Feasibility Study of Personalized Trials to Improve Sleep Quality

Study Protocol and Statistical Analysis Plan

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Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Feasibility Study of Personalized Trials to Improve Sleep Quality
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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*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
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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 assess the feasibility of using N-of-1 methods in a virtual research study; to remotely recruit and enroll participants; to assess the feasibility of using a placebo and to determine the feasibility of the proposed methods used to collect and assess participant adherence and response to a wellness strategy (in this case, melatonin for poor sleep quality). 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 pilot study will assess feasibility using a Personalized Trials model to evaluate an individual participant's experience with a wellness strategy for self-reported poor sleep quality. Participants (N=60) will be sent a Fitbit device and 3 smart pill bottles, with one containing 3 mg of melatonin, one containing 0.5 mg of melatonin, and the final bottle containing a placebo pill. Participants will be asked several questions a day sent via text message about their sleep quality, as well as their stress, fatigue, concentration, confidence, mood, and pain levels to demonstrate relevant secondary impacts of sleep quality. Participants will also have access to several videos explaining the protocol. After the end of the 14-week trial, participants will receive a summary of their observed data in a personalized report. Creating this type of report will help to assess the feasibility of using a N-of-1 trial design through user-acceptability of sleep quality 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/video call if they are non-responders) and participate in a virtual interview (such as over Microsoft Teams or a phone call) 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 include device adherence, survey adherence, website and social media engagement metrics, adherence to assigned supplement during assigned week, 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 Sleep Quality as a Personalized Trial
Participant report of poor sleep quality 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 therapy response; multiple, evidenced-based treatments; and is high priority for a Personalized Trial approach as determined by previously interviewed clinicians and patients. A recent study of US workers found the prevalence of short sleep duration to be 37.6% and poor sleep quality to be 19.2%, supporting the need for innovative treatments[15]. This instance will adapt our N-of-1 trial platform to be able to deliver an experience comparing two doses of commercially available, non-prescription melatonin supplements to a placebo. This alpha-t e 8sting will enable us to expand our N-of-1 trial platform of non-pharmacologic therapies, including Complementary Alternative Medications (CAM), for future randomized trials. Of note, it is possible that future Personalized trials of over-the-counter supplements could be conducted at the direct-to-consumer level.

Rationale for Selecting Placebo as the Control Case
Without development of innovative platforms for conducting Personalized Trials, with within-participant randomization to eligible wellness management options, including when clinically appropriate, placebo pills, 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 to better

understand the uniqueness of melatonin 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 for future randomized trials.

Rationale for Selecting Melatonin as the Intervention

Melatonin is a hormone naturally produced by the body. It is a derivative of the amino acid tryptophan produced in humans and other mammals and regulates circadian rhythm and sleep-wake cycles. Exogenous melatonin supplements are widely used to treat insomnia and sleep disorders, as well as to adjust altered sleep schedules related to jet lag. Synthetic melatonin is available as a food supplement in various dosage forms such as pills[16]. Because it is categorized as a dietary supplement, synthetic melatonin is made in factories that are not regulated by the FDA. Listed doses may not be controlled or accurate. The melatonin and placebo doses provided for this study are prepared by Pure Encapsulations Laboratory, an NSF-GMP registered laboratory that exceeds USP standards for supplement manufacturing. This laboratory has a fifty-year history of producing products for clinical research and was recommended to our Center by two outside sleep disturbance researchers.

Doses of melatonin available over the counter range from 0.3mg to a maximum of 10mg, but more commonly falls within the range of 0.3mg – 3mg[17]. Our study has chosen to test two dosages: 0.5mg and 3mg vs placebo.

Since melatonin has a very low side effect profile and limited evidence of habituation and tolerance, it is widely used among people that suffer from insomnia, sleep dysregulation, and sleep disorders. Various clinical trials have been conducted proving the efficacy of exogenous melatonin in treating sleep disorders regardless of the etiology[16, 18-20]. A 2015 review on the safety of melatonin supplements indicated that only mild side effects were reported in various short-term studies that involved adults, surgical patients, and critically ill patients. Some of the mild side effects that were reported in the studies included headache, dizziness, nausea and sleepiness[21].

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 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 intervention 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 observed effect of non-prescription dietary supplements for poor sleep quality and thus the N-of-1 trial design.

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 medication adherence device technology into an N-of-1 platform.
4. Elicit participant attitudes and opinions toward participating in a single-blinded protocol with use of a placebo arm in their Personalized Trial
5. 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*

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.

Institute of Health System Science staff must meet certain eligibility criteria before assisting with this Personalized Trial pilot. All staff members must be listed on the IRB protocol submission 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 biweekly 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 are not required to reside within travelling distance of Northwell Health. Therefore, the exclusion criteria do not preclude those living outside of New York state from passing screening., but only individuals who reside in states for which the Office of Legal Affairs (OLA) has provided approval will be cleared for participation if eligible. Individuals who do not live in a cleared state will have their enrollment workflow paused and may be removed from the waitlist if their state is cleared in the future.

Potential participants will be recruited via the following avenues:

- Paid and unpaid social media advertisements targeted to individuals who meet study eligibility demographics and identify as having poor sleep quality.
- E-mail advertisement through employee and student communication channels, both including and outside of Northwell Health and Hofstra University.
- E-mail advertisement through existing email lists from those who have previously expressed interest in participation in a Personalized Trial or who have screen failed for other Institute-led research, but who have been informed their data will be retained for future research.
- Online research listings, such as the Feinstein Institutes for Medical Research clinical trials listing (https://www.northwell.edu/clinical-trials) and ClinicalTrials.gov (https://www.clinicaltrials.gov/)
- 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 poor sleep quality

Potential participants will self-identify as having a minimum threshold of poor sleep quality over the last 30 days using the Insomnia Symptom Questionnaire (ISQ), 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:
- Age ≥ 18 years
-Fluent in English
- Ability to take melatonin and a placebo
-Self-report of disrupted sleep symptoms using the Insomnia Symptom Questionnaire (ISQ)
-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
-Agreement to adhere to lifestyle considerations including wearing a Fitbit device day and night and potentially adapting their current melatonin routine to fit the protocol throughout study duration

Exclusion:
- Age < 18 years old
- Women who are pregnant or breastfeeding
- Individuals diagnosed with depression, seasonal affective disorder, schizophrenia, autoimmune disease, or asthma
- Individuals taking MAO inhibitors or corticosteroids
- Individuals diagnosed with low blood pressure
Clinical diagnosis of a sleep disorder (e.g. Narcolepsy, Circadian Rhythm Sleep-Wake Disorders, Periodic Limb Movement Disorder, Restless Leg Syndrome, Obstructive Sleep Apnea etc.)
- Deemed unable to complete the study protocol as a result of cognitive impairment, severe medical or mental illness, or active or prior substance abuse
- Participation in shift work (evening/night shifts, early morning shifts, rotating shifts, etc.)
- Pilot or flight attendant with frequent travel across time zones
- Receiving specialty mental health care for insomnia (e.g. cognitive behavioral therapy for insomnia, medications for insomnia)
- Has even been told by a doctor or healthcare provider that it is not safe to take melatonin
- Does not own or cannot regularly access a smartphone capable of receiving text messages
- Does not possess or cannot regularly access an email account
- Lives outside the United States
- Planned surgeries within 6 months from study start date

Planned travel outside the United States within participant's intervention period will be determined on a case-by-case basis so as not to exclude interested and able participants from enrolling in the study.

As stated above, only individuals who reside in states for which OLA has provided approval will be cleared for participation if eligible.

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.*

Up to 500 potential participants will be invited to enroll. Up to 60 participants will be randomized to complete research procedures.

Of those participants who receive randomized intervention schedules, 30 participants will be randomized to receive the study protocol in the following order of two-week intervention periods: 3 mg Dose Melatonin, .5 mg Dose Melatonin, Placebo, Placebo, .5 mg Dose Melatonin, 3 mg Dose Melatonin (ABCCBA). The remaining 30 participants will be randomized to receive the study protocol in the following order of two-week intervention periods: Placebo, .5 mg Dose Melatonin, 3 mg Dose Melatonin, 3 mg Dose Melatonin, .5 mg Dose Melatonin, Placebo (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 supplement is assigned, but data are collected, including self-report of sleep quality and duration and accelerometer-derived sleep and activity data. After successful completion of the baseline period, participants will be randomized to six 2-week intervention blocks of a 3mg dose melatonin, a 0.5mg dose melatonin, and a placebo. At the end of the 14 weeks, a report containing the individual's observed data will be prepared for each participant and electronically sent to them along with a satisfaction survey (electronic, or phone if they are non-responders). Creating this type of participant report will help to assess the feasibility of using a N-of-1 trial design through user-acceptability of sleep quality and wellness-related data visualizations and the ability to choose preferred intervention (if any) based on the data. This report will be sent within 3 months of study completion. A $100 pay card (ClinCard) will be sent to each participant as compensation for their time after the successful completion of 14 weeks of data collection, satisfaction survey, and return of the Nomi smart bottles to the manufacturer. After the satisfaction survey is completed, study coordinators will reach out to each participant with an invitation to virtually interview them about their experience in Personalized Trials.

Potential participants will have the opportunity to provide preferences of start dates during their enrollment process. The study team will confirm applicability of the

chosen start dates before confirming with a participants, so that no more than 20 potential participants will begin their baseline period on the same day and ever baseline period begins on a Monday. Leading up to baseline start date, participants will receive texts from the study team with instructions preparing them for the study, including setting up their Fitbit devices and reminding them of their upcoming start date. Enrollment will be ongoing until up to 60 participants have been randomized after baseline to receive a personalized trial to improve sleep quality. We estimate that the final participant will be randomized by September 30, 2022, and data collection will cease by December 31, 2022.

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 trail methodology to resolve a chronic complaint. Thus, the primary endpoint is the system usability scale (SUS) ≥ 85[22].

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 having sleep quality concerns via in-person or virtual recruitment methods will be directed to an information site with details about the pilot study. Those who are interested in participating in this pilot study will be directed to undergo a cell-phone confirmation via text and to sign a HIPAA Authorization form before completing an initial screening survey process. The HIPAA Authorization will be electronically signed via the N1Thrive by 4Peacocks platform. The initial screening process includes identifying symptoms on the validated Insomnia Symptom Questionnaire (ISQ), as well as questions pertaining to inclusion and exclusion criteria. Consenting coordinators will review these 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 given the option to set up a 30-minute phone call with a research coordinator, where the research coordinator will describe the study process and offer an additional opportunity for the potential participant to ask any questions. After completing or opting out of 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. 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 submit their signed consent form, they will receive an onboarding questionnaire to collect more information, including a home address. A Consenting Coordinator will review this information and send the potential participant a text which will include a confirmation of the start date of their baseline period, as well as a link to a short video of what to expect during onboarding to the study. They will be receive an initial study kit including a Fitbit device via mail, and will receive a copy of their electronically signed HIPAA authorization and consent form with a URL to view the informed consent video that they watched previously.

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 receive any melatonin or placebo pills during the baseline period, and they will be asked to refrain from taking any melatonin on their own. Participants will be instructed to continue treating their sleep quality issues as they normally would.

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 pain, fatigue, concentration, confidence, mood, and stress levels at that exact moment. Each morning, baseline participants will receive a survey asking a few questions about their sleep quality the previous night using a modified version of the Consensus Sleep Diary, as well as factors that may have contributed to any sleep issues. At the end of the baseline period on Sunday evening, baseline participants will receive a slightly longer survey that includes the Insomnia Severity Index.

During the baseline period, potential participants will be asked to wear their Fitbit all day and night, even while they are sleeping. Participants will be asked to download the Fitbit app to their smart phone. Baseline participants will be instructed to sync their Fitbit device by opening the Fitbit app on their phone at least every two days and to charge their device at least every four 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 greater than 180 minutes in total. Survey adherence will be defined as submission of a given survey. Baseline participants who do not achieve at least 80% adherence of Fitbit wear and survey submission during the first 10 days of the baseline period will be given until day 14 of the trial to obtain 80% adherence. Those who still do not meet 80% adherence by day 14 will be withdrawn from the study. Those participants who do maintain at least 80% adherence during the baseline period will be randomized to one of two intervention sequences in the pilot study. Participants who are randomized to receive intervention sequences will receive confirmation including their protocol timeline. Participants will also receive a second mailed kit including medication adherence devices containing pills of a 3mg dose melatonin, pills of a 0.5mg dose melatonin, and pills of a placebo. Participants will not know when they are taking 3 mg melatonin, 0.5 mg melatonin or placebo (single blinded). Enrollment will continue until up to 60 participants have been randomized overall, with 30 participants randomized to receive ABCCBA and 30 participants randomized to receive CBAABC.

Each intervention sequence is made up of 6 2-week periods assigning either 3mg dose melatonin, 0.5mg dose melatonin, or placebo. Participants will not be aware of which pill they are taking in assigned intervention weeks. Instead, they will receive a text notification each night asking them to take one pill out of a designated container (A, B, or C) 1 hour before bed. Melatonin or placebo will be tracked remotely through electronic adherence pill bottles that record each event of a pill being removed via a cellular connection to a de-identified dashboard. Throughout each intervention sequence, participants will be asked to refrain from taking additional melatonin on their own.

Melatonin and placebo supplements will be stored at the study team office from delivery until time of dispensation to participants upon their randomization into the intervention period. The supplements will be handled only by study personnel and stored according to labeling. Records of the batch numbers of supplements provided to each participant will be maintained.

During all intervention 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 message surveys each day with questions about their pain, fatigue, concentration, confidence, mood, and stress at that current moment, as well as a morning text asking them to report on their sleep quality the previous night, using a modified Consensus Sleep Diary. Morning surveys during the intervention weeks will also include questions about any melatonin or placebo-related side-effects the participant is experiencing. At the end of each intervention period on Sunday evening (every two weeks), participants will receive a slightly longer survey that includes the Insomnia Severity Index. 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 be instructed to contact 911 or go to the nearest emergency room in the event of a medical emergency. In addition, participants will be advised to stop taking their pills if they are concerned about side effects.

Participants may receive additional text messages to those outlined above with important reminders about their protocol (e.g., transition to a new intervention period), or to remind participants to sync their data or charge their devices. We will send a maximum of 5 text message surveys per day during the study, as well as text messages of these reminders and other important study communications.

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 3mg dose melatonin intervention periods (two weeks each), two 0.5mg dose melatonin intervention periods (two weeks each), and two placebo 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. Melatonin or placebo adherence tracking will be suspended, as will daily text messages and survey prompts.

We will compile the self-reported data from questionnaires, side effects, pain, fatigue, concentration, confidence, mood, and stress assessments, as well as information from the Fitbit regarding activity (steps, heart rate, flights climbed and intensity) and sleep (duration, estimated sleep stages) for each individual participant. Melatonin or placebo adherence will be tracked via a study dashboard connected to the pill bottle adherence device and will be included in the compiled data. No identifying information associated with participants will be provided to Nomi, the medication adherence device company, or included on the adherence report provided by Nomi. We will analyze this data and create a summary report of the participant's observed data over the study period, in relation to the 3mg melatonin, 0.5mg melatonin, and placebo intervention periods.

The participant will be sent this report in a secure text through the N1Thrive platform 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 after receiving their individual report. Study participation will end upon completion of the satisfaction survey.

The satisfaction survey will be sent via text up to three times before a research coordinator will attempt to call individual participants to complete the satisfaction survey via phone.

After completion of the satisfaction survey, participants will be asked to participate in a virtual interview with 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 ask for suggestions for improvement. All interviews will be audio-recorded and transcribed via Microsoft Teams (or equivalent program) to ensure full capture of information provided during the discussion. Participants will be informed that the session will be recorded prior to initiating the interview. If the participant declines to be recorded, they may still participate in the interview and the study team will take notes of the conversation. Audio and transcription files will be stored securely on the PHI-approved SharePoint server.

Participants will be provided with instructions regarding how to return the used Nomi bottles, Nomi charger, and any unused pills to the research team to be properly disposed of. The research team will return the Nomi bottles to the manufacturer for proper sanitization and disposal. Used Nomi chargers will be stored at the research office. Unused pills will be disposed of in line with FDA and Environmental Protection Agency guidelines for disposals of over the counter supplements.

Participants will be mailed a pay card (ClinCard) valued at $100 after successful completion of the satisfaction survey as well as the successful return of the used Nomi medication adherence devices to the research team.

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 sleep quality with melatonin compared to a placebo. The numbers of sleep quality reports, questionnaires, and intervention repetitions per trial were based on expert recommendations by a statistician and estimations about maximal duration of the trial to maintain patient engagement. With n=60 randomized participants, expecting a trial completion rate of 70%, we anticipate SUS data are available in

about n =42 participants, thus giving a standard error no greater than 8% in estimating the rate of SUS ≥ 85[22]. The standard error will be the largest when the trial completion rate is at 50%. Data will be reported transparently so that individual level heterogeneity can be assessed[23].

Participants will be randomized into one of two different intervention orders, ABCCBA or CBAABC, where A=3mg dose melatonin, B=.5mg dose melatonin, and C=placebo. Although participants will be aware of their randomization order (i.e. 'A' weeks, 'B' weeks, and 'C' weeks), they will be blinded to each letter's corresponding supplement or placebo until their participant summary report. Two intervention 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 single-blinded placebo intervention (i.e., no intervention) extending through 4 weeks. CBAABC was chosen as a companion intervention order to ABCCBA to test participant acceptability with starting a Personalized Trial with a single-blinded placebo after a baseline run-in (i.e., no intervention for the first 4 weeks). Intervention order was not included as a factor in the statistical analysis because this is an acceptability and feasibility study.

The randomization schedule will be set up by a member of the Institute of Health System Science data team and provided to the data analyst assigned to Personalized Trials to Improve Sleep Quality. 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 intervention 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 80% of days, and 80% sleep data ≥ 180 minutes 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. As this pilot is not blinded to study coordinators, this concealed allocation involving the data analyst alerting the study coordinator of intervention assignment will be used to prevent bias by blinding the sequence up until time of randomization.

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 secondary outcome measures which assess the feasibility of the Personalized Trials framework include:

- Mean participant satisfaction with Personalized Trials components supplemental to the SUS,
- Qualitative satisfaction data collected during the virtual participant follow-up 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 melatonin adherence rate, defined as retraction of the appropriate pill from adherence device on assigned nights
- Mean participant placebo adherence rate, defined as retraction of the appropriate pill from adherence device on assigned nights

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

- Mean Within-Subject Difference in self-reported symptoms of sleep disturbance using the Insomnia Severity Index (ISI) during 3 treatment periods from Mean Baseline
- Mean Within-Subject Difference in self-reported sleep quality using a modified version of the Consensus Sleep Diary during 3 Treatment Periods from Mean Baseline
- 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

Other exploratory analyses include:
- Google and social media 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

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 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., northwellpt25). 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.

Medication Adherence Device
We will monitor adherence to supplement/placebo using a Nomi by SMRxT real-time medication adherence system. The Nomi is a medication event monitoring system (MEMS) that tracks pill or capsule usage without active participant input. The system includes a smart bottle that sends event information such as weight changes and bottle movement via a cellular connection to the SMRxT cloud. No patient information or identifying data is stored on the device. Participants will be instructed to return their Nomi devices back to the study team to return to the manufacturer for proper destroying at the end of the study. Compliance data will be available in real-time on a de-identified study dashboard within the Nomi system. No participant information will be stored within the Nomi dashboard system, and only unique study IDs will be used to collect data. The serial number of the device and unique study ID will be linked to subjects in our Northwell secured data management system (REDCap).

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.

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 pool results across all projects using the N1Thrive platform. Pooled results will be used to assess gaps in. This analysis will be done by unique identifier. Coded reports will be given back to the study team, who will identify the document before sending to the participant via encrypted messaging.

Interview Data

Qualitative data collected from 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. Data collected for this research will be maintained on a HIPAA-compliant Northwell-approved 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. Data collected for this study will be maintained in its original and unaltered source data state in a Northwell-approved SQL database 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. Any additional data that must be shared will be done so according to the consent form participants signed. Only research staff listed within this IRB submission will have access to identifiable information. Anonymized data may be stored indefinitely for reference following the conclusion of the study. The participant will be made aware of all data collected in the consenting process.

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 may be withdrawn from the research without their consent include failure to maintain protocol adherence, ,self-reported

adverse side effects to two or more interventions, significant cell phone carrier issues that prevent the participant from receiving study text messages, it is not in the participant's best interest to continue in the pilot, and the pilot study is stopped. We will not withdraw a participant based on non-adherence to wearing their Fitbit, taking their supplement, or completing daily surveys, as this absence of data is useful for feasibility purposes. Because of this, lack of adherence to Fitbit wear, taking the supplements, or completion of daily surveys are not considered protocol deviations.

A potential participant will not be randomized to receive the intervention 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 intervention 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 in the first 10-14 days of baseline participation. These participants will stop receiving notifications and survey prompts and will receive instructions to un-link their Fitbit device. The participant will be able to keep their Fitbit.

Participants who fail to maintain protocol during the intervention period will be contacted by a member of the study team with a reminder of the study protocol and will be informed that this may impact their continued study eligibility. Once a protocol deviation has been repeated, 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 of their withdrawal from the study by the research team via text message. 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 device. The participant will be asked to return their 3 Nomi pill bottles, the Nomi charger, and any unused pills to the study team, as they would at regular study end.

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 the participant may have. The participant will stop receiving notification and survey prompts and will be sent instructions to un-link their Fitbit device. They will be able to keep their Fitbit device. Data collection will stop the business day the letter or e-mail is received. All data up until the receipt

date of the letter or e-mail will be included in the research study. The participant will be asked to return their 3 Nomi pill bottles, the Nomi charger, and any unused pills to the study team, as they would at regular study end.

Partial withdrawal, defined as study participation and data collection without the use of one of the melatonin/placebo supplements will be allowed if a participant experiences an adverse event to one of the intervention options (3mg dose melatonin, 0.5mg dose melatonin, or placebo). In instances where participants contact the research team to self-report serious side-effects or otherwise contact the research team with concerns about their self-reported 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 intervention option from their randomized protocol (i.e. skip the intervention days and continue with placebo and/or other intervention). This will allow the participant to still evaluate their individual response to the self-reported non-aggravating intervention option. In the event that both intervention options create self-reported adverse events for the participant, they will be withdrawn from the study.

Participants who are deemed ineligible and removed from the study during the intervention period (but not the baseline period) and participants who are withdrawn from the study will still be asked to complete the end-of-study satisfaction survey and follow-up interview. These participants will not receive a personalized participant report, and therefore the questions asked in the satisfaction survey and follow-up interview will be abbreviated (will not include the approved questions about the participant report asked of other participants).

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 no greater than minimal risk to subjects. Monitoring for adverse side-effects will be performed during the N-of-1 trial. Subjects will be encouraged to adhere to the supplement protocol, but will also be told that they can discontinue intervention at any time.

Melatonin was selected for this study as a minimal-risk sleep quality intervention option that has been shown to be a safe and effective option for many people. Some people, however, may experience mild side effects from melatonin. The most common side effects are headache, dizziness, nausea and sleepiness[21]. Less common side effects include short-lasting feelings of depression, mild tremor, mild anxiety, abdominal cramps, irritability, reduced alertness, confusion or disorientation, and abnormally low blood pressure. There is a chance that participants could experience these side effects, however the chances are low given the duration and dosing proposed for this research[24, 25]. Participants will be advised to neither drive nor operate heavy machinery within 5 hours of taking their nightly supplement. Participants will only be advised to take melatonin one hour before their bedtime. Study participants document side effects daily and may withdraw from the study at any time without consequence should these side effects be viewed as bothersome.

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.

Melatonin Adverse Events
As per the manufacturer's recommendations, individuals who are pregnant or lactating, or taking MAO inhibitors or corticosteroids will be screened out, as well as those with depression, seasonal affective disorder, schizophrenia, autoimmune disease, and asthma to avoid contraindications. Potential participants with these conditions will screen out of the study.

We will emphasize to subjects in the intervention arm that they can stop taking supplements or withdraw from the N-of-1 trial completely at any point, particularly if they experience any concerning side-effects. Participants will be instructed to contact 911 or go to the nearest emergency room in the event of a medical emergency. 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.

Surveys
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.

Fitbit
There is no additional risk with using a Fitbit activity monitor for research as compared to using the device as a consumer, including mild skin irritation (i.e. contact dermatitis) which occurs among a small proportion of users. Participants will be instructed via the consent form on methods to reduce irritation (e.g. keep

the band clean and dry) and that they can remove the band for a short period of time.

Loss of Confidentiality or Privacy
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 Nomi 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 Nomi 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.*

Research-related injuries are not expected for this no greater than minimal risk project.

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 melatonin personally affects them or could possibly see a positive effect on their sleep disturbance symptoms. This may result in their being more satisfied with their sleep quality wellness regimen and in achieving reduced sleep disturbance symptoms. Through pooling N-of-1 trial data, a greater understanding of the effectiveness of melatonin will arise. Through comparing N-of-1 interventions with usual care (during the baseline run-in and placebo periods), participation by all subjects will also contribute to the understanding of the effects of engaging patients with sleep quality issues in N-of-1 trials, and this knowledge may contribute to the incorporation of N-of-1 trials into the clinical practice of sleep quality 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 wellness 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 they 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 drive to 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, except as indicated in the "Data Management and Confidentiality" section above for the purposes of sending research communications. Phone numbers and email will only be used for study-related communications, and employees will be contacted outside the study for future research opportunities only as indicated in the consent document.

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 equipment, devices, supplements, and placebos 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 ClinCard valued at $100 after successful completion of the study. As a thank you, participants will also be able to keep the Fitbit device.

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 N1Thrive by 4Peacocks platform, with a copy of the electronically signed form sent to the participants 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 prospective 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 text within 2 business days of the initial completion date of the pre-screen.

If the potential participant is deemed eligible, potential participants will opt in or out of having a 30-minute virtual 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 a text with a link to read and electronically sign the consent form. If the participant opts out of having the call, they will be sent a link to read and electronically sign the consent form. Included at the link sent to participants who opted in and out of the call will be a short, animated video that explains key aspects of the protocol and consent process. Included in these materials will be contact information to reach a consenting coordinator to answer any additional questions they have 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 sent to the potential participant along with their baseline study material.

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*

Our goal for this research is to test virtual research delivery capabilities for the digital health technology used for this specific use case. While there may be some personal benefit derived, the study is not designed to seek out or document any specific benefit, and our primary outcome measure is devoid of such calculation. We are focused on soliciting feedback from participants on the ease of platform use, if the research delivery was satisfactory, if the participant report was deemed useful, etc. In the future, it will be especially important to obtain this feedback from individuals who are non-English speaking, and the intention once we document minimum use requirements, acceptability, and proof of greater effectiveness over traditional research methods through our project's forthcoming RCT, is to seek funding so that we can work with N-1 Thrive to build virtual delivery capabilities that are fit-for-purpose in research involving individuals who are non-native English speakers. Having a platform capable of accurately displaying research requirements and study related material is especially important for speakers whose language involves characters that may not be easily displayed electronically or may introduce formatting errors. We aim to be transparent that further research is needed to assess feasibility in the

same delivery with non-English speaking individuals. Presently we hope to collect enough information to justify that this methodology offers greater benefit than standard RCT delivery to make the case that more significant financial investment should be made to have the platform scaled to larger clinical trials designed to assess safety and/or efficacy of the given interventions (e.g. melatonin). Injustice has no place in research with human subjects and undermines public trust in science, thus we are committed to enrolling a racially and ethnically diverse population in this protocol and for all research conducted by the Institute for Health System Science. Towards that commitment, we anticipate that many participants interested in this current research project will represent racial and ethnic minority groups, and we intend to advertise the research without restriction. Race and ethnicity (not just English proficiency) are strongly correlated with access to care, environmental exposures, income, employment, and other social determinants of health, which, by definition, affect health outcomes. We will collect information on all of these factors to help inform virtual research delivery and do not believe that focusing on native English speaking participants in this pilot study - those that may be from ethnically and racially diverse populations - will confirm pre-existing bias or will 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. We would be happy to further discuss considerations for equality in research and ways we as researchers and ethics professionals can address bias and structural injustices.

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.*

Since the consent process will be remote and self-directed, it is not practicable or feasible for the investigator to sign the consent form in N1Thrive or RedCap. As such, we request a waiver of the investigator's signature for this research which is no greater than minimal risk. Individuals are encouraged to reach out to the

study team via email and/or a direct phone line if they have any questions and prior to signing the consent form.

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.

This study is not targeting employees or students. However, all employees of the health system, as well as graduates and students of Hofstra University are eligible to participate in the study Northwell Health has the most diverse employee workforce in the state of New York and it services a vast number of individuals from racial and ethnic minority groups. Hofstra University also has a significant number of students

who identify as racial/ethnic minorities. As such, we expect a diverse subject population.

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, 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.

We do not intend to prevent study personnel or other employees of theInstitute of Health System Science who express an interest in the research from participating. However, no supervisory personnel will be able to enroll participants who report to them in this research. We are not intentionally targeting minorities, but expect minorities to be part of those eligible for participation.

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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