CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Behavioral Economics Approaches to Increase Physical Activity Among Patients with Elevated Risk for Cardiovascular Disease (BE ACTIVE Study)

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Outline

9.4 Process evaluation

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1. Abstract

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the United States (US). Regular physical activity has been demonstrated to reduce the risk of ASCVD and is associated with a number of other health benefits. Yet, less than 50% of adults in the US achieve enough physical activity to actually obtain these benefits. Insights from behavioral economics have been shown to both better reflect the 'predictable irrationality' of humans and to be effective in designing interventions that achieve sustained improvements in health behavior. Our prior work has demonstrated that interventions using financial incentives and gamification can leverage principles from behavioral economics to increase physical activity during 3-month interventions and sustain effects in 3-month follow-up periods. These findings warrant further investigation of longer-term effects. In this study, we conduct a four-arm randomized, controlled trial to evaluate the effectiveness of using behavioral economic approaches including gamification, financial incentives, or both to increase physical activity among patients with elevated risk for atherosclerotic cardiovascular disease during a 12-month intervention with a 6-month follow-up.

2. Overall objectives

The objective of this study is to use a randomized, controlled trial to test the effectiveness of using gamification, financial incentives, or both to increase physical activity among patients with elevated risk for atherosclerotic cardiovascular disease.

3. Aims

3.1 Primary outcome

The primary outcome is the change in mean daily steps counts from baseline to the 12-month intervention period, excluding the 8-week ramp-up phase.

3.2 Secondary outcomes

Secondary outcomes include change in mean daily steps from baseline to the post-intervention follow-up period, change in mean daily minutes of moderate-to-vigorous physical activity (MVPA) from baseline to the intervention period, and change in mean daily minutes of MVPA from baseline to the post-intervention follow-up period.

3.3 Exploratory outcomes

We will explore the change in the proportion of participant-weeks that achieve the Centers for Disease Control and Prevention Recommendation of at least 150 minutes of MVPA per week from baseline to the intervention period and baseline to the follow-up period.

4. Background

Regular physical activity has been demonstrated to reduce the risk of ASCVD and is associated with a reduced risk of diabetes, hypertension, obesity, and mortality.[1-6] Yet, less than 50% of adults in the US achieve enough physical activity to actually obtain these benefits.[7]

Behavioral economists have mapped out the ways in which people make predictable decision errors that often work against their own long-term self-interests.[8,9] These insights are important to build into the design of interventions that are geared towards achieving sustained changes in behavior. Our prior work has demonstrated that interventions using financial incentives and gamification can leverage principles from behavioral economics to increase physical activity during 3-month interventions and sustain effects in 3-month follow-up periods.[10-14] These findings indicate the potential of these approaches and the approaches developed provide a basis for testing the impact of these interventions on sustained behavior change over longer-term periods.

5. Study design

5.1 Design

This is a four-arm, randomized, controlled trial to test the effectiveness of gamification, financial incentives, or both to increase physical activity among individuals with a 10-year ASCVD risk score of 7.5% or higher. There will be a 2-week run-in period to obtain baseline measures of physical activity, followed by a 12-month intervention period and then a 6-month follow-up period.

Participants will use the Penn Way to Health research technology platform to provide informed consent and complete eligibility surveys. Eligible patients will be mailed a wearable activity tracker that captures data on daily steps counts and minutes of MVPA. They will be asked to use the device for two weeks to get accustomed to it. During this period, we will use a protocol from prior work to estimate a baseline step count using the second week of data. The first week of data will be ignored to diminish the tendency for use of devices in week 1 of receiving a new device to be significantly higher than what might be observed at steady state. To prevent risk of mismeasurement, we will ignore any daily values less than 1000 steps because evidence indicates these values are unlikely to represent capture of actual activity.[15,16] At least four days of data must be available during that second week to estimate baseline measures; otherwise the period will be extended. In prior work, we typically have 6 to 7 days of data from more than 90% of participants.[12] Participants who do not complete this run-in phase will not be randomized into the trial. Participants will also complete a series of validated surveys including risk preferences (DOSPERT),[17] social support (Medical Outcomes Study),[18] personality (Big Five) and health-related quality of life (EQ-5D).[19-21] See table in Section 8.2 for full list of surveys and timing

--Goal Setting--

Once baseline measures have been established, participants will be contacted to choose their goals using an approach we have found to work well in previous studies. They will be given their baseline step count and asked to select a step goal increase of 33%, 40%, 50% or choose a custom goal as long as it is at least 1500 steps greater than baseline. We have used this approach in the past because it gives participants the options of setting their own goal but also steers people to choose one of the options provided, any of which would be terrific from the standpoint of increasing physical activity. Leaving it completely open-ended risks having participants either pick goals that are ‘too easy’ or not likely to be attainable. In prior work, we find that on average participants chose ambitious goals and more than half selected a 50% step increase.

--Randomization—

Participants that have established baseline measures and finished goal selection will be randomly assigned to control or one of the three interventions using a 1:2:2:2 allocation and stratifying on baseline step count (< 4000 steps, 4000 – 7000 steps, > 7000 steps) using an electronic number generator through the Way to Health research technology platform. We do this because it preferentially increases power for comparison between the different intervention arms, as the differences between intervention arms are likely to be smaller than the difference between the intervention arms and control.

--Study Arms—

All participants will be asked to use the wearable device during the day and at night to measure activity. Each participant will primarily receive study communications by text message. Interventions by study arm will vary as follows:

--Arm 1: Control—

During the intervention and follow-up periods, participants in this arm will receive a daily text message stating whether or not they achieved their step goal on the prior day.

--Arm 2: Gamification intervention—

Participants in this arm will be entered into a game designed to leverage insights from behavioral economics to address predictable barriers to behavior change during the 12-month intervention period. This approach is based on our successful pilot work in this area. We will use an 8-week ramp-up period in which daily goals are increased gradually from baseline to targets, as this was found to achieve sustained behavior change in previous work. For example, if the baseline number of steps per day is 5,000 steps and the goal number of steps chosen is 7,400. In week 1 the goal would be 5,300, in week 2 the goal would be 5,600 up through the 8 week period. We have found that the rate of goal attainment is high using this gradual approach rather than encouraging the participant to go from 5,000 to 7,400 steps immediately. The components of the gamification intervention are as follows:

1) Pre-commitment: First, each participant signs a pre-commitment contract agreeing to try their best to achieve their daily step goal. Pre-commitment has been demonstrated to help motivate behavior change.[33-34]

2) Points: At the start of each week, the participant will receive 70 points (10 for each day that week). Points are endowed rather than given after goal achievement to leverage loss aversion – a concept from prospect theory that reveals that individuals are more motivated by losses than gains.[29,35] Each day the participant is informed of their step count. If the step goal was achieved, he or she retains their points. However, each day the goal is not met, they are informed that they lost 10 points. Points are replenished at the start of the week to leverage the "fresh start effect" – the concept that individuals are more motivated for aspirational behavior around temporal landmarks such as the start of the week.[84]

3) Levels: At the end of the week, if the participant has 40 points or more, he or she will advance one level. The levels include: blue (lowest), bronze, silver, gold, platinum (highest). If he or she has less than 40 points, he or she will drop down one level at the end of the week. This creates a sense of achievable

goals (goal gradients)[37] and uses loss aversion to help motivate ongoing efforts to not lose status. Each participant begins the intervention in the silver level. By starting them in the middle, the higher levels seem within reach and they will feel a sense of loss from dropping down a level in the first week if they don't achieve 40 points; this may motivate them to initiate greater activity. Every 8 weeks, we will reach out to individuals that are stuck in lower levels of blue or bronze and restart them back at silver. This allows for another "fresh start" and creates a new endowment effect as someone who is already at the bottom would otherwise not be able to drop down further and experience loss aversion. At the same time, we will also inquire if he or she would like to adjust their step goal as long as they are within the range of a 33% to 50% increase. In previous studies, we've found that some individuals set overly ambitious goals at the start of the intervention and that for participants who have trouble achieving their initial goals, we can re-engage them if goals are reset to a more reasonable level.

4) Supportive sponsor: Each participant will select a family member or friend of their choice who will serve as a supportive sponsor. This person will receive a weekly email with the participant's progress including accumulated points, level in the game, and average step count. This supportive sponsor will help to enhance social incentives to motivate the individual towards his or her goal.[31] We will encourage participants to select someone with whom he or she comes into frequent contact and is close to such as a partner, family member, or friend that they see often. Prior to starting in the study, we will conduct a three-way phone call with the participant and their supportive sponsor. We will provide an overview of study procedures for their arm assignment, and then prompt the participant and supportive sponsor to discuss ways in which they can help the participant meet their step goals. At least 3 goals will be decided upon during the conversation, and if needed, we will provide suggestions for supporting the participant. The goals that are decided upon will be entered into a survey by study staff, and will be included in weekly emails to the supportive sponsor. Every 8 weeks, we will reach out to the participant and supportive sponsor if the participant is stuck in lower levels of blue or bronze to determine if changes should be made to the original support goals.

5) Prize: At the end of the intervention period, participants in the platinum or gold levels will receive a trophy to recognize their achievement. While this is a nominal incentive of very low monetary value, it represents a culmination of participant effort, creates a sense of something to work towards while in the game, and conveys a sense of "status" to participants that achieve it.

During the follow-up period, participants in this arm will continue to receive a daily text message stating whether or not they achieved their step goal on the prior day.

--Arm 3: Financial incentive intervention—

Participants in this arm are informed that each week $14 is placed in a virtual account for them. Each day the participant is informed of their step count on the prior day. If the step goal was achieved, the balance remains. Each day the goal is not achieved, the participant is informed that $2 was taken away. We will use an 8-week ramp-up period in which daily goals are increased gradually from baseline to targets, as this was found to achieve sustained behavior change in previous work.

During the follow-up period, participants in this arm will continue to receive a daily text message stating whether or not they achieved their step goal on the prior day.

--Arm 4: Gamification + Financial Incentive intervention—

Participants in this arm will receive both of the interventions described in arms 3 and 4 above.

5.2 Study duration

This study is anticipated to take up to 5 years to complete. Each participant will be enrolled in a 12-month intervention and 6-month follow-up period.

5.3 Target population

Adult patients at the University of Pennsylvania Health System with an ASCVD 10-year risk score of 7.5% or greater, or existing ASCVD.

5.4 Accrual

We will enroll and randomize 1050 participants over a two-year period.

5.5 Key inclusion criteria

Participants will be eligible if they: 1) are age 18 years or older; 2) have a 10-year ASCVD risk score of 7.5% or greater (including those with existing ASCVD); 3) are able to provide informed consent.

5.6 Key exclusion criteria

Participants will be excluded if they: 1) are already participating in another physical activity study; 2) an 18-month physical activity program is infeasible (e.g. metastatic cancer; unable to ambulate or provide informed consent) or unsafe (currently pregnant or told by a physician not to exercise); 3) they do not have a device (e.g. smartphone, tablet, or computer) to transmit data from the wearable activity tracker; 4) baseline step count is 7,500 or greater; 5) they do not have a primary care physician in the University of Pennsylvania Health System.

6. Subject recruitment

Participants will be recruited from the University of Pennsylvania Health System (UPHS) which consists of five large hospitals including the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, Chester County Hospital, and Lancaster General Hospital. There are more than 60 primary care practice clinics affiliated with UPHS throughout Pennsylvania and New Jersey. Target population: The UPHS population includes patients of mixed socioeconomic status with a high rate of ASCVD. Based on initial evaluation, there are more than 100,000 patients at UPHS who meet criteria for with a 10-year ASCVD $\geq$ 7.5% or clinical ASCVD. This will provide an ample population from which to perform the proposed clinical trial given that we typically are able to recruit about 30% of eligible health system patients for our studies and the target sample size is 1,050 or about 1% of the eligible population.

Potentially eligible patients will be identified using data from the electronic health record and Penn Data Store, the health system's clinical data warehouse. They will be invited to participate either by e-mail or mail letters. Study coordinators will conduct follow-up phone calls to further assess interest and answer questions related to the study. In the initial invitation, patients will have the ability to opt out from any further communications. Interested patients will be instructed to visit the study website on the Way to Health research technology platform to learn more about the study, create an account, provide informed consent, and complete initial baseline and eligibility surveys.

7. Subject compensation

All participants will receive $30 for enrolling in the study, $30 for completing the 6-month assessment, $40 for completing the 12-month assessment, and $50 for completing the 18-month assessment. Each participant will receive a ClinCard, and payments will be uploaded to their card after assessments are completed.

8. Study procedures

8.1 Consent

Upon recruitment, individuals who are interested in learning more about the study will be directed to the Way to Health web portal. We will follow an IRB-approved approach taken by many studies using the Way to Health platform to obtaining informed consent. Upon reaching the portal, potential participants will be asked to create an account and will then be informed of the details of the study, including its objectives, duration, requirements, and financial payments. The Way to Health portal will then take interested participants through an online informed consent. The consent document will be divided into sections and potential participants will have to click a button to advance through each section. This is to help ensure that participants read the consent form thoroughly by breaking down the form into manageable blocks of text. Each section will have a button allowing the user to contact a researcher via email or by telephone if they have questions about the consent form. Successive screens will explain the voluntary nature of the study, the risks and benefits of participation, alternatives to participation, and that participants can withdraw from the study at any time. On the final consent screen, potential participants who click a clearly delineated button stating that they agree to participate in the study will be considered to have consented to enroll. Participants will be provided with details regarding how to contact the research team via email or phone at any time if they subsequently wish to withdraw from the study. This contact information will remain easily accessible via the participants' individual Way to Health web portal dashboards throughout the study.

8.2 Procedures

After providing informed consent, participants will complete an online questionnaire to confirm eligibility and complete the study surveys. Eligible participants will be mailed a wearable activity tracking device to wear for about two weeks to collect a baseline step count.

Participants will select step goals and then be randomly assigned as described in the Study Design section.

Surveys and interviews will be conducted as outlined in the Table:

Area	Name	# Questions	Baseline	6 Months	12 Months	18 Months	Validation Study
Screening Survey	NA		X				
Baseline (demographics)	NA		X				
Cardiovascular history/Weight/Meds	NA		X	X	X	X	
Health status	EQ-5D-5L and EQ-VAS	6	X	X	X	X	Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7): 1717-1727.
Exercise self-efficacy	Self-Efficacy for Exercise Behaviors	12	X	X	X	X	Sallis JF, Pinski RB, Grossman RM, Patterson TL, Nader, PR. The development of self-efficacy scales for health-related diet and exercise behaviors. Health Education Research. 1998;3:283-292.
Sleep	Pittsburg Sleep Quality Assessment	9	X	X	X	X	Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989;28:193-213
Mood	PHQ9	9	X	X	X	X	Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613.
Social Support	MOS Social Support	19	X	X	X	X	Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med. 1991;32(6):705-714.
Risk Preferences	DOSPERT	30	X				Blais A, Weber EU. A domain-specific risk-taking (DOSPERT) scale for adult populations. Judgement and Decision Making. 2006;1(1):33-47.
Personality	Big Five	44	X				John OP, Srivastava S. The Big-Five trait taxonomy: History, measurement, and theoretical perspectives. In L. A. Pervin & O. P. John (Eds.), Handbook of personality: Theory and research. New York: Guilford Press. 1999;2: 102–138.
Grit	Grit Scale	10	X				Duckworth AL, Quinn PD. Development and validation of the short grit scale (grit-s). J Pers Assess. 2009;91(2):166-174.
Qualitative survey	NA				X	X	
Interviews						X	

Once the study is completed and the results are published, study staff will reach out to all participants via email to disseminate the findings of the study.

9. Analysis Plan

9.1 Power and sample size

Physical activity has been demonstrated to have a direct dose relationship with reduction in the risk of cardiovascular disease and events, with even small increases significantly lowering risk.[6,22-25] We use 1000 steps as our threshold for powering statistical significance, which for the average person is about half a mile and takes about 10 minutes of MVPA.[26] Based on our prior work,[10-14] we estimate a standard deviation in the primary outcome of 2500 steps. This study has been powered for six comparisons

between arms using a common cutoff for the test statistics that ensures the familywise error rate is at most 0.05. This is the approach suggested in Follmann et al.[27] and it generalized Tukey's Honest Significant Differences approach for an unbalanced design. We estimate that a sample of 1050 participants allocated in a 1:2:2:2 distribution (150 in control and 300 in each intervention arm), will ensure 93% power to detect a 1000 step difference between each intervention arm and control, with a standard deviation of 2500 steps and an 8-minute difference in MVPA assuming a standard deviation of 20 minutes. This calculation assumes a 10% dropout rate. We estimate that we will have at least 85% power to detect a 750-step difference with a standard deviation of 2500 steps and a 6-minute difference in MVPA with a standard deviation of 20 minutes.

9.2 Comparative-effectiveness analysis

Prior to analyses, we will produce data summaries to assess data quality, examine data distribution, and randomization success. All analyses will be performed using intention-to-treat. Data can be missing for any day if the participant did not use the activity tracking device or did not upload data. For the main analysis we will use multiple imputation for step values that are missing or less than 1000 steps. We will perform five sets of imputations and results will be combined using Rubin's standard rules.[28] We will perform sensitivity analyses to assess the robustness of the findings using only collected data with and without step values less than 1000 steps. Since minutes of MVPA are derived from step counts, this process should address missing data for MVPA as well.

Similar to prior work,[12] the primary analysis will fit linear mixed effect regression models to evaluate changes in physical activity outcomes measures (primary and secondary outcomes) adjusting for each participant's baseline measure, time using calendar month fixed effects, participant random effects, and accounting for repeated measures. Secondary analyses will fit linear mixed effect regression models adjusted for other variables of interest such as participant demographic characteristics and cardiovascular history. Exploratory analyses will fit logistic mixed effect regression models to evaluate the proportion of weeks that CDC guidelines for physical activity were achieved.

We will perform subgroup analyses using available participant sociodemographic characteristics including age, sex, race/ethnicity, education, and income level. We will also conduct subgroup analyses using differences in baseline measures such as baseline step count and atherosclerotic cardiovascular disease (ASCVD) 10-year risk score. If differences in outcomes exist, we will fit a fully adjusted model that includes these covariates and interaction terms with the treatment arms to evaluate for statistical significance.

9.3 Cost-effectiveness analysis

To compare the cost-effectiveness of each intervention compared to control, we will follow recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine.[29,30] Based on the Panel's recommendations, we will use two perspectives: a health care sector perspective and a societal perspective. Our primary analysis will use differences between each intervention and control in measures of physical activity (steps and minutes of MVPA), and in health-related quality of life measured by the EQ-5D,[19-21] as the outcome measures. We will explore using a simulation model to translate changes in these measures into quality-adjusted life-years (QALYs) over a longer period.[31-34]

The costs incurred from a health care sector perspective include costs for the Way to Health research technology platform, staff, wearable devices, data storage, and financial incentives. Outcomes will be summarized in the form of incremental cost-effectiveness ratios (ICERs) that show the difference in costs between two arms of the trial (e.g., the gamification and control arms) divided by the difference in outcome (e.g., step count). Deterministic (1-way and multi-way) and probabilistic sensitivity analyses will be conducted to determine the key drivers behind the cost-effectiveness ratios.

The additional costs incurred by a societal perspective include the time participants spend on the intervention and physical activity itself and out-of-pocket costs related to the intervention such as clothing for exercise. Participants will be surveyed at the end of the study to capture these measures. These additional costs will be captured within the ICERs.

9.4 Process evaluation

In order to understand how our interventions were implemented and received by participants, we will conduct a mixed-methods process evaluation.[35] All participants will be asked to complete an end-of-study fixed response questionnaire measuring their satisfaction with the wearable device, research technology platform, and intervention design. They will also complete a series of validated surveys including MOS Social Support Survey,[18] and the EQ-5D health-related quality of life survey.[19-21] to explore changes in participant characteristics associated with strong or poor performance. All questionnaires and surveys will be administered electronically via the Way to Health portal.

We will conduct semi-structured qualitative interviews with study participants purposefully selected by performance. In each arm, we will split the participants into two groups based on performance above and below the mean of that arm. We will randomly invite up to 10 participants from each of the two groups to complete a 30-minute telephone interview (up to 80 total participants across all 4 arms, or until we reach saturation in each group). We will provide $50 for participating in the interview.

Interviews will be conducted by a trained research assistant using a semi-structured interview guide informed by the theoretical domains framework (TDF).[36,37] The TDF provides a lens through which to view the cognitive, affective, social and environmental influences on behavior in relation to the implementation of complex interventions to improve health.[38] It includes 14 domains: knowledge, skills, social role and identity, beliefs about capabilities, optimism, reinforcement, intentions, goals, decision processes, environmental context and resources, social influences, emotion and behavioral regulation. We will create open-ended interview questions informed by these domains. The guide will also include questions on the following topics: (1) factors motivating participation in the study, (2) prior experiences with trying to increase physical activity, (3) perceptions of the intervention including its impact on his or her performance and perceived risks and benefits. Participants will be asked to describe aspects of each intervention element that helped them to achieve their physical activity goals and aspects that did not. The interview guide will also elicit information about intervention burden as well as suggestions for improvement in intervention design. The interview guide will be developed, refined and piloted prior to the trial launching.

Interviews will be audio recorded and professionally transcribed. Transcripts will be uploaded to qualitative data analysis software (e.g. NVivo) for management and coding. Two trained coders will perform the coding, in close collaboration with the study PIs. We will utilize a mixed inductive-deductive

approach to analysis.[39] We will begin by reading through a subset of transcripts from respondents in both performance levels to generate our preliminary coding framework. We will create two types of codes in this phase of analysis: (1) descriptive codes based on our interview guide and factors previously identified in the literature and (2) interpretive codes that emerge from the data.

Once the coding framework has been created and discussed with the study team, the coders will read through the interview transcripts line by line and apply codes to the data. The coding framework will be open to expansion and refinement throughout analysis, should the coders come upon novel salient themes. Intercoder reliability will be assessed every fifth transcript. We will calculate a coefficient of reliability (the ratio of coding agreements to the total number of coding decisions) for one selected interview document.[40] A coefficient of greater than 0.95 will be our cut off for proceeding with the coding. If our coefficient is less than 0.95, we will review the discrepancies, refine code definitions and reeducate the coders to ensure reliability. Once the entire data set has been coded, we will perform cross-code searches and explore variation in themes across respondents by performance on the intervention and by sociodemographic characteristics to identify higher-order patterns.

9.5 Safety analysis

Participants will be asked to report any study-related injuries or hospitalizations. These will be reviewed with the Principal Investigator and the patient will be contacted if there is a risk to continuing in the trial. We will constitute a DSMB comprised of 3 experts with one being a statistical expert, another an expert in physical activity, and a third being someone who is experienced in leading trials of behavioral interventions. As per NIH guidelines we are not naming anyone now so as not to preclude reviewers from their academic institutions. All adverse events will be reported to the IRB and DSMB. We will also ask participants to report study-related injuries, falls, emergency department visits, and hospitalization on the 12-month and 18-month surveys. We will evaluate these data in a blinded fashion after 25%, 50%, 75%, and 100% of participants complete the intervention and follow-up periods. This plan will be reviewed with the DSMB and modified as necessary prior to participant enrollment. Our plan will be to have milestone-driven meetings with the DSMB likely approximately every six months.

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