Random Assignment of Intervention Messages for Developing Personalized Decision Rules to Promote Physical Activity

Protocol Number*: STUDY00009455

National Clinical Trial (NCT) Identified Number: NCT03907683

Principal Investigator*: David E. Conroy, PhD

Sponsor: The Pennsylvania State University

"Sponsor" indicates an institution, foundation, or individual who takes responsibility for and initiates a clinical investigation; often times this is the university with which the Principal Investigator is affiliated.

Grant Title: Phase 1 clinical trial to develop a personalized adaptive text message intervention using control systems engineering tools to increase physical activity in early adulthood

Grant Number*: HL142732

Funded by: NIH/NHLBI

Version Number: v.1.0

August 5, 2022

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STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials have been submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) was obtained before any participant was consented. Any amendment to the protocol was reviewed and approved by the IRB before the changes were implemented to the study. All changes to the consent form(s) were IRB approved.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: Aug 5, 2022

Name*: David E. Conroy

Title*: Professor

Investigator Contact Information

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1 PROTOCOL SUMMARY

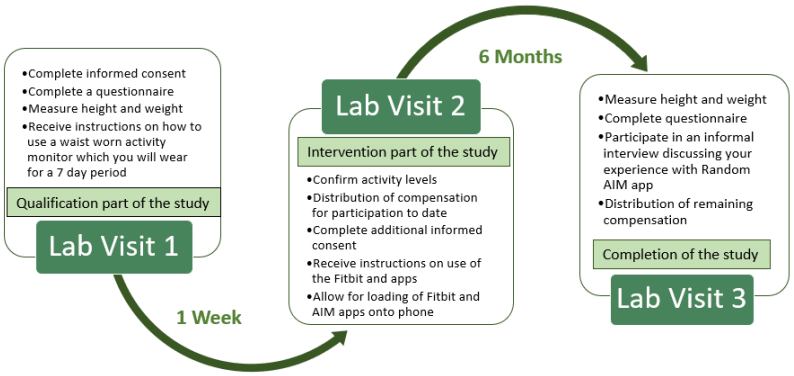
1.1 SYNOPSIS

Title:	Random Assignment of Intervention Messages for Developing Personalized Decision Rules to Promote Physical Activity
Grant Number:	R01 HL142732
Study Description:	This study aims to develop a method for characterizing the dynamics of person-specific behavioral responses of a behavioral intervention. Our long-term goal is to evaluate a personalized adaptive messaging intervention for PA based on dynamical models of historical responses to intervention (and other inputs such as weather).
Objectives*:	Primary Objective: The aim of this project is to develop personalized dynamical models of physical activity (PA) under different weather and temporal conditions.
Endpoints*:	Primary Endpoint: change in minutes of moderate-to-vigorous physical activity following each of three types of micro-interventions on weekdays and weekends
Study Population:	80 female and male adults aged 18-29 years from the United States who engage in insufficient physical activity
Phase* or Stage:	Phase 1
Description of Sites/Facilities Enrolling Participants:	N/A
Description of Study Intervention/Experimental Manipulation:	Baseline education and self-regulatory training; provision of smartwatch that provides ad libitum behavioral feedback throughout study; 0-6 micro-intervention messages/day for 6 months
Study Duration*:	18 months
Participant Duration:	6 months

1.2 SCHEMA

Random AIM: Physical Activity Study Information Sheet

- The research study is being done to determine if receiving interventional text messages can encourage physical activity, if the type of message sent performs more effectively than other messages and how the weather impacts your decision to engage in physical activity. The investigational intervention app for your phone is being tested.
- This study involves 3 lab visits to the Penn State University Park campus over the course of 6 months. The first visit will occur soon after screening. One week after beginning the study, you will return for a second 1.5 hour visit and the final visit at the end of the 6 month study period will last about 1 hour.
- You will be asked to wear a FitBit watch to monitor your physical activity levels during waking hours, receive text and image notifications and acknowledge them on your smartphone, allow for GPS location services to detect your current weather exposure and agree to monthly communications for a 6 month period.
- You can receive up to $295 in compensation and a Fitbit Versa watch for completing all procedures throughout the 6-month study.



* **Thank you for your interest in our research project.** We would like to schedule a time to speak with you regarding participation in our study. We have a few brief questions to determine whether or not you would qualify for participation. It would take about 5 minutes of your time. You can reply via email with your preferred phone number contact and a day and time which would be best to reach you at. Or you may call us at The Penn State Motivation Lab at (814) 865-7935.

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Intervention & Ambulatory monitoring	Visit 2 End of Month 6
Review Eligibility (questionnaires and accelerometer)	X			
Informed Consent		X		
Baseline assessment (demographics, motivation)		X		
Randomization		X		
Intervention			X	X
Adverse Events Reporting			X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Just-in-time adaptive interventions are a new strategy for delivering interventions to patients at moments when they are receptive and have an opportunity (or vulnerability) for behavior change. These interventions are often delivered using technology to reach people in the natural context of their daily lives. They require decision rules to specify which interventions are delivered, when they are delivered, and how often they are delivered. Our prior results raise questions about the sufficiency of a single decision rule for diverse populations. Those results showed that different people respond to different message content, responses varied on weekends and weekdays, and the timing and magnitude of responses varied. We seek to extend these results by collecting data on a larger sample of participants and enriching the model with additional data to reduce uncertainty. We focus on location-specific weather indices to enrich our models. Extensive data link physical activity with weather but, to the best of our knowledge, weather indices have never been used to inform physical activity intervention delivery. We will determine whether behavioral responses to text messages vary, for example, on sunny vs cloudy days, warm vs cool days, or rainy vs dry days. To achieve this aim, we need to collect intensive longitudinal data on behavioral responses to text messages under a variety of weather conditions.

2.2 BACKGROUND

Physical activity (PA) reduces the risk for cardiovascular disease, diabetes, and many cancers. Yet national data indicate that less than 5% of US adults attain the recommended level of PA, and activity levels consistently decrease across adulthood. Physical inactivity is also part of a constellation of lifestyle factors – with smoking and diet – that contribute to weight gain in early adulthood. This developmental period is critical because risk factors that compromise cardiovascular health begin to accumulate. Interventions that prevent decreases in PA during this time can reduce long-term chronic disease risk.

Young adults often elude preventive health interventions because they are often underinsured and do not have consistent contact with health care systems. Technological advances have made it possible to reach this segment of the population and shown promise for increasing PA. For example, short message service (SMS) interventions, have shown a consistent positive effect on PA. Yet efforts to increase SMS intervention effects via tailoring, targeting or personalizing have not realized their potential. Other approaches have emerged for tailoring interventions based on treatment responses or contextual factors that increase vulnerability/ opportunity (e.g., stepped care, just-in-time adaptive interventions). The decision rules in these approaches are assumed to generalize across the population (i.e., one rule for all participants). But behavior is complex and multiply determined so it is possible that treatment responses are idiosyncratic, necessitating personalized decision rules. Existing approaches also fail to capitalize fully on the rich information from the intensive longitudinal data available from pervasive wearable sensors. Building on interest in precision medicine, we propose a method to develop personalized adaptive messaging interventions using tools from control systems engineering (system identification and robust control synthesis). This approach can ensure that an individual only receives content to which s/he

responds when s/he is likely to respond and only as often as needed to achieve specified behavioral goals. Our long-term goal is to evaluate a personalized adaptive messaging intervention for PA based on dynamical models of historical responses to intervention (and other inputs such as weather).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Participants may find the Actigraph activity monitor worn at the waist for the run-in part of the study, uncomfortable. Participants may find wearing a Fitbit Versa slightly uncomfortable or bulky if they do not usually wear a watch. Both devices may be removed when showering/bathing. There may be some mild discomfort associated with answering some of the interview or survey questions. The participants will be instructed that they have the right to refuse to answer any questions that they find too uncomfortable. There may be a risk of feeling self-conscious or embarrassment when receiving message notifications on their smartphone. Participants will be instructed not to answer any notifications when it is not safe to do so (e.g. driving, attending meeting at work) and that the message be available for acknowledgment within 30 minutes if their situation should change. The small amount of compensation associated with the acknowledgment ($0.25) will not persuade the participant to risk their safety to respond to the message. The app collects data on the participant's location and the weather conditions at this location when messages are received and acknowledged to determine their impact on your physical activity levels at any given time throughout your day. Participants may find the disclosure of their location unsettling. There is a slight risk of soreness if physical activity is increased in sedentary participants. Participants will be given information regarding progressive adaption to minimize this risk.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the study team, but precautions will be taken to prevent this from happening and all information obtained from this research will be kept as confidential as possible. Code numbers rather than names will be used on all research records and the information linking these codes to the participants' identities will be kept separate from the research records. The confidentiality of the electronic data created by participants or the researchers will be maintained to the degree permitted by the technology used and is securely encrypted at all stages of the study. Despite our best efforts, it is not possible to guarantee absolute confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no guarantee that participants will benefit from this research. The possible benefits that participants may experience from the interventional research study include increasing their physical activity and associated health benefits.
The research may lead to the creation of personalized interventions that create long-term behavior changes in physical activity levels for young adults.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Risks involved low severity and low likelihood, and were outweighed by potential benefits of the knowledge gained.

3 OBJECTIVES AND ENDPOINTS

Provide a description of the study objectives and endpoints, as well as a justification for selecting the particular endpoints, in the table format included below. This will provide clear articulation of how the selected primary and secondary endpoint(s) are linked to achieving the primary and secondary objectives and an explanation of why endpoint(s) were chosen. Data points collected in the study should support an objective or have a regulatory purpose. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study's objectives.

*An **objective** is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., feasibility, acceptability, engagement of the intervention target, identifying mechanisms of action, mediation, moderation, efficacy, effectiveness, dissemination, implementation).*

*A study **endpoint** is a specific measurement or observation to assess the effect of the study intervention. Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct and precise definitions of the study endpoints used to address the study's primary objective and secondary objectives (e.g., specific diagnostic tests that define safety or efficacy, clinical assessments of disease status, assessments of psychosocial characteristics, patient reported outcomes, behaviors or health outcomes). A full description of study endpoints, including administration, scoring, psychometrics, adjudication of endpoints, etc., belongs in **Section 8**, **Study Assessments and Procedures**.*

A putative mechanism of action is the theorized explanation for how the intervention functions.

*Consider whether primary and secondary endpoints should be adjusted for multiple comparisons, family-wise error rates, alpha inflation, etc. Details of any such adjustments should be included in **Section 9.4.2, Analysis of the Primary Endpoint(s)** and **Section 9.4.3, Analysis of the Secondary Endpoint(s)**.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Develop and test method for estimating person-specific effects of micro-interventions on health-enhancing physical activity.	Change in moderate(or higher) physical activity duration following message receipt	Moderate-to-vigorous intensity physical activity is health enhancing.	N/A

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	is the primary endpoint		

4 STUDY DESIGN

4.1 OVERALL DESIGN

This single-site trial is in Phase 1 of behavioral intervention development with the goal of developing a method for optimizing person-specific intervention dosing to promote health-enhancing physical activity. To test the null hypothesis that each message type will not lead to increased moderate-to-vigorous physical activity, we use a within-person randomized trial design. All participants received 0-6 messages/day drawn from three content libraries (Move More, Sit Less, Inspirational Quotes). The number of messages and content source for each message was determined randomly for each participant every day. The allocation ratio was set so participants would receive approximately 40% Move More messages, 40% Sit Less messages, and 20% Inspirational Quote messages. Randomization was conducted automatically by custom software developed to deliver messages. This intervention is referred to as Random Assignment of Intervention Messages (Random AIM).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This design was selected to evaluate the heterogeneity of person-specific responses to treatment.

4.3 JUSTIFICATION FOR INTERVENTION

The intervention was delivered via smartphone notifications from a mobile application that received data from (and transmitted data to) a custom server developed for intervention delivery. A 6-month period was selected because it ensured variation in weather conditions which are associated with physical activity. The number of micro-interventions (individual digital messages) was varied to limit burden on research participants.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, and 6 months of intervention and ambulatory monitoring of physical activity.

5 STUDY POPULATION

*If the study design requires clarification of various groups of study participants, that clarification can be included directly under **Section 5**. For example, for a feasibility study that includes therapist-participants and patient-participants, clarify the distinction of those populations here. Subsequent subsections should also differentiate by participant type, where relevant.*

The following subsections should include a description of the study population(s) and participant recruitment. The study population should be appropriate for clinical trial phase/stage of the study intervention. It is essential that the population's characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities).

Behavioral studies often have unique units of measurement. For example, the study may evaluate at the clinic or classroom level, rather than at a patient or student level. In other cases, the care provider could be the subject of the intervention. It may even evaluate at multiple levels within the same protocol. The description of the study population should match the unit of measurement or level of analysis; there is no expectation that characteristics of individual participants be described if inclusion/exclusion criteria are based on group characteristics.

*Use the following guidelines when developing participant eligibility criteria to be listed in **Section 5.1, Inclusion Criteria*** **and 5.2, Exclusion Criteria***:*

- *The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment*
- *For population-based interventions, indicate if study "participant" is at a broader level, such as schools, hospitals, churches, community organizations, or other, as appropriate*
- *If participants require screening, distinguish between screening participants vs when a participant is considered enrolled/entered/randomized*
- *Indicate if screening procedures will be performed under a separate screening consent form*
- *Consider the risks of the study intervention in the development of the inclusion/exclusion criteria so that risks are minimized*
- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion)*
- *Identify specific laboratory tests or clinical, behavioral or other participant characteristics that will be used as criteria for enrollment or exclusion*
- *If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide study requirements (e.g., contraception methods, pregnancy testing)*
- *If the study involves more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation*

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Participants capable of reading, speaking and understanding English and of giving informed consent.
2. Participants between the ages of 18-29 years.
3. Participants must be free of visual impairment that would interfere with the use of a smartphone.
4. Participants must own and carry an iPhone (running iOS version 10 or higher) or Android (running operating system 7 or higher) smartphone during waking hours.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Participants self-report engaging in 90 or more minutes of moderate- or greater intensity PA each week or who record 150 or more minutes of moderate- or greater intensity PA on the research accelerometer in the screening period.
2. Participants engaged in organized programs with mandated physical activity (e.g., varsity sports, ROTC).
3. Participants with contraindications to normal physical activity on the Physical Activity Readiness Questionnaire.
4. Participants who require an assistive device for mobility or have any other condition that may limit or prevent participation in moderate-intensity physical activity.
5. Participants who are pregnant or planning to become pregnant within the next 6 months.
6. Participants with a prior diagnosis of cancer, cardiovascular disease, diabetes or metabolic syndrome.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that will not be rescreened for this trial.

A new Information report (RNI) was submitted at the beginning of the study. The run-in study was done to verify the self-reported activity levels of the participants with an accelerometer. The accelerometer was functioning properly but the software that calculates the activity was not set appropriately and did not accurately evaluate their activity levels. There were 3 participants whose activity levels were much higher than properly assessed and should have been the basis of exclusion from the intervention phase

of the study. They were enrolled in the intervention portion of the study when they should have been excluded based upon higher than reported activity levels. The participants were contacted immediately and notified of their ineligibility based upon these findings. They were offered an apology for this mistake and offered either to be compensated for their participation in the study to date.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment of participants will be accomplished using the recruitment flier posted onto campus building and community bulletin boards (grocery stores, libraries and coffee houses) throughout the State College / Central Pennsylvania area. The recruitment flier advertisements will be distributed on the Motivation Lab Facebook page and with the aid of a Facebook self-serve advertisement, using participant study demographics. Recruitment will utilize Studyfinder. Interested participants that contact the study team via email will be sent additional information (the Random AIM study information sheet) and will be asked to contact the study team via phone to go through the verbal screening process.

We plan to recruit a sample proportional to national the national demographic profile based on sex, race, and ethnicity. Prospective participants will be screened via questionnaire and a 1-week ambulatory monitoring period with a research-grade accelerometer to determine eligibility. We anticipate screening 160 participants to enroll 80 eligible participants.

Participants will keep the Fitbit smartwatch and be compensated up to $295 for participating in the study as follows:

- $25 for returning the activity monitor at the end of screening
- $85 for protocol compliance in months 1-2 ($40 for daily Fitbit wear and $0.25 for each digital message they receive and acknowledge within 30 minutes)
- $85 for protocol compliance in months 3-4 ($40 for daily Fitbit wear and $0.25 for each digital message they receive and acknowledge within 30 minutes)
- $100 for protocol compliance in months 5-6 ($55 for daily Fitbit wear and $0.25 for each digital message they receive and acknowledge within 30 minutes)

Compensation provided is an equitable amount meant to offset the time and inconvenience of participation in the study as well as to serve as an incentive. The compensation is not excessive to coerce subject participation.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The intervention included education about physical activity, goal-setting, and action planning in a baseline session, followed by 0-6 digital micro-interventions/day for 6 months during which time the participant wore a Fitbit smartwatch and had access to ad libitum behavioral feedback. The micro-interventions were digital messages from one of three content libraries: Move More, Sit Less, or Inspirational Quotes. Messages in the Move More and Sit Less libraries were based on social-cognitive theory and the intended mechanistic target was motivation and physical activity goal pursuit.

6.1.2 ADMINISTRATION AND/OR DOSING

The baseline intervention was delivered by the project coordinator during the initial meeting after participants provide informed consent. The micro-interventions were delivered via app-based notifications on the participants' smartphone.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Intervention delivery will be monitored using a web-based study dashboard that tracks message delivery and device wear.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study used a single-group design and micro-intervention delivery was automated on a random schedule so the study was not masked.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participant acknowledgement of message receipt within 30 minutes of delivery will be monitored to evaluate the fidelity of treatment receipt.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from Random AIM, they will be withdrawn from the study and replaced in the sample. We will document the reason for study intervention discontinuation.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to complete a required study visit:

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Participants will be asked to wear a Fitbit smartwatch during all waking hours to record ambulatory physical activity throughout the 6-month study period. Moderate-to-vigorous physical activity duration will be calculated as the number of minutes with 100 or more steps/min.

8.2 SAFETY ASSESSMENTS

Participants will be contacted on a monthly basis to assure well-being and their safety in the use of the interventional app for the study. Participants will be instructed to contact the study team to report any illnesses or injuries obtained throughout the time that they are actively participating in the research study, whether potentially associated with participation or not.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the intervention will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE): An untoward occurrence, whether or not considered related to a subject's participation in Human Research, that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or that requires medical, surgical, behavioral, social or other intervention to prevent such an outcome.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by the principal investigator based on temporal relationship and his clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it

can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

The principal investigator with appropriate expertise in lifestyle physical activity will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The project coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At

each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Participants who become pregnant will be withdrawn from the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the funding agency immediately upon the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 10 working days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of analysis (e.g., feasibility/acceptability, efficacy, effectiveness, implementation) and time period for which each endpoint will be analyzed. Include this information for each hypothesis being tested, if multiple hypotheses are present. If the study is intended as a feasibility or pilot study, please consider that a formal hypothesis may not be available at the time of protocol writing. If so, include a statement indicating that hypotheses will be generated or that descriptive statistics only will be calculated.

- Primary Endpoint(s): change in moderate-to-vigorous intensity physical activity following receipt of a message from each content library.

We hypothesize that, compared to behavior that would be expected based on the dynamic model without message delivery, patients who receive a Move More or Sit Less Message will have a positive steady state response for moderate-to-vigorous physical activity duration following message delivery. Alternatively, our null hypothesis is that there will be no difference in moderate-to-vigorous physical activity steady state responses following Move More or Sit Less messages.

9.2 SAMPLE SIZE DETERMINATION

Statistical power analysis is not relevant for estimating person-specific dynamic models. Our proposed sample size (n=80) is based on the upper limit for phase 1 clinical trials and will enable us to capture the heterogeneity of PA dynamics and estimate model uncertainty within the resource constraints of early stage intervention development work.

9.3 POPULATIONS FOR ANALYSES

All study completers will be analyzed.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The steady state response (i.e., final cumulative response) to each type of intervention message will be recorded as the primary outcome variable. The mean and standard deviation of steady state responses will be calculated.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

System identification will be used to estimate coefficients for person-specific dynamic models of moderate-to-vigorous physical activity durations in 15-minute epochs. Model coefficients will be used to simulate expected responses to each type of micro-intervention (separately for weekdays and weekends). Steady state responses for each message type on weekdays and weekends will be extracted as the primary outcome. An independent-sample t-test will be used to evaluate whether the average steady state response to each message type on weekdays and weekends differs significantly from zero.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

This section should demonstrate that the consent form contains all required regulatory elements. List all consent and/or assent documents and materials submitted with this protocol. Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.

If needed, describe special documents or materials (e.g., Braille, another language, audio recording).

Example text provided as a guide, customize as needed:

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: informed consent document.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Written informed consent will be a two-step process. Written informed consent for the run-in portion of the study will take place at the initial study visit. Written informed consent for the intervention portion of the study will take place at the second study visit upon verification of a participant's activity levels that are less than 150 minutes of moderate- or greater intensity PA per week.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator.

The study participant's contact information will be securely stored at the research site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered

by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in secure cloud storage provided by The Pennsylvania State University.

When the study is completed, access to study data will be provided through the principal investigator.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
David E. Conroy, Ph.D. *Professor*	*N/A*
The Pennsylvania State University	*N/A*
266 Rec Hall, University Park, PA 16802	*N/A*
814-863-3451	*N/A*
conroy@psu.edu	*N/A*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the principal investigator as approved by funder and institutional review board.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured electronically to avoid manual data entry errors.

Intervention Fidelity — Consistent delivery of the study interventions and device wear will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 STUDY RECORDS RETENTION

Paper consent forms and contact information sheets will be stored in a locked file cabinet of the locked office of the research project manager (18 A Recreation Building) for a period of three years after the end

of the study. De-identified data will be stored on a centralized, personal data server developed by our software development team, West Arete. De-identified data is stored in a relational database and encrypted during transmission. The data is stored in servers which are virtual machines hosted at a major provider, dedicated solely to our application on a network that is shared with other projects, and is protected by a host-based firewall with "default closed" policy. The security practices that are applied to the servers include antivirus protection, host-based intrusion detection, uptime monitoring, strong authentication (private key with strong password) logins, and the operating system security updates are monitored and applied nightly. Logs are monitored daily and there are encrypted off-site backups. The de-identified data will be stored indefinitely.

This study is funded by the National Institutes of Health and will be issued a Certificate of Confidentiality. Researchers will not disclose or provide any identifiable information without the subject's prior consent or where permitted according to NIH's Policy on Issuing Certificates of Confidentiality.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents and reported to the NHLBI Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting Dr. David Conroy, The Pennsylvania State University. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality

CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
	11/27/2019	Increase enrollment of participants	Increase number of participants to account for study drops to attain 80 participants for analysis
	1/29/2020	Removal of web-based recruitment tool and removal of research staff	Recruitment has ceased and personnel changed
	3/25/2020	Change in the end of study visit and alteration in compensation delivery	The pandemic halted in-person interactions so changes were made to collect final data and compensate in a remote fashion

11 REFERENCES

N/A