Personalized Trials for Stress Management Against Standard of Care
NCT05408832
Version Date: 9/14/2022

Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Personalized Trials for Stress Management Against Standard of Care
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Date Revised:	9/14/22
IRB Number:	21-0968-MRB

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.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
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- Start by entering study information into the table above, according to these rules:
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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 study is to determine if an N-of-1 study design, or what we are terming "Personalized Trials" can improve health outcomes over standard practice for common stress management techniques. This study is an expansion on lessons learned from three feasibility pilots (19-0672, 20-0230, and 20-0835) of methods to remotely implement Personalized Trials.

This study uses three different stress management interventions to improve individual self-report of perceived stress: guided mindfulness meditation, guided yoga, and guided brisk walking. Arm 1 (n=53) and Arm 2 (n=53) of the trial will deliver the interventions using a Personalized Trial format. Participants in Arm 3 of the trial (N=106) will be offered the same number of interventions, but will not be required to follow the established N-of-1 Personalized Trials framework. Participants in all arms of the study will be asked to respond to surveys daily and to wear a Fitbit device. Interventions will be delivered by virtual link to an online video or audio recorded by an experienced Zeel wellness provider. Zeel is the company that we have asked to provide the interventions for this research. It is a commercial company that provides in-home or in-office services (such as stretching or yoga). The company has been contracted to create these videos of the services they provide for our use in the research. At the end of their Personalized Trial, participants in Arms 1 and 2 will receive a summarized report of their observed Fitbit and survey data and will be asked to select which stress management intervention they would like to continue with (after 12 weeks of intervention tracking and data collection). Participants in Arm 3 will also receive a report with summarized Fitbit and survey data and be asked to select which stress management technique they would like to continue with in the same timeframe

(after 12 weeks of intervention tracking and data collection). Both arms will receive 2 additional weeks of the stress management intervention of their choosing, while continuing to answer daily assessments and wear a Fitbit device. At the end of the study, all participants will be sent a satisfaction survey. Participants will be asked to participate in a qualitative interview to discuss their experiences until a random sample of 10% from each arm is achieved.

With the popularity and accessibility of new technologies, and with the ability to process large data sets in a short period of time, we believe Personalized Trials are feasible to scale to clinical practice. Data collected to support our hypothesis include changes in Perceived Stress Scale two-weeks post intervention selection, adherence to Personalized Trial protocol components, adherence to interventions pre- and post-treatment decision, agreement between the Personalized Trial report and participant treatment selection, and satisfaction based on qualitative interviews and surveys.

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 the RCT 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 Stress Management as a Personalized Trial
Participant report of perceived stress 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 survey of 3,617 adults found that on a scale of 1 to 10, Americans reported their average stress level as 4.9, while also reporting that a healthy stress level is on average 3.8[15]. Prior studies examining the effects of mindfulness meditation, yoga, and physical activity for stress reduction found all three intervention types were associated with significant reductions in self-reported measures of stress and/or physiological measures of stress[16-19]. However, stress reduction interventions often have high levels of heterogeneity in treatment effects, indicating that not every intervention will provide uniform benefits for all patients. Very little information exists on determining which treatment will be most effective for stress reduction in an individual patient. As

personalized medicine approaches to treat depression, it is reasonable to utilize the same methods for stress treatment[20].

This instance will adapt our N-of-1 trial platform to comparing three stress interventions to standard of care.

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 incorporation of N-of-1 methodology through Personalized Trials will offer improved health outcomes over current standard clinical practice.

Thus, the goals of this study are to:
1. Conduct an RCT (N=212) of a Personalized Trial against standard practice that is delivered remotely to participants in the United States.
2. Analyze how changes in participant's perceived stress may differ from baseline after receiving the opportunity to test out three evidence-based stress management techniques in a Personalized Trial or standard practice format.
3. Analyze how a participant's personal wellness strategy may be impacted by the customized data report they receive in a Personalized Trial.
4. Incorporate lessons learned from previous pilots of Personalized Trials, including minimum viable product specifications for a technology platform to deliver Personalized Trials, and assess additional requirements to deliver a randomized controlled trial.
5. Elicit participant attitudes and opinions toward using Personalized Trials to help inform their personal wellness strategy.

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 results across all projects using the N1Thrive platform.

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*

The study team is experienced with recruiting within the Northwell employee, graduate student and patient networks, and has recently conducted a study of over 900 enrolled participants. The size of these expansive networks provides adequate opportunity for the enrollment of the projected sample size for this research and also ensures that adequate diversity in subject population may be achieved.

All individuals on the study team will be required to attend mandatory biweekly meetings with the PI and project manager to discuss the study protocol, timelines, and issues as they come up in real-time. Additionally, all consenting coordinators will be trained in the operating procedures of this study by the study clinical research supervisor.

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*

Potential participants will primarily be individuals who are current or past participants in research managed or conducted by the Center for Personalized Health. Current or past participants will be contacted via email notification to invite them to participate.

Study staff are experienced with utilizing the Northwell system's vast electronic communication tools including weekly newsletters, E-blasts and social media (Northwell Facebook Group) forums. We will access similar electronic communications that serve Hofstra University programs. Additionally, a recruitment flyer will be posted on the Personalized Trials web page.

However, 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 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 also be recruited via

- Paid and unpaid social media advertisements targeted to individuals who meet study eligibility demographics and identify as having stress

- 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 stress

Interested participants will pre-screen using an electronic survey to determine potential eligibility. If the pre-screen and longer screen surveys deem the potential participant as possibly eligible, they will be allowed to continue with the consent process.

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.*

We aim to recruit a diverse pool of participants with varied ethnic and racial backgrounds. We estimate about 70% will be female and 30% will be male.

Inclusion:
- Age ≥ 18 years
- English speaking
- Self-report of perceived stress raw score of 20 or higher using the Perceived Stress Scale (PSS)
- Owns and can regularly access a smartphone capable of receiving text messages and accessing the internet
- Can regularly wear a Fitbit device
- Lives in the United States

Exclusion:
- Women who are pregnant
- Does not speak English
- Does not own or cannot regularly access a smartphone capable of receiving text messages
- Cannot regularly wear a Fitbit device

- Deemed unable to complete the study protocol as a result of cognitive impairment, severe medical or mental illness, or active or prior substance abuse
- Planned surgeries 6 months from study start date
- Individuals who have been previously told by a doctor to not engage in brisk walking 30 minutes, three times per week
- Individuals who have been previously told by a doctor to not engage in yoga
- Does not own or cannot regularly access a smartphone capable of receiving text messages
-
- Lives outside 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.*

For this research, we will enroll up to 1000 individuals with the goal of randomizing 212 individuals total in study arms 1, 2, and 3 (53 in Arm 1, 53 in Arm 2 & 106 in Arm 3).

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 18 weeks. The first 2 weeks will be a run-in period, where no stress management interventions are given, but data are collected, including daily surveys and Fitbit-derived sleep and activity data. Those who are deemed eligible will be randomized to receive 12-weeks of a Personalized Trial or standard care experience, where they will have the opportunity to test 3 different stress management techniques while continuing to answer daily assessments and wearing their Fitbit device. At the end of the 12 weeks, participants will continue to answer daily surveys and wear their Fitbit device for 2 weeks with no provided intervention while the study team creates a report containing the individual's observed data. This report will be sent to each participant in all arms, and participants will have the opportunity to select one stress management technique to continue with for 2 additional weeks. After selection, participants will receive six additional sessions of their chosen treatment and will be observed for engagement in these additional wellness sessions. Participants will also be asked to complete daily survey assessments and Fitbit

wear for these two additional weeks. At the end of the 18-week study, a final survey will be sent assessing satisfaction with the study. A random sample of 10% of participants from each arm will be asked to participate in a qualitative interview to discuss their experiences.

Potential participants will have the opportunity to choose from within a provided list of start dates during their enrollment process. Enrollment will be ongoing until up to 53 participants have been randomized into Arm 1, 53 participants have been randomized into Arm 2, and 106 participants have been randomized into Arm 3 of the study. We estimate that the final participant will be randomized by January 31, 2023, and data collection will cease by May 31, 2023.

10. ENDPOINTS

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

The primary endpoint of this study is change in average daily perceived stress, assessed using ecological momentary assessment (EMA), two-weeks post treatment selection compared to baseline assessment.

Secondary endpoints include:
-Change in perceived stress, assessed using the Perceived Stress Scale, two-weeks post treatment selection compared to baseline assessment.
-Agreement between the Personalized Trial report and participant treatment selection
-Adherence to interventions pre- and post-treatment decision
-Usability of personalized trials based on the System Usability Scale
-Satisfaction based on qualitative interviews and surveys
-Changes in daily EMA between stress management interventions
-Changes in perceived stress, assessed using the Perceived Stress Scale, between stress management interventions

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 stress management concerns via virtual recruitment methods will be directed to an information screen with details about the study. Those who are interested in participating in this study will be directed to an initial pre-screening survey that collects contact information and their date of birth. If eligible according to prescreen, interested participants will then provide written (electronic) authorization prior to completion of the full screening survey. The screening survey includes identifying symptoms via the validated Perceived Stress Scale (PSS), as well as other questions pertaining to inclusion and exclusion criteria. If eligible, those interested in participating will be given the opportunity to provide written (electronic) consent. Once effective informed consent has been obtained, participants will receive an onboarding questionnaire to collect additional information needed to proceed to the baseline period.

A Consenting Coordinator will confirm the start date of each participant's baseline period and direct the participant to view short informational videos of what to expect during the study run-in period. Participants who do not report having their own Fitbit device that is acceptable for this study will be provided a new device before their start date to ensure equitable subject enrollment. Acceptable devices at this time are the Fitbit Sense, Fitbit Versa 3, Fitbit Charge 5, Fitbit Charge 4, Fitbit Luxe, and Fitbit Inspire 2, though new device models released by Fitbit in the future will be considered. These devices were specifically selected because they all accurately collect the data (ex: sleep stage data, heart rate, etc.) needed to analyze observed Fitbit data for participant's personalized reports. It has been our experience that participants have repeatedly requested to use their own Fitbit device during participation in our research (either a device they have personally purchased outside of the context of the research, or one they have been provisioned through prior research participation). We do not intend to deny participation to individuals who request to use their own device, and likewise do not intend to deny participation to individuals who report they do not have a Fitbit device that can be used in this research. All participants (those who request to use their own device and those who are provisioned a device) will be instructed on how to sign into the Fitbit app with a coded study ID. All baseline periods will begin on a Monday.

The baseline period will take place over the course of 2-weeks. Potential participants will not receive any stress interventions during the baseline period and will be instructed to continue managing their stress 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. At participant's preferred evening time identified by the potential participant during their onboarding survey, baseline participants will receive a text message survey asking them to report if they did anything to relieve their stress that day, and report any experienced side effects

they attribute to that activity. At the end of each week on Sunday evenings, participants will receive a slightly longer survey that includes the modified PSS-10.

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, and to charge their Fitbit device as needed.
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 or equal to 12 hours a day and recorded sleeping activity. Survey adherence will be defined as submission of a given survey, including EMAs. 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 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 that maintain at least 80% adherence during the baseline period will be randomized to one of three study arms. Participants who are randomized will receive confirmation including their protocol timeline (for Arms 1 and 2, the timeline will outline their intervention sequence, or randomization). Participants will also receive additional video instruction and information on how to view upcoming mindfulness meditation videos, yoga videos, or brisk walking audio tracks. Enrollment will continue until up to 53 participants have been randomized into Arm 1, up to 53 participants have been randomized into Arm 2, and up to106 participants have been randomized into Arm 3.

In Arm 1 (n=53), participants will receive a Personalized Trial of the 3 stress management interventions in an ABCCBA treatment order, where A=mindfulness meditation, B=yoga, and C=brisk walking. Participants in this arm will be prompted to complete 30-minute stress management sessions during applicable treatment weeks. Participants will be limited to three views of study-provided stress management content each week.

In Arm 2 (n=53), participants will receive a Personalized Trial of the 3 stress management interventions in a CBAABC treatment order, where A=mindfulness meditation, B=yoga, and C=brisk walking. Participants in this arm will be prompted to complete 30-minute stress management sessions during applicable treatment weeks. Participants will be limited to three views of the study-provided stress management content each week.

In Arm 3 (n=106), participants will receive Standard Care of the 3 stress management techniques (mindfulness meditation, yoga, and brisk walking). Participants will receive access to the same number of views of the mindfulness meditation, yoga, and brisk walking content given to participants randomized in Arm 1 and Arm 2, however they will not be prompted to complete any session according to a randomization sequence. Participants will be limited to 36 total views of study-provided stress management content.

During all intervention weeks (12 weeks total) all 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 pain, fatigue, concentration, confidence, mood, and stress at that current moment, as well as an evening text asking them to report if they did anything to relieve their stress that day, and report any experienced side effects they attribute to that activity. At the end of each week on Sunday evenings, participants will receive a slightly longer survey that includes the PSS-10. A study phone number will be available as part of each survey to contact the study team.

After 12 weeks of participants receiving the opportunity to complete mindfulness meditation, yoga, and brisk walking content for stress management, participants will continue to answer the same daily and weekly surveys they received during the intervention periodand wear their Fitbit device for 2 weeks, but participants will not receive any additional stress management content during that time to allow for a personalized report of their observed data to be generated.

Once an individualized report has been generated, participants in all study arms will receive a copy of their observed data. Participants in Arm 1 and Arm 2 will receive a Personalized Trial report with insight into their tracked outcomes during each treatment order in the study. Participants in Arm 3 of the study will receive a Standard Care report with summarized data collected. Each participant, regardless of study arm, will be asked to select one stress management technique that they would like to continue with. Based on their selection, participants will receive another 6 sessions of stress management content (e.g. if yoga is selected, participants will receive 6 additional views of the yoga content). Participants will be observed for 2 weeks, and will have access to the additional stress management content monitored by the study team.

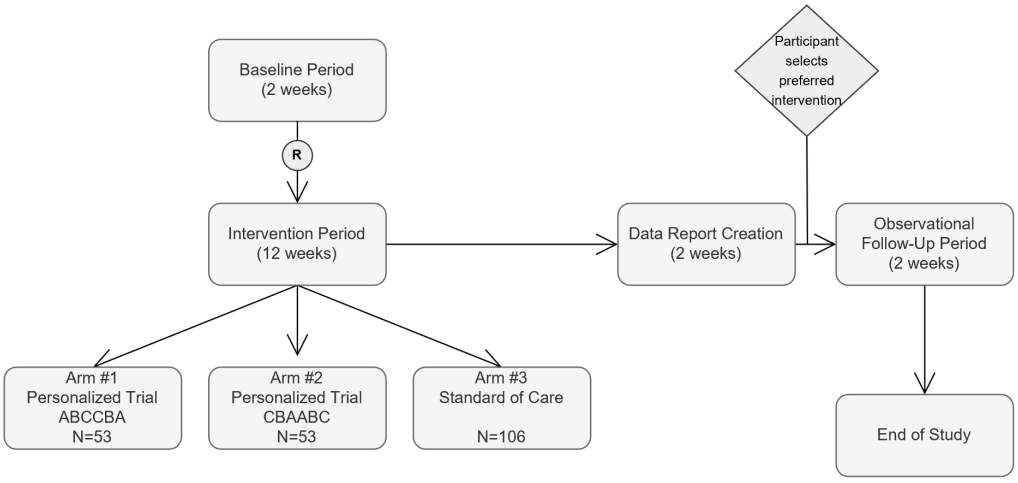

Figure 1: Study Design; For Arm #1 and Arm #2 A=mindfulness meditation, B=yoga, and C=brisk walking.

During the observational follow-up period, participants will be asked to continue wearing their Fitbit device each day and night. They will continue to receive the daily and weekly surveys they received during the intervention period. A study phone number will be available as part of each survey to contact the study team.

At the end of the 2-week observational follow-up period, participants will be given a PSS post-assessment and satisfaction survey, which will be delivered by secure messaging, phone or video conference) as per participant preference.

Participation in the study will end upon completion of the post-PSS assessment and the satisfaction survey. 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. Treatment adherence tracking will be suspended, as will daily text messages and survey prompts.

A random sample of 10% of participants from each arm will be asked to participate in a qualitative interview to discuss their experiences. Selected participants will be sent a link to share their availability for a session with a consenting coordinator(s) held via video conference. On the rare chance that a participant cannot meet via video conference, we will hold the interview via phone call. The interview will last approximately 60 minutes. 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 may receive additional text messages to those outlined above with important reminders about their protocol (e.g. transition to a new treatment period). We will send a maximum of 7 text messages per day during the study, unless there are issues with participant's data (battery/sync, etc.).

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.

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.*

Primary Hypothesis: Participants assigned to Arm 1 and Arm 2 (the personalized trial arms) will demonstrate a greater reduction in the average momentary stress from baseline (run-in) to two weeks after treatment selection, when compared to Arm 3 (the standard of care arm).

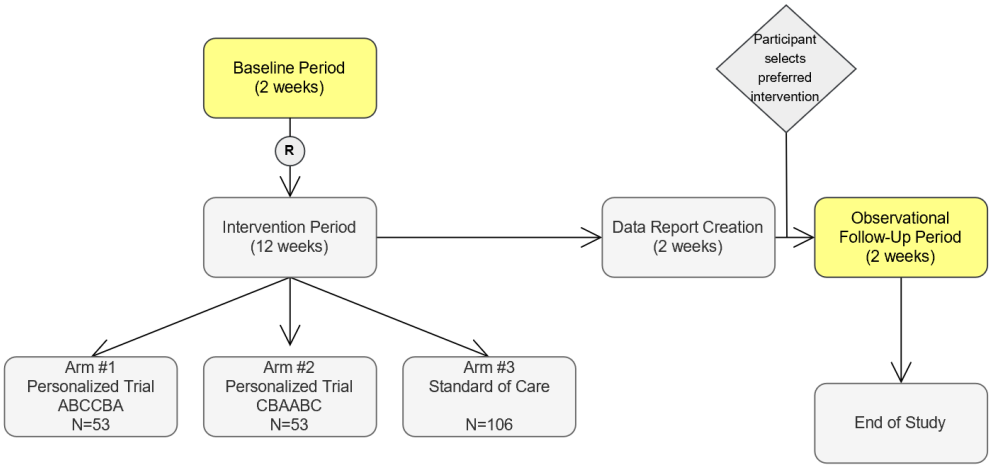

Figure 2: Hypothesized change in average momentary stress; For Arm #1 and Arm #2 A=mindfulness meditation, B=yoga, and C=brisk walking.

The primary outcome for the current study is change in average momentary stress from baseline (run-in) to two weeks after treatment selection. To test the corresponding hypothesis using two-sample t-test comparing personalized trials arms (n = 84) and the standard care arm (n = 84) with 80% power and 5% significance (two-sided). The effect size is 0.307

While the sample size is determined in accordance with the Primary Hypothesis, the power for detecting a difference in average momentary stress is 80%. The effect sizes are obtained from the findings of a pilot study (Protocol # 19-0672). To achieve a total 168 participants with complete data, under an assumed 20% attrition, we anticipate randomizing up to 212 participants total (n=106 in the personalized trial arms and n=106 in a standard care arm).

All other hypotheses and outcome measures will be secondary to this study, including:

- Change in mean within-subject difference in weekly Perceived Stress, using modified 10-item Perceived Stress Scale (PSS-10) between baseline (run-in) to two weeks after treatment selection.

- The proportion of participants in the personalized trial arm who select the treatment during follow-up recommended by their Personalized Trial report.
- Mean scores on the System Usability Scale (SUS), a validated 10-item questionnaire[21-22].
- Mean participant satisfaction with Personalized Trials components supplemental to the SUS.
- 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[23]
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Fatigue During 3 Treatment Periods from Mean Baseline
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Concentration During 3 Treatment Periods from Mean Baseline
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Confidence During 3 Treatment Periods from Mean Baseline
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Mood During 3 Treatment Periods from Mean Baseline
- Mean Within-Subject Difference in Ecological Momentary Assessment Three-Times-Daily of Stress During 3 Treatment Periods from Mean Baseline,
- 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
- Change in mean within-subject difference in weekly Perceived Stress, using modified 10-item Perceived Stress Scale (PSS-10) between 3 Treatment Periods
- 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 personalized trial intervention adherence rate, defined as a unique video views of the appropriate recorded intervention during assigned interventions
- Mean participant standard care intervention adherence rate, defined as a unique video views of the available recorded interventions

- Mean participant selection adherence rate, defined as unique video views of the selected intervention video during the follow-up period
- Descriptive content analysis of audio-recorded and transcribed qualitative interview data

As participants will not be receiving stress management interventions every day, we do not assume that meditation mindfulness, yoga, and walking will have long-lasting effects; therefore no washout period has been considered between each stress management intervention.

Quantitative Intelligence (expert group of quantitative scientists, data scientists, clinical informatics specialists and staff) will provide services such as randomization, data analytics, cleaning, etc. These individuals are not considered study personnel.

Randomization will be done in blocks of 8 with arms A (personalized arm n=53), B (personalized arm n=53), and C (usual care n=106) with randomization ratio of 1:1:2. The last block of patients will occur in a block of 4. The order in which an individual becomes eligible for one of these 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 and Fitbit wear ≥ 12 hours a day during the baseline run-in period. A member of Quantitative Intelligence will alert the research coordinator of the assigned randomization once a participant becomes eligible during the baseline run-in period.

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 study will use personally-owned (or provided if necessary) 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 and participants will be instructed on how to exit their personal account to access the study account. The email address of the study account contains a unique identifier (e.g. northwellstudy25). Data collected will include daily steps, heart rate, floors climbed, activity, intensity, sleep duration, estimated minutes in sleep stages, and battery charge status, last sync date. 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. Data collected from Fitbit wear will remain stored in a Northwell-approved drive indefinitely.

Fitabase
This 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, heart rate, 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.

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.

Video Adherence Data
Zeel is a commercial company that provides in-home or in-office services (such as stretching or yoga). The company has been contracted to create these videos of the services they provide for our use in the research. No individual level data, nor any research data will be shared with Zeel. Recorded video and audio stress management content will be stored on a commercial website, Vimeo. No information that could be used to identify a participant will be stored on Vimeo. Participants will be provided with a link and password to access their stress

management content, and will not be asked to provide any personal identifying information. Data collected will include views, unique viewers, video finishes, video impressions, percentage/minutes of videos watched, views by device type, views by source URL, views by region, and date video was viewed. See confirmation from Vimeo that IP address or other identifying information is not collected.

Survey Data

Survey data will be collected by 4Peacocks/N1Thrive, a company that was formed specifically for the development of technology to support N-of-1 methodology. Additional study data will be collected and stored using the Northwell REDCap system. Coded data using unique generic participant IDs will be shared with 4Peacocks in order to assist with analyzing the individual reports and to pool 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 message or email. Pooled results will be used to assess gaps in phenotypic understanding to empirically determine if modeling precise therapy is feasible.

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.

A limited data set (ie. dates such as dates associated with research procedures, date of birth, city, state, five digit or more zip code; and ages in years, months or days or hour) may be provided to IHSS faculty for cohort analyses and/or for future research. These individuals will be unable to readily ascertain the identity of the subjects to whom the coded information pertain because they have entered into an agreement with the Principal Investigator prohibiting the release of the key to those

individuals under any circumstances, or unless they are added as research personnel to this protocol. These individuals are not considered integral nor engaged in the research and thus are not listed as study personnel.

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. As per the charter, the DSMB will meet at least once a year to review the research. 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 follow study protocol, self-reported adverse side effects to two or more treatments, it is not in the participant's best interest to continue on this study, and the study has stopped. We will not withdraw a participant based on non-adherence to wearing their Fitbit, completing their interventions, or completing daily surveys, as this absence of data is useful for feasibility purposes. Because of this, lack of adherence to Fitbit wear, completing interventions, or completion of daily surveys are not considered protocol deviations.

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 document. Participants who fail to maintain minimum adherence during baseline will be notified by the research team after 14 days of baseline participation. Participants who fail to maintain protocol adherence during the intervention period will be contacted by a member of the study team with a reminder of the study protocol.
Should a participant choose to withdraw from research, they will be instructed email or securely message the study team to withdraw. 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 email is received. All data up until the receipt date of the letter will be included in the research study.

Partial withdrawal with continued data collection will be permitted on a case by case basis if a participant experiences an adverse event to one of the intervention options and chooses to stop receiving that intervention. 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 usual care). This will allow the participant to still evaluate their individual response to the self-reported non-aggravating treatment option.

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.

Intervention Adverse Events

Mindfulness meditation, yoga and brisk walking have been shown to be safe and effective stress management options for many people. Some people, however, may experience mild physical side effects from yoga and/or brisk walking. The most common side effect is feeling sore 1-2 days after treatment. This should be a minor discomfort and temporary. Mindfulness meditation may include experiences that are pleasant, unpleasant, or neutral. It can lead to states of ease, joy, relaxation, peace and a sense of wellbeing. Unpleasant experiences such as agitation, physical discomfort, sleepiness, sadness and anger are also common. Such experiences are usually temporary.

If participants experience discomfort during their treatment sessions, they will be instructed to immediately stop the activity and contact a research coordinator.

Surveys

Survey questions may make a participant feel uncomfortable. 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.

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.

Participants who are experiencing anxiety or side effects related to study participation may withdraw from the study without negative consequences. Participants have access to study coordinators via email, secure messaging, and cellular phone should they be concerned about their symptoms, and will be referred to their primary care provider should they express continued concern.

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*

Participants may or may not receive any direct benefit from participation in this research. Sometimes yoga and brisk walking increase a participant's chance of being healthier, and mindfulness meditation can sometimes result in pleasant experiences. Although participants may not experience any personal, physical benefit from participation, there is a chance that participation in this study may help them better understand their individual response to different stress interventions so that they can learn how to manage stress.

This may result in their being more satisfied with their stress management regimen and in achieving reduced feelings of stress. Through pooling N-of-1 trial data, a greater understanding of the effectiveness of mindfulness meditation, yoga, and brisk walking will arise. 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).*

Recruitment links will lead to a study web page with more information about study requirements, eligibility, and who to contact for more information. Interested individuals will then sign authorization to undergo brief screening to assess if they are eligible for participation, after which they will sign consent via a HIPAA compliant Northwell Health approved electronic platform. Individuals may call the research team at any time to ask questions prior to signing consent. Should this occur, research personnel will ensure that the individual is in a private location for open conversation to protect the privacy interests of the individual. All study-related communications will be delivered via a secure, NWH email or via the NWH approved e-platform.

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, services, and devices 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.*

All participants who are randomized into the study will be eligible for a weekly lottery of $100. If the participant selected has maintained at least 80% adherence to survey responses and Fitbit wear for that week, they will be given a $100 Clincard. If the selected participant has not maintained at least 80% adherence, they will be advised to try again the following week. Although not likely, a participant can potentially be selected for the weekly lottery up to 12 times totaling $1200. Separate secure messaging notifications will be sent each week (see attached study related document).

Participants who are invited to participate in a qualitative interview with a consenting coordinator(s) and who complete this qualitative interview will be given a $25 Clincard.

For participants who do not report having their own Fitbit device that is acceptable for this study, or if a participant's personal Fitbit device malfunctions or breaks, the study will replace the participant's device at no charge. Participants will be allowed to keep devices provisioned at the end of the research, should they wish.

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.*

Each subject will receive written explanations of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding. All questions will be answered via email or phone, and if all inclusion criteria are met, and the subject volunteers to participate, digital written informed consent will be obtained.

Written, electronic consent (e-consent) will be obtained via REDCap, a web-based platform capable of recording electronic signature. The e-consent document will contain all of the elements of informed consent required by applicable federal regulation for the protection of human subjects and elements of authorization required by the HIPAA Privacy Rule, and will begin with a concise and focused presentation of the key information that is most likely to assist participants in understanding the reasons why he/she might or might not want to participate in the research.

Because consent will be obtained remotely, the electronic platform will be designed such that the consent form is easy to navigate. We will also employ interactive electronic-based technology such as instructional videos and a comprehensive knowledge check at the end of the consent process. Potential participants may view informational videos or opt in or out of having a 30-minute phone call/video conference to go over study details with a consenting coordinator to address any questions they may have. After the phone call/video conference takes place, the consenting coordinator will send the potential participant an email or 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 in 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.

The system will also incorporate electronic strategies to encourage participants to access all of the consent material before documenting his/her consent. Participants may contact a member of the research team at any time with questions about the research prior to signing consent.

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. Both the research phone and email inbox will be monitored daily by consenting coordinators. Potential participants will need to correctly answer 4 questions about the protocol to demonstrate their understanding of the consent form. Research coordinators will review names and signatures of all completed consent forms. Participants that do not provide effective consent (e.g. a slash, line or dot) will be contacted by a consenting research coordinator to confirm their identity and eligibility for the study. PDF copies of signed consent forms will be made available to all participants. A copy of all signed forms will be stored in a HIPAA-secured, Northwell approved storage drive with protected access to only the PI and research personnel listed on the study protocol.

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. 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 this RCT, is to seek funding so that we can work with N1Thrive 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. 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.

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 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 <u>OR</u> 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 the Institute 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.

We exclude women who are pregnant given yoga is a wellness strategy used in this research (yoga video that is pre-recorded for general use, excluding pregnant women, i.e. the poses cannot be modified for pregnant women). If this personalized trial research strategy is proven successful, additional research using video intervention specifically designed for pregnant women (i.e. prenatal yoga) will be evaluated.

In addition, our goal for this research is to test virtual research delivery capabilities for the digital health technology used for this specific use case. 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 this RCT, is to seek funding so that we can work with N1Thrive 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. 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.

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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