Re-engineering Precision Therapeutics Through N-of-1 Trials: Feasibility Study of Personalized Trials of Light Therapy for Fatigue

Research Protocol Document

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Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Re-engineering Precision Therapeutics Through N-of-1 Trials: Feasibility Study of Personalized Trials of Light Therapy for Fatigue
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Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
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1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

The purpose of this pilot study is to determine the feasibility of using N-of-1 methods in a virtual research study, to assess the feasibility of using online web and social media advertising to recruit and enroll participants in a virtual research study, and to determine the feasibility of methods used to collect and assess participant symptoms in response to a wellness strategy (in this case, light therapy for symptoms of fatigue). This pilot will help determine if an N-of-1 study design, or what we are terming Personalized Trials, can have widespread use in future research and clinical practice to address high public health burdens with a high heterogeneity of response.

This study will assess feasibility using a Personalized Trial model to evaluate an individual participant's experience using bright or dim light therapy on symptoms of fatigue. Participants (N=60) will be sent a Fitbit device and receive a commercially-available light therapy device (bright blue light) and a dim light therapy device (dim blue light). Participants will be asked several questions a day via text message about their symptoms of fatigue, as well as their pain, concentration, confidence, mood, and stress levels to demonstrate relevant secondary impacts of fatigue. Participants will also have access to several videos explaining the protocol. After 14 weeks, participants will receive a summary of their observed data. Creating this type of report will help to assess the feasibility of using a N-of-1 trial design through user-acceptability of fatigue and wellness-related data visualizations and the ability to choose preferred intervention (if any) based on the data. Participants will be asked to complete a satisfaction survey (electronic or phone if they are non-responders) and participate in a phone interview to inform acceptability of protocol requirements, study materials, and personalized reports.

We believe Personalized Trials are feasible to scale to a large randomized controlled trial, and eventually clinical practice specifically to address frequent chronic complaints with the custom N-of-1 pathways we are developing. Data collected to support our hypothesis includes device adherence, survey adherence, adherence to video views, website and social media engagement metrics, and participant satisfaction based on qualitative interviews and surveys. Results from this pilot study will inform the future development of N-of-1 methodology in the research and clinical space.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

This project represents a pilot project under the umbrella of the NIH-funded grant "Re-engineering precision therapeutics through N-of-1 trials" (Northwell IRB 19-0572-MRB) which is funded to test use cases appropriate for N-of-1 methodology and evaluate them for acceptability and scalability.

The overarching objective of our parent grant is to develop, test, and implement an innovative technology platform for conducting N-of-1 trials that transforms precision therapeutics. Right now, clinicians are engaging in clinical encounters in which they are trying to determine the best therapy for individual patients. These encounters are likely to be unsuccessful. Clinicians rely on the best available evidence (e.g., results from parallel group, phase III randomized clinical trials; RCTs) for recommending therapies to a patient. Yet, conventional, between-group RCTs only provide estimates of the effect of therapies on the hypothetical 'average' patient in those trials. Individual patients, however, often respond differently than the hypothetical average patient in the phase III RCTs, and thus, heterogeneity of therapy response plagues clinical decisions made for an individual patient every day.

The most scientifically rigorous — and potentially transformative — method for determining optimal therapy for a patient is a single-patient (N-of-1) trial. N-of-1 trials are multiple crossover trials, usually randomized, and often masked, conducted within a single patient, with data collected objectively, continuously, and in the real-world, for a sufficient time period to determine whether the therapy, compared to a placebo or other active therapy, is optimal for a particular patient. They also yield information on off-target actions, such as side-effects or unintended consequences, so that a more complex picture can emerge about the overall benefits and harms of the therapy for that one individual patient. Clinicians and

patients do not routinely engage in this type of scientific endeavor because they lack the tools.

In many ways, **Personalized or N-of-1 Trials are the foundational design for a truly patient-centered approach by serving as a clinical decision tool for patients.** Historically, in introducing evidence-based medicine, Guyatt and others have described Personalized Trials as the pinnacle of the evidence-based design pyramid.(1) Clinicians can use these techniques to monitor and make treatment decisions in chronically ill patients,(2) of whom 25% experience adverse treatment effects.(3) Personalized Trials are specifically designed to help patients and their clinicians make healthcare decisions that are informed by high-integrity, evidence-based information uniquely relevant to the outcomes and values important to them.(4) In a series of demonstration trials, Personalized Trials led to valuable changes in treatment, cessation of treatment, or confirmation of the original treatment.(5-8) For example, of 71 N-of-1 trials for patients with any chronic pain, 46 patients (65%) decided to change their pain medication due to trial results.(9) However, Personalized Trials are conducted infrequently in clinical practice.(10-12) In post-mortem assessments as to why Personalized Trials had yet to become commonly employed, proponents concluded that they were insufficiently appealing to patients or clinicians to justify the cost and effort needed to design and implement them.(10, 11) Specifically, Personalized Trial design specifications had mostly been driven by clinicians or researchers,(13, 14) with little input from patients.

Rationale for Selecting Blue Light as an N-of-1 Trial for Fatigue
Participant report of fatigue meets all of our criteria for selection as a use case as outlined in our umbrella grant: it has high public health burden, high heterogeneity of observed outcomes, and is high priority for a Personalized Trial approach as determined by previously interviewed clinicians and patients. This instance will adapt our N-of-1 trial platform to comparing a complementary and alternative medicine (CAM) therapy for fatigue symptoms (bright light therapy) to (dim light therapy). This alpha-test will enable us to expand our N-of-1 trial platform of non-pharmacologic therapies, including CAM. Of note, it is possible that N-of-1 trials of CAM could be conducted at the direct-to-consumer level.

Rational for Selecting Blue Light
Blue light has been chosen for this study because it has been shown in multiple research studies to be either equal or more efficacious than bright white light in light therapy treatments for a variety of therapies, including fatigue (15-19). It has also been shown in a number of studies that the blue wavelength of light is a key component to the shift of fatigue measures in patient reported outcomes (15-18). Additionally, the use of blue light therapy rather than white light therapy allows for a lower strength bright light, reducing the eye glare in treatments (17). This allows for a more comfortable, low-risk light therapy experience and resulting observed outcomes to support the trial methodology.

Rationale for Selecting Usual Care over Dim Light as the Control Condition
Patients don't frequently ask is treatment A better than Treatment B, but rather should I use Treatment A? That is, is Treatment A better than what I'm using for fatigue management now? This was indicated to us by the results on our patient focus groups and survey; when asked what the most acceptable control condition was, over 80% of patients preferred Usual Care as the control for their Personalized Trial. We are including a dim blue light therapy device given our prior experience conducting pilot studies utilizing light therapy. In those studies, participants often chose the "sham" device as the one to which they were most responsive. In addition, we include a usual care condition to control for and observe the influence of any expectancy effect on the self-reported data. Usual care data collection will enable us to test the effect of bright light therapy compared to usual care, and to obtain estimates of the cost-effectiveness of the N-of-1 approach. For this reason, we will use usual care as our control condition for light therapy Personalized Trials.

Without development of innovative platforms for conducting Personalized Trials, with within-participant randomization to eligible wellness management options, including when clinically appropriate, usual care, patients and clinicians cannot obtain the objective data they need to empirically choose the optimal precise therapy. Scientists may be able to use Personalized or N-of-1 trials in the future to better understand the uniqueness of light therapy responders versus non-responders. Off-target responses (such as increased stress or decreased physical activity) could also be detected in this methodology, as the unique responsiveness of one patient to several time periods of therapy exposure will be available. Should this pilot demonstrate acceptability by participants, scalable implementation and satisfaction with this methodology amongst participants, it will be a critical step in broadening the application and utilization of this methodology.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

We believe the delivery of N-of-1 methodology through Personalized Trials is feasible to scale to a large randomized controlled trial, and eventually to standard clinical practice. In order to demonstrate this feasibility, we must be able to collect data illustrating that Personalized Trials can be a low-burden, satisfactory tool that can be scaled to individuals and clinicians.

We will additionally examine the novel individual-level heterogeneity of treatment effect and observed outcomes-made possible by the N-of-1 trial design, and will test the feasibility of pooling real-world N-of-1 results across patients to efficiently estimate the overall effectiveness of light therapy and thus the N-of-1 trial design. To determine whether this "precision therapeutics" paradigm-shifting approach

creates added value for the learning healthcare system, and to confirm engineering these innovations into one platform and system to empirically determine the precise therapy for each patient is feasible, we will pool N-of-1 results across all projects using the N1Thrive platform.

Thus, the goals of this pilot study are to:
1. Conduct a pilot test (N=60) of a Personalized Trial that is delivered remotely to participants in the United States.
2. Collect data regarding Minimum Viable Product (MVP) specifications for a future technology platform to deliver Personalized Trials.
3. Incorporate web-based research advertising and recruitment in the pilot study.
4. Elicit participant attitudes and opinions toward using Personalized Trials to help inform their personal wellness strategy.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
    - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

Fatigue remains one of the most highly-cited patient complaints to their primary care provider(20), yet there are relatively few treatment options available. We have conducted focus groups as part of prior grants to determine what chronic symptoms or conditions are most acceptable for a Personalized Trial, and fatigue was selected by both patients and their health providers(19). With such a broad group experiencing symptoms of fatigue, we have planned for a broad base of recruitment efforts to potentially recruit a diverse representation of this population.

Northwell employs over 70,000 individuals and Hofstra University has over 11,000 students enrolled. While these are two organizations that are easily accessible, we will be expanding our scope of potential participants through the use of social media. Social media and web-based advertisements remain a largely untapped resources for research recruitment, and we will be exploring the use of online postings to reach several more thousand potential participants through online paid advertisement and links to a study website.

Center for Personalized Health staff must meet certain eligibility criteria before assisting with this Personalized Trial pilot. All staff members must be listed on the IRB and be up-to-date with trainings and attestations as required by the Northwell Health Human Research Protection Program. Additionally, staff will be required to participate in weekly meetings with the Principal Investigator, and an additional weekly meeting with the Project Manager, in order to stay informed about the study protocol, staff duties and functions, and to answer any questions that come up

within the group. Staff will have daily access to the Project Manager, Director of Clinical Research, and Principal Investigator to answer any protocol questions they may have outside these established weekly meetings.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

Since the proposed study will take place virtually, potential participants can reside anywhere within the United States.

Potential participants will be recruited via the following avenues:
- Paid social media advertisements targeted to individuals who meet study eligibility demographics and identify as having chronic fatigue**.**
-E-mail advertisement through employee and student communication channels, both including and outside of Northwell Health and Hofstra University.
-E-mail advertisements through existing email lists from those who have previously expressed an interest in participation in a Personalized Trial with the Center for Personalized Health.
-Flyers, shared at urgent care/walk-in and physician clinics, within and outside of the Northwell Health network.
-Short promotional videos shared online or in clinic waiting rooms.
-Recruitment posts within online wellness groups, such as those that discuss recurring fatigue.

Potential participants will self-identify as having a minimum threshold of fatigue over the last 30 days using PROMIS Fatigue measures, and interest in participating in a Personalized Trial. Participants will receive a pay card valued at $100 for completing all study requirements.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*

- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Up to 60 participants will be randomized to receive this pilot study protocol. We estimate about 70% will identify as female and 30% will identify as male. We aim to recruit a diverse pool of participants with varied ethnic and racial backgrounds.

Inclusion criteria:
-Age 18 - 59 years old ~~of age~~
-Fluent in English
-Self reported fatigue results score $\geq$ 12 on a modified PROMIS Fatigue Short Form 8a scale
-Able to participate in blue light therapy
-Owns and can regularly access a smartphone capable of receiving text messages
-Owns and can regularly access an e-mail account
-Lives in the United States

Exclusion criteria:
- <18 years old or >60 years old
- Pregnant women
-Previous diagnosis of a serious mental health condition or psychiatric disorder, such as bipolar disorder
-Previous diagnosis of eye disease, such as cataracts, glaucoma, macular degeneration, Stargardt or family history of Stargardt, retinitis or retinopathy, or other retinal disorders
-Previous diagnosis of diabetes
- Previous eye surgery
-Sensitivity to light or use of medication causing sensitivity to light
-Epilepsy or a history of seizures
- Participation in shift work (evening/night shifts, early morning shifts, rotating shifts, etc.)
-Lives outside of the United States

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

We expect to pre-screen up to 750 potential participants in this study. Up to 150 potential participants will be invited to enroll. Up to 60 participants will be randomized to complete research procedures.

Of those participants who receive randomized treatment schedules, 30 participants will be randomized to receive the protocol in the following order of two-week treatment periods: Bright Blue Light Therapy, Dim Blue Light Therapy, Usual Care, Usual Care, Dim Blue Light Therapy, Bright Blue Light Therapy (ABCCBA). The remaining 30 participants will be randomized in the following order of two-week treatment periods: Usual Care, Dim Blue Light Therapy, Bright Blue Light Therapy, Bright Blue Light Therapy, Dim Blue Light Therapy, Usual Care (CBAABC).

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

The study will take place over the course of 14 weeks. The first two weeks will be a baseline period, where no light therapy is assigned, but data are collected, including self-report of fatigue and accelerometer-derived sleep and activity data. After successful completion of the baseline period, participants will be randomized to six 2-week treatment blocks of bright blue light therapy, dim blue light therapy, and usual care. In usual care treatment periods, participants will be instructed to not use any light therapy device and will be asked to continue answering survey questions and wearing their Fitbit device. At the end of the 14 weeks, a report containing the individual's analyzed data will be sent to each participant, along with a satisfaction survey. This report will be sent within 3 months of study completion. After the satisfaction survey is completed, study coordinators will reach out to each participant to interview them about their experience in Personalized Trials. A $100 pay card (CliniCard) will be mailed to each participant as compensation for their time after the successful completion of 14 weeks of data collection, satisfaction survey, and phone interview.

Potential participants will have the opportunity to choose from within a provided list of start dates during their enrollment process. No more than 20 potential participants will begin their baseline period on the same day. Enrollment will be ongoing until up to 60 participants have been randomized after baseline to receive a personalized trial of light therapy for self-reported fatigue. We estimate that the final participant will be randomized by September 30, 2021, and data collection will cease by December 31, 2021.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

This study is a feasibility pilot whose primary objective is to assess the acceptability, scalability of implementation and participant satisfaction with a personalized trial methodology to resolve a chronic complaint. Thus, the primary endpoint is trial completion in the first 3 months.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

Potential participants who self-identify as experiencing chronic symptoms of fatigue will be directed to an information screen with details about the pilot study. Those who are interested in participating in this pilot study will be directed to sign a HIPAA Authorization form before completing screening survey process that includes validated PROMIS measures of fatigue, as well as questions pertaining to inclusion and exclusion criteria. Consenting coordinators will review this data and determine whether or not a potential participant is eligible to participate. Those who are eligible will receive a link to a short video about key details from the consent form, as well as an electronic copy of the consent form. Potential participants will also be asked to set up a 30-minute phone call with a research coordinator, where the research coordinator will describe the study and consent process and offer an opportunity for the potential participant to ask any questions. After the phone call, the potential participant will be sent a link to view and electronically sign the consent form via the N1Thrive by 4Peacocks platform, which meets 21 CFR 11 standards for collecting electronic signature. Before being able to sign and submit the consent form, potential participants must demonstrate understanding of the protocol by correctly answering 4 questions pertaining to the information presented in the consent form.

Once potential participants successfully submits their signed consent form, they will receive an onboarding questionnaire to collect more information including a cell phone number and home address. A consenting coordinator will review this information and send the potential participant an email which will include a confirmation of the start date of their baseline period, as well as a short video of what to expect during onboarding to the study. They will be mailed an initial study kit including a Fitbit Charge 3 device and a printed copy of their electronically-

signed HIPAA authorization and consent form with a URL to view the informed consent video that they watched previously. Potential participants will be asked to download the Fitbit app to their smart phone. All baseline periods will begin on a Monday. No more than 20 participants will be permitted to begin on the same day.

The baseline period will take place over the course of 2 weeks. Potential participants will not use light therapy during the baseline period. At three randomized times each day during waking hours, (identified by the potential participant during their onboarding survey), baseline participants will receive a text message asking them to rate their fatigue, pain, concentration, confidence, mood, and stress levels at that exact moment. Each evening, baseline participants will receive a survey asking a few questions about their fatigue that day. At the end of the week on Sunday evenings, baseline participants will receive a slightly longer survey asking them to reflect on their symptoms of fatigue that week.

During the baseline period, potential participants will be asked to wear their Fitbit all day and night, even while they are sleeping. Baseline participants will be instructed to sync their Fitbit device by opening the Fitbit app on their phone at least every two days.

Ten days into the baseline period, a consenting coordinator will review individual adherence to Fitbit wear and to survey responses. Adherence to Fitbit wear will be defined as recorded activity of greater than 12 hours a day, and recorded sleeping activity. Survey adherence will be defined as submission of a given survey. Baseline participants that do not achieve at least 80% adherence of Fitbit wear and survey submission during the first 10 days of the baseline period will be withdrawn from the study. Those that maintain at least 80% adherence will be randomized to one of two treatment sequences in the pilot study. Participants who are randomized to receive treatment sequences will receive email confirmation including their protocol timeline. Participants will also receive a second mailed kit including a bright blue light commercial AYO light therapy device, and a dim blue light research AYO light therapy device. Enrollment will continue until up to 60 participants have been randomized into one of two treatment sequences.

Each treatment sequence is made up of 6 2-week periods dedicated to either bright blue light therapy, dim blue light therapy, or usual care. During both bright blue light and dim blue light therapy weeks, participants will receive a text message within an hour of their self-reported wake time instructing them to use their designated light therapy device for 30 minutes. During usual care treatment periods, participants will not receive any text notifications to complete light therapy, and will instead be asked to refrain from using either AYO device.

During all treatment weeks (12 weeks total), participants will be asked to continue wearing their Fitbit device each day and night. They will continue to receive 3 randomized text messages each day with questions about their fatigue, pain, concentration, confidence, mood, and stress at that current moment, as well as an

evening text asking them to reflect on their fatigue and any side-effects they may be experiencing from their light therapy treatment (if applicable). Participants will receive slightly longer surveys on Sunday evenings, asking them to reflect on their symptoms of fatigue that week. A study phone number and email address will be available as part of each survey to contact the study team if a participant is concerned about any side effects they are experiencing. Participants will also be instructed to stop their light therapy sessions if they are concerned about their side effects.

Participants may receive additional text messages to those outlined above with important reminders about their protocol (e.g. transition to a new treatment period), or to remind participants to sync their data. We will send a maximum of 6 text messages per day during the study, including these reminders and the survey questions outlined above.

In the event of an unanticipated circumstance that temporarily prevents a participant from completing study activities (illness, injury, death in the family, etc.), the participant will have the option of pausing their study to resume once their circumstance has been positively resolved.

Participants will complete remote data monitoring after they have gone through one baseline period (two weeks), two bright blue light therapy periods (two weeks each), two dim blue light therapy periods (two weeks each), and two usual care periods (two weeks each), or 14 weeks total. Alternatively, a participant may choose to withdraw from the study, or be withdrawn from the study by the research team. Upon completion of data monitoring, participants will be given instructions on how to un-link their Fitbit from the study account. Daily text messages and survey prompts will be cancelled for participants who are withdrawn from the study.

We will compile the self-reported data from questionnaires, treatment adherence, side effects, pain, fatigue, concentration, confidence, mood, and stress assessments, as well as information from the Fitbit regarding activity (steps, flights climbed and intensity), sleep (duration, estimated sleep stages) for each individual participant. Treatment adherence will be tracked via an AYO research web portal and will be included in the compiled data. No identifying information will be provided to AYO or included on the treatment adherence report provided by AYO. We will analyze this data and create a summary report of the participant's data and symptoms over the study period, relation to the bright blue light therapy, dim blue light therapy, and usual care treatment periods.

The participant will be sent this report in an encrypted email and secure web link by our study team. Participants will also be sent links to several online videos explaining the terms and data visualizations available in their summary report. These videos will be general to the template report and will not contain any

individual results or health information. Participants will be sent a satisfaction survey along with their individual report.

The satisfaction survey will be sent via email up to two times before a research coordinator will attempt to call individual participants to complete the satisfaction survey via phone. Participants will be mailed a pay card (Clinicard) valued at $100 after successful completion of the satisfaction survey.

Within 3 months of an individual ending their remote data monitoring, regardless of when that takes place, participants will be asked to schedule a phone call from a member of our study team to discuss their study experience. We will ask several questions about their experience and opinion toward Personalized Trials, as well as for suggestions for improvement for future Personalized Trials. Study participation will end after successful completion of this participant phone interview.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

The sample size of 60 participants was chosen to have a sufficient number of patients to obtain a preliminary assessment of the feasibility of personalized trials of light therapy for management of symptoms of fatigue. The numbers of questionnaires and treatment repetitions per trial were based on expert recommendations by a statistician and estimations about maximal duration of the trial to maintain patient engagement. Specifically, the primary endpoint is trial completion in the first 3 months. We aim to demonstrate a trial completion rate greater than 50% in randomized participants. With n = 60, using a one-sample binomial test at 2.5% significance one-sided, this will give us about 90% power if the true completion rate is 70%. Data will be reported transparently so that individual level heterogeneity can be assessed(21).

Participants will be randomized into one of two different treatment orders, ABCCBA or CBAABC, where A=bright light, B=dim light, and C=usual care. Two treatment orders were chosen to test out the feasibility of carrying out a virtual, N-of-1 study. ABCCBA was chosen as an order to test participant acceptability with back-to-back usual care treatment (i.e. no treatment) extending through 4 weeks. CBAABC was chosen as a companion treatment order to ABCCBA to test participant acceptability with starting a Personalized Trial with a usual care treatment after a baseline run-in (i.e. no treatment for the first 4 weeks). Treatment order was not included as a factor in the statistical analysis because acceptability and feasibility study.

The randomization schedule will be set up by a member of the Center for Personalized Health data team and provided to the data analyst assigned to Personalized Trials of Light Therapy for Fatigue. Randomization will occur with a fixed seed value for the purposes of repeatability and auditability, and the list of 60 participants will be split into two groups of 30 using a random shuffle function that takes that seed as in input. The order in which an individual becomes eligible for one of these 60 randomizations will determine the placement given (i.e. the first person eligible will be randomized to the treatment order given to participant 1, and continue sequentially). Eligibility is obtained by a participant maintaining at least 80% adherence of survey response, Fitbit wear ≥ 12 hours a day, and 80% sleep data available through the baseline run-in period. The data analyst will alert the research coordinator of the assigned randomization once a participant becomes eligible during the baseline run-in period.

The primary outcome measure will be a mean usability score, obtained using the System Usability Scale (SUS), a validated 10-item questionnaire originally developed by John Brooke in 1986 that asks users to score each item on a Likert scale from Strongly Disagree (rating of 1) to Strongly Agree (rating of 5). The SUS will be presented to the participant as addressing the ease of use, complexity, consistency of the Personalized Trials system as a whole, from recruitment to receipt of the report. Individual results are calculated to arrive at a composite measure out of 100. Participant SUS scores will be averaged together. Higher scored values correlate to a more usable system, and therefore a better outcome.

Other outcome measures assessing feasibility of the Personalized Trials framework include:

- Mean participant satisfaction with Personalized Trials components supplemental to the SUS,
- Qualitative satisfaction data collected during the participant phone interview,
- Mean participant survey adherence rate, defined as completion of each assigned survey
- Mean participant Fitbit adherence rate, defined as recorded heart rate data for ≥ 12 hours each day,
- Mean participant Fitbit sleep rate, defined as recorded sleep and wake cycles
- Mean participant bright AYO adherence rate, defined as completion of each assigned 30-minute session
- Mean participant dim AYO adherence rate, defined as completion of each assigned 30-minute session
- Google Ad metrics
- Social media activity, including but not limited to:
    - Social media conversion rate, defined as total impressions compared to total click-through
    - Cost per social media conversion
- Website activity, including but not limited to:

- Total number of website visits per traffic source
- Website bounce rates
- Mean user total time on website

In order to share a summary report of observed trends back to the participant to assess acceptability and satisfaction with the participant report, additional outcomes will be analyzed on an N-of-1 level including:

- Mean Within-Subject Difference in Self-Reported Daily Fatigue During 3 Treatment Periods from Mean Baseline using the PROMIS Item Bank v1.0 – Fatigue 7b Daily Short Form
- Mean Within-Subject Difference in Self-Reported Weekly Fatigue During 3 Treatment Periods from Mean Baseline, using the PROMIS Item Bank v1.0 – Fatigue 8a Short Form
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Pain During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Fatigue During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Concentration During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Confidence During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Mood During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Stress During 3 Treatment Periods from Mean Baseline, using the Numeric Pain Rating Scale adapted from McCaffery, Beebe et al. 1989
- Mean Within-Subject Difference in Self-Reported Side Effects from Baseline, using the average number of days side effects were reported during treatment periods.
- Mean Within-Subject Difference in Device-Recorded Daily Steps from Mean Baseline, using participant Fitbit data
- Mean Within-Subject Difference in Device-Recorded Nightly Sleep from Mean Baseline, using participant Fitbit data
    - The effects of treatment on sleep quality will be assessed using generalized estimating equations (GEE) with an unstructured

variance-covariance matrix for measures on the same day. This model accounts for possible autocorrelation and linear trends between self-reported sleep quality ratings over time.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

N/A

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
  - *What information will be included in that data or associated with the specimens?*
  - *Where and how data and specimens will be stored?*
  - *How long the data will be stored?*
  - *Who will have access to the data?*
  - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

Fitbit

This pilot study uses non-NFC, Fitbit Charge 3 devices to remotely monitor participant activity and sleep. All enrolled participants will be provided with a study account that has been created by the research team with no identifying information to the participant. The email address of the study account contains a unique identifier (e.g. northwellf25). Data collected will include daily steps, floors climbed, activity intensity, sleep duration, and estimated minutes in sleep stages. A file linking the Fitbit identifier to the study participant will be housed in a Northwell-approved drive to store PHI, and be accessible only by members of the study team listed in the IRB application. Coded data from Fitbit will remain stored in a Northwell-approved drive indefinitely with the file linking the Fitbit identifier to the study participant stored separately. Data collected for this study may also be maintained in its native state on a Northwell-approved drive to store PHI indefinitely. Data collected under this research may be used for future research in coded format without additional consent as per the consent form participants sign and with appropriate IRB approval as required.

Fitabase

This pilot study will use Fitabase to retrieve Fitbit data from participants. Fitabase is a secure, online portal. The Fitbit study account provided to the participants will be linked to an identification number in the Fitabase system (e.g. FLT01). No information that could be used to identify a participant will be stored on Fitabase. Only the research team will have access to data that will be able to connect a research participant to their Fitabase ID. Data collected will include last sync date, battery charge status, daily steps, floors climbed, activity intensity, sleep duration, and estimated minutes in sleep stages. Fitabase will stop tracking participant data at the trial end date selected by the research coordinator. As an added measure, participants will be instructed to remove the Fitbit study account from their device if they plan on keeping the Fitbit.

Treatment Delivery

This pilot study will use commercially-available bright-blue light therapy glasses called AYO, as well as a dim blue light therapy device developed by AYO for research purposes. The research team will have access to a dashboard that will track light therapy device used (bright/full or dim), duration, and date and time based on a generic application user ID (e.g. Northwell_001). No information that could be used to identify a participant will be stored on the AYO research web portal, nor on the AYO device itself. Only the research team will have access to data that will be able to connect a research participant to their generic AYO user ID.

Eligibility, Consent, and Survey Data

A goal of this pilot study is to help determine Minimal Viable Product (MVP) specifications for the development of a technology platform to support the delivery of Personalized Trials. To achieve this goal, we are partnering with a company (N1Thrive by 4Peacocks) that was formed specifically for the development of technology to support N-of-1 methodology. Data will be collected and stored using N1Thrive by 4Peacocks, a Northwell security-review approved system for collecting and storing research data, including PHI. The study team will have access to all data, including PHI, throughout the study. Coded data using unique generic participant IDs will be shared with 4Peacocks in order to assist with analyzing the individual reports and to pool N-of-1 results across all projects using the N1Thrive platform. Coded reports will be given back to the study team, who will identify the document before sending individualized reports to the participant via encrypted email. Pooled N-of-1 results will be used to assess gaps in phenotypic understanding to empirically determine if modeling precise therapy is feasible.

Interview Data

Qualitative data collected from phone interviews with research participants will be collected and stored via REDCap, a Northwell-approved system for collecting and storing research data, including PHI.

The study team takes data confidentiality very seriously. The participant will be made aware of all data collected and the companies/technology employed to collect the data via the consent process. All coded data will be maintained by the study team on a Northwell-approved drive to store PHI or stored in its native state in a SQL database. All members of the research team with access to identifiable and coded data will be trained and included on the IRB submission for approval. Regular meetings will take place with the PI and other members of the study team to ensure protocol adherence and data accuracy.

This research is funded by the NIH, thus a Certificate of Confidentiality has been issued for this research. Certificates of Confidentiality (CoCs) protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

Attached please find the Charter document for the Personalized Trials Pilots DSMB. Personnel, roles, and areas of expertise are listed. All voting members of the DSMB are independent of the study.

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Circumstances under which participants will be withdrawn from the research without their consent include failure to maintain protocol adherence, repeated failure to complete light therapy treatments, and self-reported adverse side effects to bright blue light or dim blue light therapy. A potential participant will not be randomized to receive the treatment protocol until he/she has demonstrated at least 80% adherence to continuous Fitbit monitoring (activity recorded > 12 hours/day, and recorded sleep activity) and response to survey questionnaires during the baseline period.

Potential participants will be notified of the possibility of being removed from the study before treatment randomization due to adherence issues in the informed consent. Participants who fail to maintain minimum adherence during baseline will be notified by the research team after 10 days of baseline participation. Participants who fail to maintain protocol adherence or who deviate from the protocol will be contacted by a member of the study team with a reminder of the study protocol, and warning that this may impact their continued study eligibility. Once a protocol deviation has been repeatedly recorded, the Principal Investigator will determine the participant's continued eligibility in the study, with consultation of the DSMB if needed. If it is determined that the participant will be withdrawn from the study, the participant will be notified by the research team via email and phone call. The participant will stop receiving notifications and survey prompts, and will be sent instructions to un-link their Fitbit device. The participant will be able to keep their Fitbit and one of the AYO light therapy devices.

Should a participant choose to withdraw from research, they will be instructed to send a letter or e-mail to the attention of the Principal Investigator at our 130 East 59th Street office, or to email personalizedtrials@northwell.edu, an e-mail account monitored by IRB-approved members of the research team. Participants will be contacted by a member of the research team confirming their study withdrawal, and to answer any questions they may have. The participant will stop receiving notification and survey prompts, and will be sent instructions to un-link their Fitbit device. Data collection will stop the business day the letter or email is received. All data up until the receipt date of the letter will be included in the research study.

Partial withdrawal, defined as study participation and data collection without the use of one of the light therapy devices will be allowed if a participant experiences an adverse events to one of the treatment options (bright blue light or dim blue light therapy). In instances where participants contact the research team with concerns about their self-reported treatment side-effects, participants will be permitted to continue their involvement in the study, should they be interested. Participant data will continue to be collected and monitored, while removing the self-reported adverse treatment option from their randomized protocol (i.e. skip the treatment days and continue with usual care). This will allow the participant to still evaluate their individual response to the self-reported non-aggravating treatment option. In the event that both treatment options create self-reported adverse events for the participant, they will be withdrawn from the study.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to results*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

This study poses low risk of physical harm to subjects. Bright blue light therapy is a mainstream treatment for fatigue symptoms. Several transient side-effects have been observed when monitoring patients including jumpiness/jitteriness, headache, and nausea, and mania has been infrequently observed in patients with bipolar disorder. These side-effects typically resolve soon after cessation of light therapy. Monitoring for adverse side-effects will be performed during the N-of-1 trial. Subjects will be encouraged to adhere to the light therapy protocol, but will also be told that they can discontinue treatment at any time.

AYO glasses have 4 Light-emitting diodes (LEDs) with a dominant wavelength of approximately 470nm ± 2nm and typical irradiance (100% intensity) of approximately 250 μW/cm². Although there are minimal direct safety standards for blue light within the United States, the photochemical blue light hazard can be evaluated based on several global standards. AYO glasses are compliant with the following: Directive 2014/30/EU (EMC) EN 55014-1:2006 + A2:2011 EN 55014-2:2015, Directive 2011/65/EU (RoHS), IEC 62321:2008, IEC 62321-3-1:2013, IEC 62321-4:2013, IEC 62321-5:2013, Radio-Equipment Directive 2014/53/EU, EN 62479:2010, EN 300328:2015, EN 301489-1:2011, EN 301489-17:2012, RoHS Directive 2011/65/EU of the European Parliament, the Council from 08/06/2011 on restriction of the use of certain hazardous substances in electrical and electronic appliances, and with the international standard and conformity assessment IEC 62471 "Photobiological safety of lamps and lamp systems."

The international standard and conformity assessment (IEC 62471) provides guidance for evaluating the photobiological safety of lamps and lamp systems, including luminaires, and specifies the exposure limits, reference measurement technique and classification scheme for the evaluation and control of photobiological hazards from all electrically powered incoherent broadband sources of optical radiation, including LEDs in the wavelength range from 200 nm through 3000 nm. IEC 62471 classifies light sources into Risk Groups 0, 1, 2 and 3 (from 0 = no risk through to 3 = high risk) and provides for cautions and warnings for consumers as needed. These risk groups are determined by spectral irradiance and radiance measured at a specified distance, spectral weighting of measurements and maximum allowed exposure time based on the hazard type. Radiance measurements are used to assess retinal exposure to radiation. Irradiance measurements are used to assess skin and the outer eye (lens and cornea) exposure to radiation. Retinal Thermal weighting is used to assess risk from localized heating of tissue and Blue Light weighting is used to assess photochemical risk to tissue. The four-tier classification structure in IEC 62471, ranging from RG0 or "Exempt" to "Risk Group (RG) 3."

RG classification of the source or luminaire is as follows: 1. A luminaire employing a light source classified RG0 or RG1 requires no warning or caution. 2. If a luminaire uses a light source from a higher risk group (RG2 or RG3), product information must indicate the mentioned RG class and include suitable warnings or cautions. In this manner, the end use product is suitably labelled if a potential risk exists. **AYO blue light glasses are in the "exempt" group (RG0) for photo-biological risk. The device does not cause photoretinits or retinal burn. In addition, AYO uses narrow band blue light at approximately 470nm, is UV and IR free, and the light prism disperses the light making the light source very diffused and not concentrated. As such, unlike laser or highly focused or intense sources of light, the AYO light is gentle to the eyes and does not reach the levels that can cause harm.** In addition, the design of the glasses is such that the LED band sits above the eye and is not directed *into* the eye. The participant

would need to direct their eyes upward in order to experience central retinal exposure to prompt a photochemical hazard.

In order to ensure participants adhere to the defined time for use/exposure and thus to ensure safety, we will have access to a dashboard that enables us to track the participants' use of the light therapy device (both bright/full or dim), duration, and date and time.

AYO light properties are within referent values of one of the most researched, direct-to-consumer, blue light products: the Philips goLiteBLU. Numerous trials using the Phillips device with human subjects have demonstrated minimal adverse effects and confirm its irradiance is much lower than what is currently recommended for light treatment. (21, 22) In comparison, the optical power projected on the eye is 300 μWatt/cm2 for the Phillips device vs 250 μWatt/cm2 for the AYO device. In addition, the Philips device operates at at 70% of the limits stated in the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines on limits of exposure to incoherent visible radiation, whereas the AYO device operates at 10.5% of the "Blue Light Hazard" limit, far from the considered critical or dangerous levels identified as a "Thermal Hazard."

Lastly, the Philips device emits a wavelength of blue light at 460 nm in comparison to AYO's wavelength of 470nm. Although the Philips device range falls within wavelengths considered "harmless," Tosini et. al confirmed "exposure to blue light in the 470–490 nm range may be less damaging to the eye compared to blue light in the 400–460 nm range...**[D]evelopment of LEDs with a peak emission of around 470–490 nm may represent an important advancement in the safety of LEDs for ocular health. Thus, LEDs with an emission peak of around 470–480 nm should be preferred** to LEDs that have an emission peak below 450 nm." (23) This wavelength range is important to note given studies have shown that peak effectiveness for a photic maculopathy (photochemical injury of the retina) occurs at approximately 435 – 440 nm. (24) See below for functional categories of the blue light spectrum comparing harmful vs healthy blue light ranges.(25)

There is also the potential risk of loss of privacy of information pertaining to research material collected by the study. Yet, we will take precautions, described below, to minimize these risks.

Treatment Adverse Events

As per the manufacturer's recommendations, individuals below 18 years old, individuals who have or had eye disease such as cataracts, glaucoma, macular degeneration or other retinal disorders, those who have had previous eye surgery, and individuals who have sensitivity to light, epilepsy, or a history of seizures will screen out for study participation. We will emphasize to subjects in the intervention arm that they can stop light therapy or withdraw from the N-of-1 trial completely at any point, particularly if they experience any concerning side-effects. Additionally,

the Principal Investigator will review any serious adverse events and these will be reported to the DSMB. All data concerning adverse outcomes will be reviewed by the DSMB at least once a year. Any serious adverse effects will also be reported to the IRB.

Loss of Confidentiality or Privacy

One risk of taking part in this study is the possibility of a loss of confidentiality or privacy. The study team plans to protect privacy by only sharing necessary information about participants to those outlined in the consent form.

All subjects will be informed that their responses are confidential and that they may refuse to participate in the project or withdraw at any time without explanation, and that such action will not affect their future interactions with their health care providers, employment, educational studies, or the research study. The risk of loss of confidentiality will be minimized by securely storing data including PHI in a Northwell-approved database and minimizing the use of PHI. To ensure confidentiality, all data containing personal identifiers, and used to track contact with patients, will be kept in a secure, password-protected, encrypted Northwell-approved database. No paper documents with personal identifiers will be kept. The PI will be responsible for ensuring that the confidentiality of the data is maintained at all times. All data will be obtained specifically for research purposes.

Personal or identifiable information is not stored on any of the devices used in this study. No information about the participants or the participants' health history will be shared with AYO or Fitbit, except for the information the participants directly share themselves should they choose to use the device for personal use at the conclusion of the study. There is no additional risk with using AYO or Fitbit as part of this research study as compared to using the device as a consumer.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

Should a participant experience an adverse event, they will be advised to contact their primary care provider. The DSMB and IRB will be notified according to timelines established in their Charter/Policy and Procedure manual. Should a participant report emotional distress in responding to survey questions, the research coordinators will refer to our Principal Investigator (a licensed clinical psychologist), who will recommend follow-up.

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

Although not a primary endpoint, participants randomized to the intervention may receive an indirect benefit, i.e. they may gain a better understanding of how bright blue light therapy personally affects them or could possibly see a positive effect on their fatigue symptoms. This may result in their being more satisfied with their fatigue treatment regimen and in achieving reduced fatigue symptoms. Through pooling N-of-1 trial data, a greater understanding of the effectiveness of bright blue light therapy will arise. Through comparing N-of-1 interventions with usual care, participation by all subjects will also contribute to the understanding of the effects of engaging fatigued patients in N-of-1 trials, and this knowledge may contribute to the incorporation of N-of-1 trials into the clinical practice of fatigue management. Additionally, the information collected from participant involvement will inform the development of future Personalized Trials to help other research participants and eventually patients discover which treatment options are best for them as an individual.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Names and email addresses from potential study participants will not be collected until participants have read through web information explaining the research study and protocol and indicated their interest in the study. This information will be stored in a Northwell-approved database store PHI, and it will only be accessible to research staff listed on the approved IRB protocol. Names or other identifying information will not be shared with those outside the research team. Phone numbers and email will only be used for study-related communications, and employees or students will only be contacted outside the study if they indicate interest in participating in a future Personalized Trial.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

This research study is funded by the National Institutes for Health (NIH). All study related devices and platforms will be provided to participants at no cost. Participant insurance will not be billed. This study uses text messaging to deliver notifications, reminders, and study questionnaires. Standard message and data rates from the participant's wireless carrier may apply to the study participant. Study participants will not be compensated for any costs related to data usage or sending or receiving text messages by the study or by members of the study team.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Study participants will receive a Clinicard valued at $100 after successful completion of this study. As a thank you, they will also be able to keep their Fitbit Charge 3 (a value of $120), and one AYO light therapy glasses device (a value of $299).

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

Consent and written authorization will be obtained electronically via the 21 CFR 11-approved N1Thrive by 4Peacocks platform, with a copy of the electronically signed form mailed to the participants along with their study instructions and devices. Before being sent a copy of the consent form, potential participants will be sent through a series of web pages that summarize

the study, as well as collect pre-screening information with written authorization. If a potential participant is deemed ineligible, or if the potential participant is eligible but needs to be waitlisted due to demand, the consenting coordinator will notify the potential participant via email within 2 business days of the initial completion date of the pre-screen. If the potential participant is deemed eligible, potential participants will schedule a 30-minute phone call to go over study details with a consenting coordinator, and have the opportunity to have any of their questions answered. After the phone call takes place, the consenting coordinator will send the potential participant text with a link to read and electronically sign the consent form. Included in this survey will be a short animated video that explains key aspects of the protocol and consent process. Included in these materials will contact information to reach a consenting coordinator to answer any additional questions before signing the consent form. In order for the consent form to be signed and submitted successfully, potential participants will need to correctly answer 4 questions about the protocol to demonstrate their understanding. PDF versions of signed consent forms will be maintained electronically on a HIPAA-compliant, Northwell Health-approved share drive, accessible only to members of the research team listed on the IRB protocol. A copy of the consent form and signed signature page will be mailed to the potential participant along with their baseline study materials.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

N/A

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*
  - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

N/A

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

This is a pilot study to assess the N-of-1 trial design and methodology for data collection and reporting to participants only, not to test an intervention designed to provide therapeutic benefit. Should we be able to collect data that supports the feasibility of such a trial design, we anticipate the methodology would be scaled to larger clinical trials designed to assess safety and/or efficacy. Non-English speaking individuals would then be included as participants in those separate studies per the principles of justice and autonomy. Exclusion of non-English speaking participants in this pilot study will not later negatively impact equitable access, participant comprehensibility or research design applicability to the diverse populations that may be solicited for participation in future clinical trials run under an N-of-1 design.

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS ☒ N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *Explain why it is not possible to conduct this research without using the information or biospecimens in an identifiable form*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

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25. WAIVER OF HIPAA AUTHORIZATION ☐ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*
- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)*

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☐ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☒ *NSLIJ Employees, residents, fellows, etc*
- ☐ *poor/uninsured*
- ☒ *Students*
- ☐ *Minorities*

☐ *Elderly*
☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

Although the study will target social media recruitment for participants, all employees of the health system will be eligible to participate in the study. Potential participants will go through online documents explaining that participation in this research will not impact their employment or standing with Northwell Health. Individuals with a supervisory relationship over an employee will not enroll any individual who reports to them in this study. Employee participation or non-participation in this study will have no bearing on an individual's position at Northwell Health.

Similarly, all students of Hofstra School of Medicine will be eligible to participate in the study. Online documentation in the consent process will explain that their participation is voluntary, and that their participation will not impact the educational enrollment or standing Hofstra University, nor have any bearing on current or future health services received from Northwell Health. Professors or supervisory staff will not enroll individuals who report to or work or study under them. Student-participation or non-participation will have no bearing on an individual's position at Hofstra University or Northwell Health.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

N/A

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

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