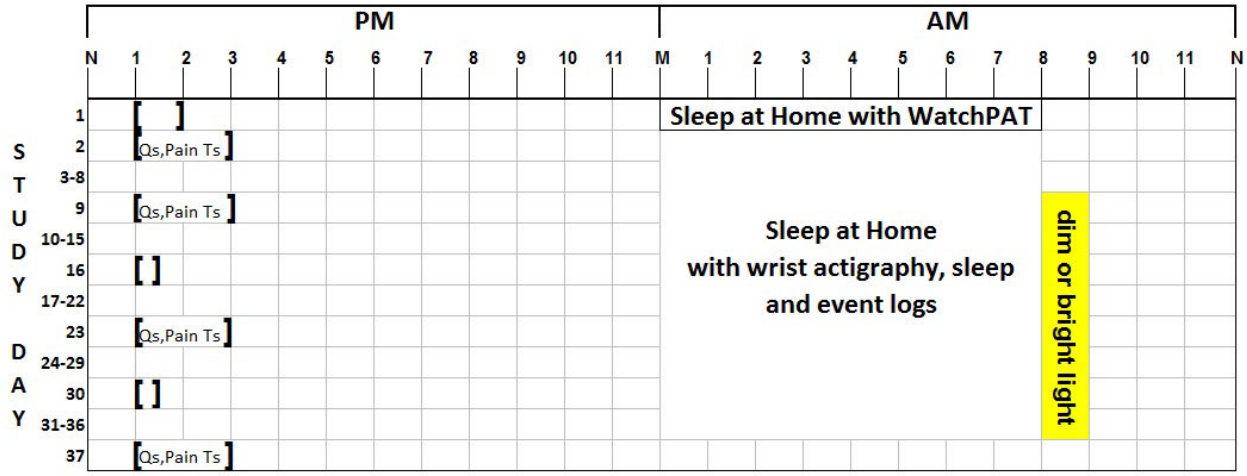
NIH Behavioral and Social Clinical Trial Protocol Template

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Bright Light Treatment At Home To Improve Symptom Management of Fibromyalgia Syndrome
Study Description:	A double-blinded RCT looking at the effect of light therapy on symptoms associated with fibromyalgia syndrome
Primary Objective	Fibromyalgia Impact Questionnaire-Revised
Secondary Objectives	PROMIS Pain Intensity Heat pain sensitivity – threshold Heat pain sensitivity - tolerance
Study Population:	Men and women ages 18 or older with fibromyalgia
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Michigan Medicine Sleep and Circadian Research Laboratory, a renowned facility housed within the Depression Center at the Rachel Upjohn Building
Description of Study Intervention:	The study intervention is daily exposure to bright light therapy. Participants will self-administer the therapy at home for 60 minutes each day for 4 consecutive weeks.
Study Duration:	3 years
Participant Duration:	5 weeks

1.2 SCHEMA



Sample protocol for average 12 to 8am sleeper. [ ] = subject times in lab. Qs = questionnaires. Pain Ts = Pain Sensitivity Tests (heat, ischemia). All visits with Qs and Pain Ts will be scheduled for the same time of day.

1.3 SCHEDULE OF ACTIVITIES

OnCore Study Phase	On Study									On Arm/On Treatment																											Off Study
Study Phase	Practice		Baseline							Treatment																												
Day Number[1]	1	2	3	4	5	6	7	8	9[8]	10	11	12	13	14	15	16	17	18	19	20	21	22	23[9]	24	25	26	27	28	29	30	31	32	33	34	35	36	37[10]
Visit Number	V1	V2							V3							V4							V5							V6							V7
Informed consent	X																																				
Demographics	X																																				
Clinical history	X																																				
Concomitant medications	X																																				
Blood Pressure	X																																				
Anthropometrics	X																																				
Vision testing	X																																				
Receive WatchPat[2]	X																																				
Breathalyzer	X	X							X							X							X							X							X
Urine drug screen (dipstick)[3]	X																																				
Eligibility confirmation[4]	X																																				
Treatment expectation									X																												
Seasonality Questionnaire		X																																			
Complex Medical Symptom Index		X																																			
Multidimensional Inventory of Subjective Cognitive Impairment		x																																			
Questionnaires[5]		X							X														X														X
MEQ[6]		X							X														X														X
BDI-II[7]		X							X							X							X							X							X
Heat pain test		X							X														X														X
Ischemic pain test		X							X														X														X
Accelerometry & Sleep Log		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AppleWatch and app (substudy-optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Daily medication log		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization									X																												

Treatment (active or placebo) in AM @ home & Log										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment fidelity																X							X							X								X
SAFTEE questionnaire																X							X							X								X
Treatment satisfaction																																						X
Follow-up questionnaire																																						X

[1] All outcome assessment visits have a ± 7 day window; [2] Participants receive WatchPat (a study-provided device) on D1 and return it to the lab for data download on D2; [3] Urine drug screen via dipstick is conducted using study-provided supplies; [4] Participants go through an extensive pre-screening process in the days prior to enrollment; [5] Battery includes: FIQR, PROMIS physical function, pain interference, pain intensity, sleep disturbance, anxiety, anger, pain catastrophizing, Fibromyalgia Fatigue, Insomnia Severity Index, Negative Affect, Catastrophizing & depression; [6] Morning-eveningness questionnaire; [7] Beck Depression Inventory; [8] Baseline visit; [9] mid-treatment assessment; [10] post-treatment assessment

2 INTRODUCTION

2.1 STUDY RATIONALE

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain, sleep disturbance, fatigue, and cognitive dysfunction [7,8]. People with FMS report high distress, disability, unemployment, reliance on medical services, and poor quality of life [9, 10]. FMS is also related to medical [11,12] and psychiatric comorbidities [13,14]. Estimates suggest that FMS affects more than 6.5 million Americans [15,16], and represents an important public health problem [17]. Development of effective treatments has been hampered by an incomplete understanding of the etiology and pathophysiology of FMS. Pharmacological agents have been tested, but findings indicate only small effects [18,19] with a high rate of dropout due to adverse side-effects [18]. Non-pharmacological alternatives (cognitive behavioral therapy [CBT], exercise) have also been tested, but with only small to modest effects [20-22]. Thus, an urgent need exists to develop adjunctive approaches to manage FMS symptoms that have optimal treatment effects, minimal side effects, are readily available and affordable, and are easily implemented by patients without extensive support from specialized personnel.

2.2 SPECIFIC AIMS

SPECIFIC AIM 1: To determine the effect of bright versus dim (placebo) morning light treatment on function, pain intensity, and pain sensitivity in individuals with FMS.

> Hypothesis 1: Function, pain intensity and pain sensitivity will improve significantly more in the bright light treatment group than in the dim (placebo) light treatment group, at mid-treatment and at post-treatment.

SPECIFIC AIM 2: To determine the effect of bright vs. dim (placebo) morning light treatment on potential treatment mediators: morningness-eveningness, sleep, mood, pain catastrophizing, analgesic medication use. [All outcomes associated with Specific Aim 2 are exploratory.]

> Hypothesis 2: Morningness will increase, sleep will improve, and mood, pain catastrophizing, and analgesic medication use will reduce significantly more in the bright light treatment group than in the dim (placebo) light treatment group, at mid-treatment and at post-treatment.
>
> Hypothesis 3: Changes in these potential mediators will be associated with changes in function, pain intensity, and pain sensitivity, at mid-treatment and at post-treatment (both groups combined).

EXPLORATORY AIM: To explore whether sleep apnea severity and/or subject sex moderate treatment effects.

2.3 BACKGROUND

2.3.1 Fibromyalgia and the Need for Adjunct Chronic Pain Management Strategies

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain, sleep disturbance, fatigue, and cognitive dysfunction [7, 8]. People with FMS report high distress, disability, unemployment, reliance on medical services, and poor quality of life [9, 10]. FMS is more prevalent

in women than men (9:1 [7]), and is the second most common disorder diagnosed in rheumatology practices [57]. FMS affects ~2-6% of the US population [15, 16], or more than 6.5 million Americans, representing an important public health problem. FMS appears due to amplification in the central processing of pain, with an increase in pain facilitating signals and reduction in pain inhibitory signals [58, 59]. A range of pharmacological agents have been tested for FMS, including antidepressants, antiepileptics, and opioid analgesics, but recent meta-analyses indicate they have small incremental effects over placebo in reducing pain [18, 19], and small to negligible effects on fatigue, sleep, and quality of life [18]. Also, many patients drop out of treatment because of intolerable side effects [18]. Nonpharmacological treatments such as cognitive behavioral therapy (CBT) to teach adaptive coping skills [20] and exercise to increase functional capacity [60] appear effective in reducing pain and distress compared to control conditions, but again with small to modest effects [20-22]. Such psychosocial interventions also require the availability and affordability of specialized personnel for delivery and high patient motivation to maintain substantial changes in behavior. Thus, there is an urgent need to develop adjunctive approaches to manage FMS symptoms that have optimal treatment effects but low side effects, and which are readily available, affordable, practical, and easily implemented by patients without extensive support from specialized personnel.

2.3.2 Later (Delayed) Circadian Timing and More Eveningness is Associated with Greater Pain in FMS.

The central circadian clock is located in the suprachiasmatic nuclei (SCN [61]) in the hypothalamus. Circadian timing in humans can be estimated from the onset of melatonin secretion in dim light (DLMO, [62]), and from the Morningness-Eveningness Questionnaire (MEQ) [63] which correlates with the DLMO (e.g. r=-0.70, [3]). On average, the central circadian clock has a period of ~24.2 h [64, 65] and therefore requires phase advances (shifts earlier) to remain synchronized to the external 24 hour day. Much of this daily shifting is accomplished through light captured by retinal photoreceptors [66-68], which transmit the light signal to the SCN [69]. Light in the evening shifts rhythms later (phase delay, more eveningness) and light in the morning shifts rhythms earlier (phase advance, more morningness) [70, 71]. Thus, morning light is essential for corrective advances, whereas evening light exacerbates the endogenous tendency to drift later (promotes misalignment). Correct circadian timing is essential for optimal sleep, function, mental and physical health [72- 75]. Centrally controlled circadian timing is likely to impact pain sensitivity via: (1) circadian control of melatonin secretion - a potent anti-inflammatory that modulates opioid and GABA receptor function [76-79], and reduces FMS pain [28-30]; and (2) via the paraventricular nucleus, the SCN sends afferents to the amygdala, part of the descending pain system [23, 24, 80]. To date, 3 studies have examined circadian timing (melatonin rhythm) in FMS (all n≤10). Two studies reported later circadian timing in FMS vs. controls [25, 26]. A third found no difference, but patients stabilized their sleep timing before assessment which likely masked any preexisting delays [81]. In a large sample (n=1,548) of FMS patients, those with more eveningness reported worse symptoms, even after controlling for age, sex, and employment [27]. Thus, delayed circadian timing may relate to FMS pain, and advancing circadian timing (more morningness) could reduce pain.

2.3.3 Morning Bright Light May Reduce Pain via Advances in Circadian Timing (More Morningness)

Bright light causes shifts in circadian timing [82, 83]. Phase advances of ~1 h are seen after a week of a 1 hour pulse of bright light after usual wake time [1, 2]. Morning bright light is used to treat winter depression [5, 84- 86], nonseasonal depression [87-89], improves mood in controls [90], and increases sleep efficiency [89, 91]. Phase advances and reductions in depression occur within the first few days of treatment [86, 92, 93]. These effects are attributed mostly to circadian phase

advances, but bright light also has rapid mood enhancing effects (e.g.[4]). Two published studies examined effects of bright light on pain. In one, a light visor was tested in FMS (n=14) [94]. No changes in pain, affect, or sleep were observed, but subjects reported the bright light was more efficacious than no bright light. There were no measures of compliance. Subjects found the visor uncomfortable, and the light source was above the eyes, while people often gaze down. In the other study, 14 days of a 1 h morning bright light treatment from a light box reduced abdominal pain and headache [95]. There are no other studies testing bright light for chronic pain, except for our studies.

2.3.4 Poor Sleep and Negative Affect: Potential Mediators?

Pain degrades sleep quality/quantity [96-100], and sleep quality/quantity influence pain [101]. Sleep disturbance is common in FMS [102], and in FMS patients poor sleep on one night predicts greater pain the next day [103]. Sleep quality in FMS also predicted pain 1 year later [104]. Sleep disturbance also predicts the risk of pain-free women developing FMS >10 years later, even after controlling for psychological well-being (OR 2.05-3.43) [44, 105]. Improving sleep in FMS reduces pain [50, 52, 54-56, 106]. Research also indicates significant relationships between negative affect (NA), such as anxiety, anger and depressive symptoms, and chronic pain intensity (r=0.29 to 0.51) [107-110]. In a sample of FMS patients (n=462), cross-sectional correlations among pain intensity, depressive symptoms, and function ranged from r=0.22 to 0.43 [111]. Anxiety is also related to elevated FMS pain [112, 113]. In treatment studies for FMS, depression predicted poorer outcomes [114], and changes in cognitive and affect factors during therapy for FMS were significantly related to changes in pain and function (r's>0.35) [115]. While sleep and NA impact pain, delayed circadian timing and more eveningness negatively impacts NA [31, 32] and sleep [35, 36]. Even small 1-2 hour circadian delays negatively impact sleep [38, 39], are associated with depression [37, 74, 116-120], and increase NA in controls [33, 34]. Thus, circadian timing may directly, and indirectly (via sleep, NA) influence pain.

3 RISK-BENEFIT ASSESSMENT

3.1 KNOWN RISKS

3.1.1 Distress when sharing personal information

Participants might feel uncomfortable at having to share personal information during the pre-screening process and in response to the questionnaires. Participants may refuse to answer any question with which they are uncomfortable. In the case of eligibility assessment, failure to answer certain questions may preclude enrollment.

3.1.2 Brief moderate intensity acute pain associated with pain sensitivity testing

Participants will experience brief, moderate intensity pain during both the ischemic and heat pain sensitivity assessments. Participants have total control over the duration of their exposure, and thus may end the task by indicating when they have reached their limit. Both pain sensitivity testing paradigms have been used previously in numerous studies involving both healthy and chronic pain patients without incident [126, 145].

3.1.3 Discomfort and disrupted sleep from WatchPat

Participants might experience discomfort from the wearing the WAtchPat, an FDA-approved device for the in-home assessment of obstructive sleep apnea. It is widely used in clinical practice, and the

PI has worn the device herself and found that her sleep was only mildly disturbed by the presence of the equipment. Participants will be told of the potential for mild sleep disruption in return for the benefit of an assessment for sleep apnea. The data from the WatchPat will be downloaded by the study team and reviewed by the Co-I, Dr. Cathy Goldestein (MD). Individuals will be referred to treatment for sleep apnea if their WatchPat evaluation suggests an apnea/hopopnea index (AHI) ≥ 15 which reflects the presence of at least mild obstructive sleep apnea.

3.1.4 Side effects of morning light treatment

While light therapy is a relatively benign therapy, some individuals will report headache, eyestrain, nausea and agitation [86], but often these side effects spontaneously remit [86, 141], and are rarely cause for discontinuation of therapy. Likewise, the circadian phase shifts (~1-2 hours) resulting from active morning light treatment may lead to transient feelings akin to jet lag after crossing 1-2 time zones including transient sleepiness, fatigue and headache. These symptoms are similar to those one might experience on a Monday morning after a late weekend. It is expected that these feelings of "jet lag" will be short lived and the circadian phase shifts likely complete within the first few days of morning light treatment. Side effects to treatment will be assessed (SAFTEE; see Section 9.2, Safety Assessments) the day after session #1, and weekly thereafter.

A rare, but serious side effect is mania in bipolar patients who overexpose themselves to light [86, 141]; individuals with bipolar depression are excluded from this study, and all participants are instructed to limit their light treatment to 1 hour/day. Note that mania in response to morning light treatment is so rare that light treatment has even been clinically tested in bipolar patients and found to be safe [158].

The device used in this study, the Re-timer®, is commercially available and in use by the general population. The device meets international ultraviolet and blue light hazard safety standards. The light intensities used in this study are greater than most indoor light, but much dimmer than sunlight on a bright day.

3.1.5 Worsening of pain, affect and/or sleep overall

The overall risk level of this study is minimal; however, participants may experience a worsening of their FMS or changes in their mood by the mere act of changing their daily routine. To minimize the potential worsening of pain and mood, participants are closely monitored throughout the study. During the baseline phase, if an individual seems to be deteriorating significantly in terms of pain, emotional or sleep condition, the PI and study team will refer them to appropriate treatment, and potentially withdraw them from further participation.

Weekly visits that include a standardized side effects assessment (SAFTEE) will ensure that any exacerbations will be documented and addressed in real-time. Furthermore, participant are told to immediately contact the study team (24-hour availability) if they experience any unexpected or significant deleterious changes in their condition.

3.1.6 Confidentiality and privacy risks

The risk of research data or PHI being accessed without study or clinical care need is very low given the standard safeguards used by Michigan Medicine, and by those on the study team. Access to study records is granted on a need-basis by the lab manager or PI. Interviews, the informed consent process and study visits will be conducted in private spaces within the Sleep and Circadian Research Laboratory by PEERRS and GCP-trained staff.

Information collected during the screening process will only be used to assess eligibility. Select data of non-eligible individuals will be entered into the screening database for assessment of population characteristics and enrollment criteria. These data will be de-identified.

All paper and computer research records will be identified by subject ID number rather than name or other personally identifying information. Paper records are stored in a double-locked environment to which only authorized study team members have access. The link between subject ID and subject name will be kept in a separate password protected database. Consent documents and any other forms with identifying information will be maintained separately from research data files (identified by subject ID only).

3.2 Unknown risks

As with any research study, there are risks that are unknown to the study team. Our standard procedures for safety and adverse events monitoring are such that both ad hoc and systematic queries should allow us to document any heretofore unknown risks.

3.3 Potential Benefits

Participants may experience an improvement in their function, pain, mood and/or sleep because of being in this study. Additionally, all participants will receive a screening for obstructive sleep apnea.

The benefit to society is the potential for a minimal risk adjuvant treatment to manage symptoms associated with FMS. Light therapy has the potential to be a readily available and affordable option that is easily implemented by patients without extensive support from specialized personnel.

3.4 Risk-benefit Assessment

Given that the probability and magnitude of potential harm or discomfort associated with this study is not greater than that ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests, it is not unreasonable that the expected personal and societal benefits outweigh small chance of experiencing an adverse event. The safety of participants will be ensured by the continued monitoring of their mental health and clinical status throughout their time in the study. Furthermore, they will all have access to their usual treatment (unless contraindicated by the protocol) and other treatment-as-usual services to address any study-induced adverse effects or other clinical concerns.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	Timeframe
Primary	
Fibromyalgia Impact Score-Revised	Post-treatment @ 5 weeks
Secondary	

OBJECTIVES	Timeframe
PROMIS Pain Intensity	Post-treatment @ 5 weeks
Heat pain sensitivity – threshold	
Heat pain sensitivity – tolerance	

5 STUDY DESIGN

5.1 OVERALL DESIGN

Study Design

- Double-blinded, placebo-controlled randomized trial
- Parallel groups

Study Arms

- Control Group: placebo (dim light) therapy delivered via the Re-Timer®
- Experimental Group: bright light therapy delivered via the Re-Timer®

An optional sub-study looking at use of an app paired with an Apple Watch to identify changes in sleep and circadian phase across the study period will be offered to eligible participants of the main study. Details are located in the appendix (Section 13).

This study is designed as a 5-week protocol. Potential participants are pre-screened using both an online survey and a telephone interview. Eligibility is confirmed at the first visit. On Day 1, subjects will come to the lab, complete the consent process, confirm eligibility and receive a WatchPAT device to wear as they sleep at home that night. On Day 2, subjects will return to the lab and complete a practice session of questionnaires and pain tests. They will also receive a wrist activity monitor, daily sleep logs and event logs while they sleep ad lib at home, following their usual sleep schedule. On Day 9 (baseline), subjects will complete the questionnaires and pain tests and have their wrist actigraphy and daily logs reviewed. Then they will be randomized to either bright or dim (placebo) Re-timer® and treatment expectations will be assessed. Subjects will begin their light treatment the next morning at home. Then there will be weekly lab visits for wrist activity monitor and Re-timer® data downloads and subjects will receive feedback on their adherence to the light treatment. On Day 23 subjects will also complete questionnaires and pain tests for the mid-treatment assessment, to help us assess treatment duration effects. On Day 37 subjects will also complete a post-treatment assessment and treatment satisfaction rating.

Data collection for the entire study will occur over 18-24 months with a plan to enroll 6 subjects/month except in Nov and Mar when seasonal time changes restrict the enrollment period thus contributing to potentially fewer accruals during those months. For example, an individual could be enrolled the week after a seasonal time change, but we are unlikely to enroll someone whose study duration would span the time change because of the confounding effects on individual sleep habits and circadian rhythms.

5.2 RANDOMIZATION

Participants are will be stratified by sex and randomized to either the experimental study arm (Bright Light Therapy) or the control study arm (Dim Light Therapy, placebo) at Baseline (Day 9).

6 STUDY POPULATION

The population under study includes male and female patients with fibromyalgia who are willing to travel to the lab for multiple visits across the study duration. We plan to enroll 80 people with FMS for a final sample of n=60 (~80% women, 30 per group), assuming ~25% attrition during the 37-day study. We have chosen inclusion/exclusion criteria to permit as many people with FMS as possible to participate safely, while ensuring the treatment and outcome measures are not significantly confounded, to maximize generalizability of findings.

We will assess for FMS at the phone screening using the ACR 2011 Diagnostic criteria ([135, 136]): no other disorder is present to explain the pain, symptoms must have been present ≥3 months, and the pain must meet widespread (widespread pain index, WPI) and symptom severity (SS) criteria (WPI≥7 & SS≥5 or WPI=3-6 & SS ≥9). To characterize the sample, information will also be gathered about the onset of FMS pain, medical interventions to date, exacerbating and ameliorating factors, and medications used currently and in the past.

6.1 INCLUSION CRITERIA

- Adults ≥18 years
- Meet ACR 2011 FMS Diagnostic criteria for fibromyalgia syndrome
- Ability to understand English well enough to participate
- Ability to travel to study
- Current stable therapeutic regimen (e.g. medications, cognitive behavioral therapy, physical therapy, etc.) for at least 30 days prior to enrollment

6.2 EXCLUSION CRITERIA

- Significant chronic disease (including but not limited to uncontrolled diabetes, advanced liver disease, cancer, kidney failure, significant cardiovascular disease*, seizures) that might otherwise confound study outcomes and/or procedures
- Retinal pathology or history of eye surgery
- Use of photosensitizing medications
- Severe hearing or memory problems
- Any light treatment in the past year
- Pending medical leave applications at workplace
- Past or present psychotic, bipolar disorders or acute suicidal ideation (relevant items from the SCID-5-RV, [137])
- Current alcohol or substance abuse problems (SCID, urine drug screen),
- Current pregnancy, breastfeeding, or actively trying to get pregnant**
- Night work or travel outside the eastern time zone within 1 month of the study
- Other research participation

- Frequent number of special events during study period special events (weddings, concerts, exams, etc).
- Current melatonin use – individuals must be off for at least 30 days prior to enrollment and for the duration of the study
- Self-reported allergy to plastics

*This does not include hypertension (unless measurement is greater than or equal to 140/90 mmHg at the screening visit). If excluded for this reason, participants will be referred to their primary care physician.

**Bright light therapy is not contraindicated for pregnant or breastfeeding individuals, and in fact, has been used to treat peri/post-partum depression in these women; however, pregnancy and breastfeeding can independently (of FM) impact sleep and mood thereby confounding many study measures including pain report and pain sensitivity.

6.3 LIFESTYLE CONSIDERATIONS

6.3.1 Alcohol Use

Participants are asked to refrain from alcohol consumption for 24 hours prior to their study visits. Any participant breathalyzing positive will be:

- Rescheduled to start the study anew if positive test occurs at Visit 3 (between days 1-9)- (prior to initiation of light treatment).
- Withdrawn from the study if positive test occurs at any Visit 4-7 (after day 16) – (after initiation of light treatment).

6.3.2 Sleep-wake patterns

Additionally, participants are asked to maintain their usual sleep-wake patterns as documented during the initial week of activity monitoring (approximately Days 2-9), and to refrain from napping in the 4 hours immediately after light therapy, which counteracts the effects of the light treatment.

6.3.3 Medication and Concomitant therapies

Participants are asked to maintain their current (from time of enrollment) treatments including all medications and non-pharmacological strategies throughout their participation in the study.

6.3.4 Naps

Participants are asked not nap within 4 hours of completing their treatment.

6.4 SCREEN FAILURES

Participants will be considered a screen failure if:

- Urine drug screen at baseline indicates current or recent drug use not accounted for by their self-reported medications
- Their blood pressure exceeds 140/90 mmHg upon measurement
- Study team learns of any new exclusion criterion that arises during the first two study visits

6.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The eligibility criteria were designed to include as many people with FMS as possible, meaning that contraindications to the proposed treatments or inability to fulfill study requirements are the two primary reasons why someone would not be able to participate. Our recruitment avenues are designed to reach individuals with FMS living within routine driving distance of the Sleep and Circadian Research Lab.

6.5.1 Recruitment

Community/internet advertisements: Our online recruitment strategies will include craigslist.com, Facebook, and umclinicalresearch.org, the University of Michigan Research Registry. We will also place IRB approved fliers on The University of Michigan Campus and surrounding Ann Arbor, Detroit, and Ypsilanti communities. Subjects may also be recruited via word of mouth as a result of community/internet advertisements.

Previous research participants: IRB fliers will also be sent to participants who have previously participated in Dr. David Williams' (co-investigator on grant) fibromyalgia research studies and have indicated they are willing to be contacted about future research studies.

Support Groups and the Fibromyalgia Seminar: IRB-approved fliers will also be sent to local support groups and be available at the bi-weekly Fibromyalgia Seminar (https://medicine.umich.edu/dept/cpfrc/events/fibromyalgia-seminars) held at Domino's Farms (across the street from the Sleep and Circadian Research Lab). If research staff are available, they will attend select seminars to talk to potential participants in person.

6.5.2 Data Direct/EMERSE

We will use two of the online self-serve tools provided by the University of Michigan Data Office for Clinical and Translational Research to access clinical data as a means of identifying potential participants with fibromyalgia and/or chronic pain. Once identified, these individuals will be approached initially via an introductory letter, email, or text inviting them to contact the study team for information.

6.5.3 Pre-screening

Prospective participants will participate in series of pre-screening surveys: first they complete an online survey (REDCap) to determine basic suitability (e.g. meeting criteria for FMS, desired schedule, etc.) for the FibroLight study followed by a telephone interview during which screening questions for psychiatric disorders, and other potentially sensitive exclusion criteria are discussed.

The PI and/or lab manager will review the pre-screening (both REDCap & phone interview) information to confirm preliminary eligibility. Once deemed eligible at this stage, prospective participants will be scheduled for the initial study visit at which additional screening procedures will occur.

6.5.4 Accrual

We intend to enroll 80 people with FMS with the intent of achieving a final sample size of n=60. With an accrual period of approximately 18 months we will strive for 6 new participants each month.

6.5.5 Retention

Our pilot data suggest that this is a motivated population who respond well to frequent contact and support. We use daily texts as a means of promoting treatment adherence, but also as a way of maintaining contact throughout the study period.

Weekly visits allow for more personal contact between the study team and participant. Individual sleep and treatment data are shared with participants to help promote adherence and retention.

6.5.6 Participant incentives

Participants will be paid a total of $670 for study their participation. This payment includes incentive for participation and completion of study procedures in addition to covering costs associated with traveling to the 7 laboratory visits. The schedule of payments is as follows:

- $50 for completing the 1 night wearing the WatchPAT device and returning it to the research staff
- $100 for completing each week of the study (up to $500)
- $50 bonus for completing the study (at Visit 7)
- $10 travel stipend for each visit (up to $70)

Participants will be paid only for the parts of the study they complete.

7 STUDY INTERVENTION(S)

7.1 STUDY INTERVENTION DELIVERY

Both the study intervention and the placebo intervention are self-administered by the participants in their own homes. Participants will be randomized and receive their Re-Timer® at study visit 3 (approximately Day 9), and will start their 1-hour daily morning light treatment (regardless of study arm) the next morning within a few minutes of their assigned wake up time, determined as their average wake time from the baseline week of activity monitoring, or up to 1 hour earlier to accommodate their morning schedule (work, child care) [1, 2]. Participants will be provided with an alarm set to the start of the light treatment, and will also use their own alarm as a backup. A light log to note light on/off times and any interruptions to light treatment will be provided. Participants are also given a list of written reminders to charge the Re-timer®, only turn it on during the scheduled time, and not to nap in the 4 hour window after the light treatment. Subjects will be instructed to maintain their baseline sleep duration.

7.1.1 Control (placebo) intervention

- Dim-light therapy via the Re-Timer®
- Daily use
- For the first hour after waking
    - Can wake up 1 hour earlier than usual for therapy
- 60 minutes/day
- Fill out treatment log

7.1.2 Study intervention

- Bright light therapy via the Re-Timer®
- Daily use

- For the first hour after waking
    - Can wake up 1 hour earlier than usual for therapy
- 60 minutes/day
- Fill out treatment log

7.1.3 Re-Timer® Storage

The Re-Timer® glasses will be stored in the locked PI office when distributed. Participants will be asked to store the device in its provided storage case and away from extreme cold or heat while it is in their possession. Each pair will be wiped clean with alcohol swabs between participants.

7.2 FIDELITY

- Participants will complete a daily treatment log indicating times of use and any interruptions or alterations to the treatment session
- Use time of the Re-Timer® (both arms) and activity monitor data will be downloaded and reviewed weekly at study visits 4, 5, 6 and 7. Data will be reviewed by PI or lab manager (unblinded) and shared with the participant.
- Participants will receive daily text prompts asking Yes/No question completion of light therapy.
- Re-Timers® will be custom fitted to each participant to ensure proper placement and delivery of light therapy.

7.3 MEASURES TO MINIMIZE BIAS

7.3.1 Randomization

Participants will be stratified by age (18-29 vs. 30 and older) and randomized in a 1:1 ratio to one of the two study arms.

7.3.2 Blinding

The outcome assessors and participants will be blinded to condition. The PI and lab manager will remain unblinded, and perform the fidelity and side effects assessments (SAFTEE). Participants are asked and reminded throughout the study to only speak about their light treatment with either the PI or lab manager.

7.4 CONCOMITANT THERAPY

Patients are allowed to continue their usual care, including medications and non-pharmaceutical therapies throughout the study. All concomitant treatments must be stable for at least 30 days prior to enrollment, *and* be maintained throughout the study period. **Allowable therapies** include, but are **not limited to**:

- Prescribed hypnotics, over-the-counter sleep aids, anti-epileptics, antidepressants, opioid analgesics, and muscle relaxants; melatonin is NOT allowed
- Psychological interventions (e.g. cognitive behavioral therapy, counseling, etc.) are permitted only if treatment started at least 30 days prior to enrollment *and* will continue throughout the study duration

- Physical therapy and exercise, etc. are permitted only if started at least 30 days prior to enrollment *and* will continue throughout the study duration

7.5 CONTRAINDICATED THERAPY

Current use of melatonin is an exclusion criterion. Participants must be melatonin-free for at least 30 days prior to enrollment.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 DISCONTINUATION OF STUDY INTERVENTION

Use of the Re-Timer® will be stopped in the event of any of:

- Hospitalization of the patient due to a significant decline in health
- Any new diagnosis that would be considered part of the original exclusion criteria for this study
- At the request of the patient to discontinue therapy
- At discretion of Dr. Goldstein after review of side effects/SAFTEE data and speaking to participant

Reasons for discontinuation will be documented, and all outcome assessments will proceed as scheduled, if possible.

8.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Reasons why a subject might be withdrawn from the study:

- Subject request
- Subjects who begin treatment for sleep apnea during the study period
- Positive breathalyzer test at the study visit 4 or later (approximately Day 16 onward)
- Start of new treatment or therapy during study period
- Significant study intervention non-compliance, i.e. inability or unwillingness to complete study intervention or outcome assessments
- Any clinical event or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) any time after the first two study visits (approximately Day 3 onward)
- Lost-to-follow up

If possible, reasons for withdrawal will be documented. Data from dropouts or withdraws will be kept until the end of the study, including study analyses. Subjects who are excluded from the study during the screening phase will be informed of their reason for exclusion in general terms only, in order to prevent bias and enrollment of other subjects who do not meet specific criteria. Due to heavy recruitment via word of mouth, informing subjects of their specific reason for exclusion could impact validity of this research.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 ASSESSMENTS

9.1.1 Demographics

Participants will complete a basic demographics survey

9.1.2 Clinical history & Concomitant Medications

Participants will fill out medical history and concomitant medication forms to document co-morbidities, clinical history related to fibromyalgia, and to evaluate for any contraindicated medications

9.1.3 Blood Pressure

Participants will have their blood pressure measured as part of the screening procedures. Upon an initial reading of 140/90 mmHg or higher, participants will be asked to lay down for 10 minutes and then re-evaluated. If participant blood pressure remains above this level, they will be dropped from the study and advised to contact their primary care physician as soon as possible.

9.1.4 Height & Weight

Participant height and weight will be measured in the clinic.

9.1.5 Vision Testing

Participants will undergo a brief vision test that involves standing a set distance from a standard Snellen-type eye chart as well as a screening for color-blindness using a common color vision test that involves looking at a circular pattern comprised of many dots of various colors, brightness and sizes.

9.1.6 WatchPat

The WatchPAT device consists of a wrist monitor and finger probe. Subjects will wear the WatchPAT device for 1 night of sleep and return it to the lab the next day. The WatchPAT device is FDA approved to assess the severity of any sleep disordered breathing, which will be used in the study's data analytical approach. Dr. Goldstein (co-investigator) will inform the subjects of the results and refer them for treatment if necessary (apnea-hypopnea index ≥15). Subjects who begin treatment prior to the end of the study will be dropped, however, due to delays in seeing a physician and receiving a CPAP machine (≥ 4 weeks), this is unlikely to affect many subjects.

9.1.7 Wrist Activity Monitor and Sleep & Medication Log

After the WatchPAT night, subjects will be required to wear a wrist activity monitor, the Actiwatch Spectrum, which looks like a wrist watch, for the entirety of the study. This will record movement and sleep patterns. After the light treatment starts (see below), study staff will download data from the wrist monitor during the weekly appointments to confirm subjects are waking at the assigned light treatment time and not napping in the 4 hours after the light treatment.

In conjunction with the activity monitor, participants will be asked to fill out a daily sleep log that queries in-bed time, other factors related the previous night's sleep, and any medications used during the previous 24 hours.

9.1.8 Treatment expectation

Participants will complete a brief survey about their expectation for treatment

9.1.9 Surveys

Participants will be asked to complete questionnaires that assess pain, function, mood and sleep:

- Fibromyalgia Impact Questionnaire, Revised (FIQ-R)
- PROMIS Fatigue-Fibromyalgia Profile
- PROMIS Physical Function (Item Bank v2.0 SF 8b)
- PROMIS Pain Interference (Item Bank v1.0 SF 8a)
- PROMIS Pain Intensity – 3-item, numeric rating scale
- Morningness-Eveningness Questionnaire (MEQ)
- PROMIS Sleep Disturbance (Item Bank v1.0 SF 8b)
- PROMIS Sleep-related Impairment (Item Bank v1.0 SF 8a)
- Insomnia Severity Index (ISI)
- Patient Health Questionnaire (PHQ)
- PROMIS Anxiety (Item Bank v1.0 SF 8a)
- PROMIS Anger (Item Bank v1.1 SF 5a)
- Pain Catastrophizing Scale
- SAFTEE questionnaire to assess treatment side effects
- Beck Depression Inventory - II
- Seasonality Questionnaire
- Complex Medical Symptom Index
- Multidimensional Inventory of Subjective Cognitive Impairment
- Treatment expectation
- Treatment satisfaction
- Follow-up Questionnaire on study experience
- Health history questionnaire
- For Females Only Questionnaire

9.1.10 Pain sensitivity testing

Participants will undergo two different quantitative sensory testing paradigms to evaluate pain sensitivity.

- *Heat Pain Test*: Pain threshold and tolerance will be assessed during a heat pain task using a Medoc TSAII NeuroSensory Analyzer. We will use an ascending method of limits protocol [126]. Four trials each will be conducted for threshold and tolerance, with each trial conducted sequentially at 1 of 4 different non-overlapping sites on the non-dominant ventral forearm. An interval of 30 secs between successive stimuli will be used. For pain threshold trials, the probe will start at an adaptation temperature of 32°C, with temperature increasing at a ramp rate of 0.5°C/sec until the subject indicates that the stimulus feels "painful". For each tolerance trial, the probe will start at an adaptation temperature of 40°C, with temperature increasing at a ramp rate of 0.5°C/sec until the subject indicates tolerance. Means of the 4 trials will be derived. Subjects can stop at any time, and the Medoc device has a 52°C automatic cutoff to prevent injury.
- *Ischemic Pain Test*: Pain threshold and tolerance will be assessed during an ischemic pain task [144, 145]. Subjects will engage in 2 minutes of dominant forearm muscle exercise using a hand dynamometer at 50% of max grip strength (determined earlier), and then raise their dominant forearm overhead for 15 secs. A blood pressure (BP) cuff will be inflated on the dominant bicep to 200 mmHg SBP, and will remain inflated until tolerance is reached (max 480 secs). Threshold is time elapsed from task onset to when sensation is first

described as painful. Tolerance is time elapsed from task onset to subjects' desire to terminate the task.

9.2 SAFETY ASSESSMENTS

9.2.1 SCID Screening & Beck Depression Index for suicidality

At screening, all potential participants will be assessed for suicidal thoughts and behaviors with the SCID, and will be excluded. Weekly administration of the Beck Depression Inventory (BDI-II) will be used to assess suicidality throughout the trial; participants with significant suicidality will be excluded.

For any potential subject in whom we detect concerning suicidal thoughts/behaviors (defined according to the BDI-II or SCID), the PI will be notified and a risk assessment of the patient will be conducted, including the identification of risk factors (e.g., substance abuse, active psychosis, hopelessness), mitigating factors (e.g., social support, degree of control over suicidal thoughts, religious beliefs against suicide) and the level of suicidal ideation/behavior (documented in the SCID). An intervention plan will be formulated, taking into account the level of risk and treatment resources available to the potential participant. This could include monitoring by family, contact with a treating clinician (with the patient's permission), follow-up phone calls, or urgent evaluation in the psychiatric emergency room. For individuals without a treating clinician, referrals to available community resources will be made.

9.2.2 SAFTEE for treatment side effects

Either the PI or the lab manager (unblinded) will administer the SAFTEE (Systematic Assessment for Treatment Emergent Events) the first morning after light treatment, and thereafter at weekly study visits.

If a participant reports a significant worsening of symptoms as indicated by a score of 4 ("bothered quite a bit") or 5 ("bothered extremely"), or endorses any of the following trigger points, the study team will contact Dr. Goldstein as soon as possible who will then contact the participant for additional information, and make the ultimate decision to retain or withdraw the participant from the study, and/or refer them to appropriate treatment.

9.2.2.1 Trigger Point Items from the SAFTEE

- Loss of consciousness (2 or more)
- Seizures (2 or more)
- Difficulty swallowing (3 or more)
- Chest pain (2 or more)
- Shortness of breath (2 or more)
- Rapid heart rate (2 or more)
- Irregular heart beat (2 or more)

9.2.3 Changes in Clinical Status

Symptom surveys will be scored in relative real-time allowing for ongoing monitoring of symptoms and overall clinical status. Participants showing a 25% worsening of a symptom (e.g. mood state) will be flagged and presented to the PI for review. Participants showing a 50% worsening in a symptom will be flagged and presented to co-I, Dr. Goldstein for review and possible referral to

treatment. Of note, in the PI's previous studies, it is very rare that participants experience a 50% worsening.

9.3 ADVERSE EVENTS

The Data Safety and Monitoring Plan is the definitive source for this project's strategy for upholding data integrity and participant safety. Briefly, this project is considered to be "minimal risk" because the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests. Safety of subjects will be ensured by the continued monitoring of their mental health and medical status. Subjects will all have access to treatment-as-usual services to address any study-induced adverse effects or other clinical concerns.

NINR has requested an Independent Monitoring Committee consisting of an M.D. physician (board-certified in sleep medicine) and familiar with sleep and circadian treatments, a Ph.D. biostatistician with extensive experience in clinical trials, and a Ph.D. experienced clinical researcher and psychologist also be formed to review the study.

The PIs will provide quarterly updates to the Committee on study performance including subject accrual and status of subjects. For any non-serious adverse events (protocol deviations, non-compliance, and other events that meet reporting criteria, see below), the Study Monitors and IRB will be notified on a quarterly basis and provided with event information and steps taken to resolve the situation. The efforts of the Committee will supplement the ongoing data inspections conducted by the PIs, who will inspect the data weekly and review it with the research team at weekly meetings.

9.3.1 Adverse Events

Serious adverse events will be reported per occurrence to the Study Monitors, IRB, and NINR, within 3 business days or sooner. We agree to abide by the resulting directives of the Study Monitors, IRB, and NINR, and if requested the study will be suspended until the Study Monitors, IRB and NINR resolve the concerns to their satisfaction. The PIs will be responsible for rectifying any study problems and notifying all parties as to the resolution of the situation.

9.3.1.1 Adverse events definition

Any unfavorable or unintended symptom, sign, or disease associated with a medical treatment or procedure that may or may not be related to the treatment or procedure. Adverse events can be related to the treatment or to the disorder being treated (e.g. pain exacerbation), as well as to a concurrent disorder or treatment (e.g. MDD or its treatment), or they could be entirely unrelated to any of these (e.g., motor vehicle accident).

9.3.1.2 Serious adverse event definition

In this study, we will use the FDA definition of serious adverse events (SAE, e.g., death, hospitalization, emergency room visits, suicide plans or attempts). Adverse events and SAE will be systematically assessed at each lab visit. Again, any SAE, whether or not related to study intervention, will be reported to the Study Monitors, IRB, and NINR within 3 business days or sooner. In addition, the PIs will prepare an annual report on data collection and occurrence of any adverse events for review by the Study Monitors, IRB, and NINR. Any initial SAE report will be followed by submission of a completed resolution report to the Study Monitors, IRB, and NINR.

In the event that a patient withdraws from the study or the investigators decide to discontinue a patient due to SAE, the patient will be monitored by the PIs via ongoing status assessment until:

- A resolution is reached (i.e., the problem has resolved or stabilized with no further changes expected)
- The SAE is determined to be clearly unrelated to the study intervention, or
- The SAE results in death

Should a large number of unexpected SAEs occur, we will modify or terminate the trial if the events are severe. We will also monitor safety alerts, defined as events that are relevant to the study populations and pose safety risks to study subjects. Examples of safety alerts would include a sudden increase in pain symptoms, change in the type of pain experienced, a clinically significant increase in patient depression or anxiety, or certain responses on the SAFTEE. Both SAEs and safety alerts will be tracked using a standardized form recording the date of the event, type of event, attribution of the event (e.g., judgment regarding whether it was intervention related), whether the event was resolved or controlled, and the resolution date.

9.3.1.3 Adverse events grading scale

(0) No adverse event or within normal limits
(1) Mild adverse event – did not require treatment
(2) Moderate adverse event – resolved with treatment
(3) Severe adverse event – resulted in inability to carry on normal activities and required professional medical attention
(4) Life threatening or disabling adverse event
(5) Fatal adverse event

9.3.1.4 Adverse event attribution scale

- Definite: The adverse event is clearly related to the investigational agent(s)
- Probable: The adverse event is likely related to the investigational agent(s)
- Possible: The adverse event may be related to the investigational agent(s)
- Unlikely: The adverse event is doubtfully related to investigational agent(s)
- Unrelated: The adverse event is clearly not related to investigational agents(s)

9.4 UNANTICIPATED PROBLEMS

Unanticipated problems, in general, will include any incident, experience, or outcome that meets ALL of the following 3 criteria:

- It is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document, or other research materials; and (b) the characteristics of the subject population being studied.
- It is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- It suggests that the research places subjects or others at a risk of unknown harm or addition/increased frequency of harms (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size & Power Analysis

We will enroll 80 adults (≥18 years) with FMS. We conservatively estimate ~25% attrition (final n=60) which includes dropouts (failed drug tests not accounted for by medications, illness, job offers, family crises), and noncompliance (<25% of morning light [121]), based on light treatment trials (4 week bright light treatment 6% attrition [121], 12 week bright light treatment 19% attrition [159]). Subjects who obtain only 25% of the prescribed light (15 min/day) should still obtain some benefit, as only 12-20 mins of morning light can be effective [4, 160, 161]. Our primary outcome measure is the FIQR. If we assume a 22% decrease in FIQR with the bright Re-timer® as per our pilot study, a 5% decrease with dim light (control arm), and baseline mean and SD FIQR from a large FMS sample (mean 62.4, SD 14.1 [162]), then using a two-sample t-test for differences at the final time point with 30 subjects/group, we will have 81.7% power (α=0.05). This is adequate for a pilot study to estimate effect sizes for a future larger trial.

10.2 Specific Aim 1

To determine whether baseline to mid- to post-treatment changes in FIQR (primary outcome measure), PROMIS Physical Function, Pain Interference, Pain Intensity, heat pain threshold and tolerance, ischemia pain threshold and tolerance are greater in bright vs. dim light conditions.

First, balance in randomization (baseline FIQR, age, sex, race/ethnicity, season) between the two arms will be examined using descriptive measures (mean, SD for continuous variables; percentages for categorical variables) and differences tested with t-tests and Chi-square tests. If imbalances occur, we will use propensity score based corrections in regressions.

Second, we will use linear mixed effects regression models with subject specific intercepts and slopes to account for variability in average levels at baseline and changes over time. Light Condition (bright vs. dim light) x Time (baseline, mid-treatment, post-treatment with baseline as reference time) interactions will test whether changes in outcomes depend on treatment. These analyses will be intent-to-treat. We will also focus on the time course of outcome changes: modeling quadratic terms to determine: (1) whether both baseline to mid- and/or mid- to post-treatment changes in variables are significant, (2) the relative degree of change in each treatment interval indexed by appropriate contrasts of regression coefficients. These analyses will determine when significant outcome changes occur during treatment.

10.3 Specific Aim 2

To determine whether baseline to mid- to post-treatment changes in morningness-eveningness, sleep, NA, pain catastrophizing, and analgesic medication use are greater in the bright vs. dim light conditions.

We will examine the time course of changes in these variables using the analyses described for Aim 1. We will also test the degree to which baseline to mid- to post-treatment changes in these variables are associated with baseline to mid- to post-treatment changes in function, pain intensity and pain sensitivity with a regression. These analyses will identify potential treatment mediators to fully test in a future larger study.

10.4 EXPLORATORY AIM

To explore whether obstructive sleep apnea severity and/or subject sex moderate treatment effects.

The analyses described above for Aim 1 will be rerun to test Light Condition x OSA (normal to mild AHI<15 vs. moderate to severe AHI≥15) x Time for outcomes. We anticipate recruiting ≥20% males (see Human Subjects), and will examine possible sex differences in response to bright light treatment by testing Light Condition x Sex x Time interactions similar to analyses used in Aim 1.

[Note: Descriptions of planned analyses are illustrative. Actual analyses may differ from those described here.]

11 SUPPORTING INFORMATION & OPERATIONAL CONSIDERATIONS

11.1 INFORMED CONSENT PROCESS

The recruitment and informed consent process is designed to provide information about study participation multiple times and in different format. Individuals expressing interest will be provided with a verbal explanation of study procedures and the risk-benefit profile or be able to read basic study information on the umhealthresearch.org website. From there, individuals are provided with an IRB-approved copy of the consent document to review at their leisure.

The informed consent dialog will take place at the initial study visit (Day 1). It will consist of a dialog between the study team and the potential participant. The discussion will focus on the voluntary nature of research, expectations for participation, a discussion of the risks and benefits associated with being in the study, and include time for questions. Individuals will have an opportunity to see the study materials (e.g. activity monitor, WatchPat, etc.) prior to signing the consent document.

The physical location for the consent dialog will be private research space within the Sleep and Circadian Research Laboratory.

11.2 DATA RETENTION

Research data will be retained for both study record-keeping purposes and for future unspecified research use according to IRBMED guidelines for federally-funded projects. All paper and computer records will be identified by the subject ID code rather than name or other identifier. Consent documents and other forms with identifiers will be stored in a separate double-locked setting.

Data from participants who withdraw from the study will be retained in the study database.

11.2.1 Study-record keeping

Hard copies of the data will be maintained for 7 years after which they will be destroyed. Files will be stored in double-locked environment and access-limited under the purview of the PI. All research records will be identified by subject ID; pre-screening records will be scrubbed of identifiers and date shifted to preserve confidentiality.

Study database records will be identified by subject ID, and the link between identifiers and subject ID will be maintained by the PI and lab manager. **The link will be destroyed after submission of the NIH final report or publication of the primary outcomes manuscript, whichever is later**.

11.2.1.1 Protected Health Information (PHI)

We will abstract basic eligibility and contact information from the Michigan Medicine electronic medical records system, MiChart. These data will be stored separately from study data, and will retained with identifiers throughout the duration of the study. Once the study concludes, the identifiers will be destroyed.

11.2.2 Data for future unspecified research use

De-identified study databases will be locked and archived for future unspecified research. These data will be used for analyses related to the main study, new analyses, and in grant proposals for new research.

- The data will be stored on Michigan Medicine servers in REDCap and/or statistical datasets that are stripped of identifiers
- Access to data will be at the discretion of the PI
- Any data shared with collaborators will shared using secure data transfer methods (e.g. MiShare)

11.3 Quality Assurance and Quality Control

11.3.1 Quality Control of Data Collection

The study will use the Michigan Medicine instance of REDCap, a web-based electronic data capture system that is secure and HIPAA-compliant. Access is restricted to individuals with a Michigan Medicine Level 2 password, and can then be further restricted by role within the study database. Data validation and data quality rules will be implemented to minimize errors in data capture, entry and analysis.

REDCap provides automated export procedures to common statistical packages in which automated syntax can be used to score questionnaire responses thereby reducing errors associated with hand calculations or Excel formulas. It is standard procedure in the Burgess Lab that all data manipulations are double-checked and initialed by a second study team member.

Weekly team meetings in which data are reviewed will further serve as a quality assurance measure. Data reviewed will include information about mental and physical health symptoms of participants, and various psychological characteristics gleaned from the questionnaire battery and participant report.

11.4 Safety Monitoring Committee Members

Todd Arnedt, PhD	James Abelson, MD, PhD	Philip Boonstra, PhD
Associate Professor of Psychiatry	Professor of Psychiatry	Research Asst. Professor of Biostatistics, School of Public Health

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12 REFERENCES

1. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: A placebo-controlled trial. Arch Gen Psychiatry. 1998;55:883-9.

2. Burgess HJ, Fogg LF, Young MA, Eastman CI. Bright light therapy for winter depression - Is phase advancing beneficial? Chronobiol Int. 2004;21:759-75.

3. Kantermann T, Sung H, Burgess HJ. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the dim light melatonin onset. J Biol Rhythms. 2015;30(5):449-53.

4. Goel N, Etwaroo GR. Bright light, negative air ions and auditory stimuli produce rapid mood changes in
a student population: a placebo-controlled study. Psychol Med. 2006;36(9):1253-63.

5. Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, Blood ML, Jackson JML. Morning vs evening light treatment of patients with winter depression. Arch Gen Psychiatry. 1998;55:890-6.

6. Holt C, Heimberg R. The Reaction to Treatment Questionnaire: Measuring treatment credibility and outcome expectancies. Behav Ther. 1990;13:213-4.

7. Landis CA. Sleep, pain, fibromyalgia, and chronic fatigue syndrome. Handb Clin Neurol. 2011;98:613-37.

8. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62(5):600-10.

9. Winkelmann A, Perrot S, Schaefer C, Ryan K, Chandran A, Sadosky A, Zlateva G. Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study. Appl Health Econ Health Policy. 2011;9(2):125-36.

10. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, Martin SA. Patient perspectives on the impact of fibromyalgia. Patient Educ Couns. 2008;73(1):114-20.

11. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet. 2007;369(9565):946-55.

12. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states--maybe it is all in their head. Best Pract Res Clin Rheumatol. 2011;25(2):141-54.

13. Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. Acta Biomed. 2007;78(2):88-95.

14. Brummett CM, Clauw DJ. Fibromyalgia: a primer for the anesthesia community. Curr Opin Anaesthesiol. 2011;24(5):532-9.

15. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33(2):160-72.

16. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, Barton DL, St Sauver J. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res. 2013;65(5):786-92.

17. Schaefer C, Mann R, Masters ET, Cappelleri JC, Daniel SR, Zlateva G, McElroy HJ, Chandran AB, Adams EH, Assaf AR, McNett M, Mease P, Silverman S, Staud R. The comparative burden of chronic widespread pain and fibromyalgia in the United States. Pain Pract. 2016;16(5):565-79.

18. Hauser W, Wolfe F, Tolle T, Uceyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. CNS Drugs. 2012;26(4):297-307.

19. Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. Cochrane Database Syst Rev. 2013;10:CD010782.

20. Bernardy K, Fuber N, Kollner V, Hauser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2010;37(10):1991-2005.

21. Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: a meta-analysis. Pain. 2010;151(2):280-95.

22. Busch AJ, Webber SC, Richards RS, Bidonde J, Schachter CL, Schafer LA, Danyliw A, Sawant A, Dal Bello-Haas V, Rader T, Overend TJ. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev. 2013;12:CD010884.

23. Peng ZC, Bentivoglio M. The thalamic paraventricular nucleus relays information from the suprachiasmatic nucleus to the amygdala: a combined anterograde and retrograde tracing study in the rat at the light and electron microscopic levels. J Neurocytol. 2004;33(1):101-16.

24. Moga MM, Weis RP, Moore RY. Efferent projections of the paraventricular thalamic nucleus in the rat. J Comp Neurol. 1995;359(2):221-38.

25. Wikner J, Hirsch U, Wetterberg L, Rojdmark S. Fibromyalgia--a syndrome associated with decreased nocturnal melatonin secretion. Clin Endocrinol (Oxf). 1998;49(2):179-83.

26. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, Haus E, Demitrack MA, Crofford L. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999;26(12):2675-80.

27. Kantermann T, Theadom A, Roenneberg T, Cropley M. Fibromyalgia syndrome and chronotype: late chronotypes are more affected. J Biol Rhythms. 2012;27(2):176-9.

28. Reiter RJ, Acuna-Castroviejo D, Tan DX. Melatonin therapy in fibromyalgia. Curr Pain Headache Rep. 2007;11(5):339-42.
29. Hussain SA, Al K, II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. J Pineal Res. 2011;50(3):267-71.

30. de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, Xavier F, de Souza IC, Deitos A, Torres IL, Caumo W. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014;15:40.

31. Merikanto I, Lahti T, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Salomaa V, Partonen T. Evening types are prone to depression. Chronobiol Int. 2013;30(5):719-25.

32. Toomey R, Panizzon MS, Kremen WS, Franz CE, Lyons MJ. A twin-study of genetic contributions to morningness-eveningness and depression. Chronobiol Int. 2015;32(3):303-9.
33. Yang CM, Spielman AJ, D'Ambrosio P, Serizawa S, Nunes J, Birnbaum J. A single dose of melatonin prevents the phase delay associated with a delayed weekend sleep pattern. Sleep. 2001;24:272-81.

34. Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, Minors DS, Totterdell P, Waterhouse JM. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry. 1997;54:145-52.

35. Taillard J, Philip P, Bioulac B. Morningness/eveningness and the need for sleep. J Sleep Res. 1999;8:291-5.

36. Vitale JA, Roveda E, Montaruli A, Galasso L, Weydahl A, Caumo A, Carandente F. Chronotype influences activity circadian rhythm and sleep: differences in sleep quality between weekdays and weekend. bChronobiol Int. 2015;32(3):405-15.

37. Levandovski R, Dantas G, Fernandes LC, Caumo W, Torres I, Roenneberg T, Hidalgo MP, Allebrandt KV. Depression scores associate with chronotype and social jetlag in a rural population. Chronobiol Int. 2011;28(9):771-8.

38. Harrison Y. The impact of daylight saving time on sleep and related behaviours. Sleep Med Rev. 2013;17(4):285-92.

39. Taylor A, Wright HR, Lack LC. Sleeping-in on the weekend delays circadian phase and increases sleepiness the following week. Sleep Biol Rhythms. 2008;6:172-9.

40. Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. Pain. 2006;124(3):321-9.
41. Salovey P, Birnbaum D. Influence of mood on health-relevant cognitions. J Pers Soc Psychol. 1989;57(3):539-51.

42. Tang NK, Salkovskis PM, Hodges A, Wright KJ, Hanna M, Hester J. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. Pain. 2008;138(2):392-401.

43. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. Neuroimage. 2009;47(3):987-94.

44. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. Arthritis Rheum. 2012;64(1):281-4.
45. Kaaria S, Laaksonen M, Rahkonen O, Lahelma E, Leino-Arjas P. Risk factors of chronic neck pain: a prospective study among middle-aged employees. Eur J Pain. 2012;16(6):911-20.

46. Smith MT, Klick B, Kozachik S, Edwards RE, Holavanahalli R, Wiechman S, Blakeney P, Lezotte D, Fauerbach JA. Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. Pain. 2008;138(3):497-506.

47. Gupta A, Silman AJ, Ray D, Morriss R, Dickens C, MacFarlane GJ, Chiu YH, Nicholl B, McBeth J. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology. 2007;46(4):666-71.

48. Canivet C, Ostergren PO, Choi B, Nilsson P, af Sillen U, Moghadassi M, Karasek R, Isacsson SO. Sleeping problems as a risk factor for subsequent musculoskeletal pain and the role of job strain: results from a one-year follow-up of the Malmo Shoulder Neck Study Cohort. Int J Behav Med. 2008;15(4):254-62.

49. Roehrs TA, Harris E, Randall S, Roth T. Pain sensitivity and recovery from mild chronic sleep loss. Sleep. 2012;35(12):1667-72.

50. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med. 2005;165(21):2527-35.

51. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. J Clin Sleep Med. 2009;5(4):355-62.

52. Moldofsky H, Inhaber NH, Guinta DR, Alvarez-Horine SB. Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. J Rheumatol. 2010;37(10):2156-66.

53. Walsh JK, Muehlbach MJ, Lauter SA, Hilliker NA, Schweitzer PK. Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. J Rheumatol. 1996;23(2):245-52.

54. Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res. 2012;64(4):597-606.

55. Spaeth M, Bennett RM, Benson BA, Wang YG, Lai C, Choy EH. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. Ann Rheum Dis. 2012;71(6):935-42.

56. Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol. 2003;30(5):1070-4.

57. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA. 2004;292(19):2388-95.

58. Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. Mayo Clin Proc. 2011;86(9):907-11. 59. Bazzichi L, Sernissi F, Consensi A, Giacomelli C, Sarzi-Puttini P. Fibromyalgia: a critical digest of the recent literature. Clin Exp Rheumatol. 2011;29(6 Suppl 69):S1-11.

60. Latorre PA, Santos MA, Heredia-Jimenez JM, Delgado-Fernandez M, Soto VM, Manas A, Carbonell-Baeza A. Effect of a 24-week physical training programme (in water and on land) on pain, functional capacity, body composition and quality of life in women with fibromyalgia. Clin Exp Rheumatol. 2013;31(6 Suppl 79):72-80.

61. Moore RY. Organization and function of a central nervous system circadian oscillator: the suprachiasmatic nucleus. Fed Proc. 1983;42:2783-9.
62. Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int. 1989;6(1):93-102.

63. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97-110.
64. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science. 1999;284:2177-81.

65. Burgess HJ, Eastman CI. Human tau in an ultradian light-dark cycle. J Biol Rhythms. 2008;23(4):374-6.

66. Hannibal J, Hindersson P, Ostergaard J, Georg B, Heegaard S, Larsen PJ, Fahrenkrug J. Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. Invest Ophthalmol Vis Sci. 2004;45:4202-9.

67. Berson DM. Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci. 2003;26:314-20.

68. Brainard GC, Hanifin JP. Photons, clocks, and consciousness. J Biol Rhythms. 2005;20:314-25.

69. Gooley JJ, Lu J, Chou TC, Scammell TE, Saper CB. Melanopsin in cells of origin of the retinohypothalamic tract. Nat Neurosci. 2001;4(12):1165.

70. Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. J Physiol. 2003;549.3:945-52.

71. Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, Ronda JM. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science. 1989;244:1328-33.

72. Wright KP, Jr., Hull JT, Hughes RJ, Ronda JM, Czeisler CA. Sleep and wakefulness out of phase with internal biological time impairs learning in humans. J Cogn Neurosci. 2006;18(4):508-21.

73. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci. 2009;106(11):4453-8.

74. Emens J, Lewy A, Kinzie JM, Arntz D, Rough J. Circadian misalignment in major depressive disorder. Psychiatry Res. 2009;168(3):259-61.

75. Partonen T. Pay attention to evening owls. Ann Med. 2013;45(5-6):395-6.

76. Ambriz-Tututi M, Rocha-Gonzalez HI, Cruz SL, Granados-Soto V. Melatonin: a hormone that modulates pain. Life Sci. 2009;84(15-16):489-98.

77. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gogenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. J Pineal Res. 2011;51(3):270-7.

78. Srinivasan V, Lauterbach EC, Ho KY, Acuna-Castroviejo D, Zakaria R, Brzezinski A. Melatonin in antinociception: its therapeutic applications. Curr Neuropharmacol. 2012;10(2):167-78.
79. Landis CA. Is melatonin the next "new" therapy to improve sleep and reduce pain? Sleep. 2014;37(9):1405-6.

80. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci. 2014;17(2):192-200.

81. Klerman EB, Goldenberg DL, Brown EN, Maliszewski AM, Adler GK. Circadian rhythms of women with fibromyalgia. J Clin Endocrinol Metab. 2001;86:1034-9.

82. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve to a 1h pulse of bright white light. J Physiol. 2012;590(Pt 13):3035-45.

83. Burgess HJ, Crowley SJ, Gazda CJ, Fogg LF, Eastman CI. Preflight adjustment to eastward travel: 3 days of advancing sleep with and without morning bright light. J Biol Rhythms. 2003;18:318-28.

84. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, Wisner KL, Nemeroff CB. The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. Am J Psychiatry. 2005;162:656-62.

85. Rosenthal NE. Diagnosis and treatment of seasonal affective disorder. JAMA. 1993;270:2717-20.

86. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N, Kasper S. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology. 2011;64(3):152-62.

87. Naus T, Burger A, Malkoc A, Molendijk M, Haffmans J. Is there a difference in clinical efficacy of bright light therapy for different types of depression? A pilot study. J Affect Disord. 2013;151(3):1135-7.

88. Wirz-Justice A, Bader A, Frisch U, Stieglitz R, Alder J, Bitzer J, Hosli I, Jazbec S, Benedetti F, Terman M, Wisner KL, Riecher-Rossler A. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry. 2011;72(7):986-93.

89. Lieverse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light

treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry. 2011;68(1):61-70.

90. Leichtfried V, Mair-Raggautz M, Schaeffer V, Hammerer-Lercher A, Mair G, Bartenbach C, Canazei M, Schobersberger W. Intense illumination in the morning hours improved mood and alertness but not mental performance. Appl Ergon. 2015;46 Pt A:54-9.

91. van Maanen A, Meijer AM, Van der Heijden KB, Oort FJ. The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev. 2016;29:52-62.

92. Westrin A, Lam RW. Long-term and preventative treatment for seasonal affective disorder. CNS Drugs. 2007;21(11):901-9.

93. Reeves GM, Nijjar GV, Langenberg P, Johnson MA, Khabazghazvini B, Sleemi A, Vaswani D, Lapidus M, Manalai P, Tariq M, Acharya M, Cabassa J, Snitker S, Postolache TT. Improvement in depression scores after 1 hour of light therapy treatment in patients with seasonal affective disorder. J Nerv Ment Dis. 2012;200(1):51-5.
94. Pearl SJ, Lue F, MacLean AW, Heslegrave RJ, Reynolds WJ, Moldofsky H. The effects of bright light treatment on the symptoms of fibromyalgia. J Rheumatology. 1996;23(5):896-902.

95. Solov'eva AD, Fishman E. The effects of phototherapy on psychoautonomic neurotic disorders. Neurosci Behav Physiol. 1999;29(1):111-6.

96. Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T. Disturbed sleep in patients complaining of chronic pain. J Nerv Ment Dis. 1982;170(7):429-31.

97. Smith MT, Perlis ML, Smith MS, Giles DE, Carmody TP. Sleep quality and presleep arousal in chronic pain. J Behav Med. 2000;23(1):1-13.

98. Pilowsky I, Crettenden I, Townley M. Sleep disturbance in pain clinic patients. Pain. 1985;23(1):27-33.

99. Drewes AM, Nielsen KD, Arendt-Nielsen L, Birket-Smith L, Hansen LM. The effect of cutaneous and deep pain on the electroencephalogram during sleep--an experimental study. Sleep. 1997;20(8):632-40.

100. Morin CM, Gibson D, Wade J. Self-reported sleep and mood disturbance in chronic pain patients. Clin J Pain. 1998;14(4):311-4.

101. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539-52.

102. Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci. 1998;315(6):367-76.

103. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain. 1996;68(2-3):363-8.

104. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Rheum. 2008;59(7):961-7.

105. Sivertsen B, Lallukka T, Salo P, Pallesen S, Hysing M, Krokstad S, Simon O. Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway. J Sleep Res. 2014;23(2):124-32.

106. Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. J Rheumatol. 2011;38(12):2653-63.

107. Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: A diathesis-stress framework. Psych Bulletin. 1996;119(1):95-110.

108. Bruehl S, Chung OY, Burns JW. Anger expression and pain: an overview of findings and possible mechanisms. J Behav Med. 2006;29(6):593-606.

109. Burns JW, Quartana PJ, Bruehl S. Anger inhibition and pain: conceptualizations, evidence and new directions. J Behav Med. 2008;31(3):259-79.
110. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain. 2004;111(1-2):77-83.

111. Van Liew C, Brown KC, Cronan TA, Bigatti SM, Kothari DJ. Predictors of pain and functioning over time in fibromyalgia syndrome: an autoregressive path analysis. Arthritis Care Res. 2013;65(2):251-6.

112. Vural M, Berkol TD, Erdogdu Z, Kucukserat B, Aksoy C. Evaluation of personality profile in patients with fibromyalgia syndrome and healthy controls. Mod Rheumatol. 2014;24(5):823-8.

113. Diaz-Piedra C, Catena A, Miro E, Pilar Martinez M, Sanchez AI, Buela-Casal G. The impact of pain on anxiety and depression is mediated by objective and subjective sleep characteristics in fibromyalgia patients. Clin J Pain. 2014;30(10):852-9.

114. de Rooij A, Roorda LD, Otten RH, van der Leeden M, Dekker J, Steultjens MP. Predictors of multidisciplinary treatment outcome in fibromyalgia:a systematic review. Disabil Rehabil. 2013;35(6):437-49.

115. Wicksell RK, Kemani M, Jensen K, Kosek E, Kadetoff D, Sorjonen K, Ingvar M, Olsson GL. Acceptance and commitment therapy for fibromyalgia: a randomized controlled trial. Eur J Pain. 2013;17(4):599-611.

116. Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. Proc Natl Acad Sci. 2006;103(19):7414-9.

117. Courtet P, Olie E. Circadian dimension and severity of depression. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S476-81.

118. Kitamura S, Hida A, Watanabe M, Enomoto M, Aritake-Okada S, Moriguchi Y, Kamei Y, Mishima K. Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. Chronobiol Int. 2010;27(9-10):1797-812.

119. Reid KJ, Jaksa AA, Eisengart JB, Baron KG, Lu B, Kane P, Kang J, Zee PC. Systematic evaluation of

Axis-I DSM diagnoses in delayed sleep phase disorder and evening-type circadian preference. Sleep Med. 2012;13(9):1171-7.

120. Hasler BP, Buysse DJ, Kupfer DJ, Germain A. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. Psychiatry Res. 2010;178(1):205-7.

121. Michalak EE, Murray G, Wilkinson C, Dowrick C, Lam RW. A pilot study of adherence with light treatment for seasonal affective disorder. Psychiatry Res. 2007;149(1-3):315-20.

122. Suhner AG, Murphy PJ, Campbell SS. Failure of timed bright light exposure to alleviate age-related sleep maintenance insomnia. J Am Geriatr Soc. 2002;50:617-23.

123. Crowley SJ, Carskadon MA. Modifications to weekend recovery sleep delay circadian phase in older adolescents. Chronobiol Int. 2010;27(7):1469-92.

124. Burgess HJ, Park M, Ong JC, Shakoor N, Williams DA, Burns J. Morning versus evening bright light treatment at home to improve function and pain sensitivity for women with fibromyalgia: A pilot study. Pain Med. 2016; Jul 29 [epub ahead of print].

125. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. 1991;18(5):728-33.

126. Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Kinner E, Schuster E, Passik S, France CR. Endogenous opioid function mediates the association between laboratory evoked pain sensitivity and morphine analgesic responses. Pain. 2013;154(9):1856-64.

127. Redondo JR, Justo CM, Moraleda FV, Velayos YG, Puche JJ, Zubero JR, Hernandez TG, Ortells LC, Pareja MA. Long-term efficacy of therapy in patients with fibromyalgia: a physical exercise-based program and a cognitive-behavioral approach. Arthritis Rheum. 2004;51(2):184-92.

128. Menga G, Ing S, Khan O, Dupre B, Dornelles AC, Alarakhia A, Davis W, Zakem J, Webb-Detiege T, Scopelitis E, Quinet R. Fibromyalgia: can online cognitive behavioral therapy help? Ochsner J. 2014;14(3):343-9.

129. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol. 2009;36(6):1304-11.

130. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and affect. Nat Rev Neurosci. 2014;15(7):443-54.

131. Lovato N, Lack L. Circadian phase delay using the newly developed re-timer portable light device. Sleep Biol Rhythms. 2016;14:157-64.

132. Wright HR, Lack LC, Kennaway DJ. Differential effects of light wavelength in phase advancing the melatonin rhythm. J Pineal Res. 2004;36(2):140-4.

133. Wright HR, Lack LC, Partridge KJ. Light emitting diodes can be used to phase delay the melatonin rhythm. J Pineal Res. 2001;31(4):350-5.

134. Zeitzer JM, Dijk DJ, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol. 2000;526.3:695-702.

135. Bennett RM, Friend R, Marcus D, Bernstein C, Han BK, Yachoui R, Deodhar A, Kaell A, Bonafede P, Chino A, Jones KD. Criteria for the diagnosis of fibromyalgia: validation of the modified 2010 preliminary American College of Rheumatology criteria and the development of alternative criteria. Arthritis Care Res. 2014;66(9):1364-73.

136. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113-22.

137. First M, Williams J, Karg R, Spitzer R. Structured Clinical Interview for DSM-5 - Research Version (SCID-5 for DSM-5, SCID-5-RV). Arlington, VA.: American Psychiatric Association; 2015.
138. Burns JW, Glenn B, Bruehl S, Harden RN, Lofland K. Cognitive factors influence outcome following multidisciplinary chronic pain treatment: a replication and extension of a cross-lagged panel analysis. Behav Res Ther. 2003;41(10):1163-82.

139. Burns JW, Kubilus A, Bruehl S, Harden RN, Lofland K. Do changes in cognitive factors influence outcome following multidisciplinary treatment for chronic pain? A cross-lagged panel analysis. J Consult Clin Psychol. 2003;71(1):81-91.

140. Glenn B, Burns JW. Pain self-management in the process and outcome of multidisciplinary treatment of chronic pain: evaluation of a stage of change model. J Behav Med. 2003;26(5):417-33.

141. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. CNS Spectrums. 2005;10:647-63.

142. Gallin PF, Terman M, Reme CE, Rafferty B, Terman JS, Burde RM. Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. Am J Ophthalmol. 1995;119:202-10.

143. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009;11(4):R120.

144. Maurset A, Skoglund LA, Hustveit O, Klepstad P, Oye I. A new version of the ischemic tourniquet pain test. Methods Find Exp Clin Pharmacol. 1992;13(9):643-7.

145. Burns JW, Bruehl S, Chung OY, Magid E, Chont M, Goodlad JK, Gilliam W, Matsuura J, Somar K. Endogenous opioids may buffer effects of anger arousal on sensitivity to subsequent pain. Pain. 2009;146(3):276-82.

146. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006;29(9):1155-73.

147. de Souza L, Benedito-Silva AA, Pires MLN, Poyares D, Tufik S, Calil HM. Further validation of actigraphy for sleep studies. Sleep. 2003;26:81-5.

148. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med.
2001;2:389-96.

149. Burgess HJ, Revell VL, Molina TA, Eastman CI. Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. J Clin Endocrinol Metab. 2010;95(7):3325-31.

150. Burgess HJ. Partial sleep deprivation reduces phase advances to light in humans. J Biol Rhythms. 2010;25(6):460-8.

151. Burgess HJ, Eastman CI. Short nights reduce light-induced circadian phase delays in humans. Sleep. 2006;29(1):25-30.

152. Burgess HJ, Eastman CI. Early versus late bedtimes phase shift the human dim light melatonin rhythm despite a fixed morning lights on time. Neurosci Lett. 2004;356:115-8.

153. Burgess HJ, Eastman CI. A late wake time phase delays the human dim light melatonin rhythm. Neurosci Lett. 2006;395:191-5.

154. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297-307.

155. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess. 1995;7(4):524-32.

156. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:53-63.

157. Rosenfeld VW, Rutledge DN, Stern JM. Polysomnography with quantitative EEG in patients with and without fibromyalgia. J Clin Neurophysiol. 2015;32(2):164-70.

158. Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. Psychiatry Res. 2012;196(1):57-61.

159. Friedman L, Zeitzer JM, Kushida C, Zhdanova I, Noda A, Lee T, Schneider B, Guilleminault C, Sheikh J, Yesavage JA. Scheduled bright light for treatment of insomnia in older adults. J Am Geriatr Soc. 2009;57(3):441-52.

160. Virk G, Reeves G, Rosenthal NE, Sher L, Postolache TT. Short exposure to light treatment improves depression scores in patients with seasonal affective disorder: A brief report. Int J Disabil Hum Dev. 2009;8(3):283-6.

161. Chang AM, Santhi N, St Hilaire M, Gronfier C, Bradstreet DS, Duffy JF, Lockley SW, Kronauer RE, Czeisler CA. Human responses to bright light of different durations. J Physiol. 2012;590(Pt 13):3103-12.

162. Spaeth M, Alegre C, Perrot S, Wang Y, Guinta DR, Alvarez-Horine S, Russell I, Sodium Oxybate

Fibromyalgia Study G. Long-term tolerability and maintenance of therapeutic response to sodium oxybate in an open-label extension study in patients with fibromyalgia. Arthritis Res Ther. 2013;15(6):R185.

163. Shaver JL, Wilbur J, Robinson FP, Wang E, Buntin MS. Women's health issues with fibromyalgia syndrome. J Womens Health (Larchmt). 2006;15(9):1035-45.

164. Shaver JL, Wilbur J, Lee H, Robinson FP, Wang E. Self-reported medication and herb/supplement use by women with and without fibromyalgia. J Womens Health (Larchmt). 2009;18(5):709-16.

165. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder
(N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2015;11(10):1199-1236.

166. Reid KJ, Burgess HJ. Circadian rhythm sleep disorders. Prim Care. 2005;32:449-73.

167. Buskila D. Pediatric fibromyalgia. Rheum Dis Clin North Am. 2009;35(2):253-61.

168. Touitou Y. Adolescent sleep misalignment: a chronic jet lag a matter of public health. J Physiol Paris. 2013;107(4):323-6.

Appendix 1

13 Optional Sub-study: Apple Watch & Sleep Phase Identification

13.1 Sub-study Introduction

The FDA-approved method of longitudinal sleep tracking in the ambulatory environment is actigraphy. Although actigraphy is highly useful, consumer available wearable devices are less expensive, easily interface with mobile health applications, and may be more acceptable to patients. As such, we have developed an app that houses algorithms to estimate sleep stages when applied to raw heart rate and acceleration data from the Apple Watch. Our algorithm demonstrated excellent sensitivity and specificity (80% and 76%) when compared to the gold standard for sleep measurement (polysomnogram, PSG) (Walch unpublished). Additionally, mathematical models that use light exposure and movement to estimate circadian phase have been well-described and also available through the same app (Walch 2016).

Therefore, we aim to use the Apple Watch and our app in a subgroup of participants from the main study, Bright Light Treatment at Home to Improve Symptom Management of Fibromyalgia Syndrome, to identify changes in sleep and circadian phase over the 5-week study period. This data may be used to assist in validating the Apple Watch App, and may also be used in HUM00122578.

13.2 Sub-study Risk-Benefit Assessment

Participation in this sub-study does not appreciably alter the risk-benefit profile of the main study as the only additional risk is that of small increased in burden associated with wearing the Apple Watch and using the app. Some people might find wearing the study watch, plus their own watch (if applicable) and the accelerometer a bit annoying. The Apple Watches themselves are comfortable to wear, and don't pose any additional comfort risks.

Participation in this sub-study also requires downloading the study app onto one's personal cell phone. Some individuals might find this intrusive. Overall, these risks are no different than those associated with using the Apple Watch and affiliated apps on their own.

The risk to privacy and confidentiality are likewise similar to those listed for the main study and typical consumer use of a smart watch and app. The investigators will protect all study data as described in Sections 3.1.6 and 11.3

Participants in the main study are under no obligation to also enroll in this sub-study. Declining enrollment will not change the relationship between the participant and the study team.

13.3 Sub-Study Population

Participants for this sub-study will be drawn from those individuals already presenting for enrollment into the main study.

13.3.1 Eligibility Criteria

Inclusion criteria include all of those associated with the main study, plus the following: 1) enrollment in the main study; 2) ownership of an iPhone; 3) ability to operate a mobile application on said iPhone; and 4) a willingness to wear an Apple Watch.

13.4 SUB-STUDY PROCEDURES

At visit 1, consented individuals will be given a study Apple Watch, and work with the study team to download the app on their personal cell phones. They will receive instructions on how to wear the Apple Watch (e.g. which wrist, when, how often, how/when to charge it, etc.), and how to use the app to enter light exposure information.

The app uses the innate heart rate and accelerometer data from the Apple Watch, and will be transmitted via HTTP request from the phone. While most of the data collection will be passive; participants will be asked to press an indicator button prior to onset of sleep on some nights.

13.5 SUB-STUDY INCENTIVE

Participants will receive $40 per week of wearing the Apple Watch (up to $200 total) *in addition to* the remuneration in place for the main study.

13.6 SUB-STUDY REFERENCE

Walch OJ, Cochran A, Forger D. A global quantification of “normal” sleep schedules using smartphone data. Sci Adv 2016;2(5):e1501705