Final Study Protocol

A Randomized, Controlled Trial Evaluating Methods to Increase Physical Activity After Hospitalization for Acute Coronary Syndrome

Study Protocol

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1. Abstract

Cardiovascular disease is the leading cause of mortality in the United States. Among patients that survive an acute myocardial infarction (AMI), cardiac rehabilitation (CR) has been demonstrated to effectively reduce risk of re-infarction, cardiac mortality, and all-cause mortality. However, despite CR being a Class I (standard of care) recommendation in multiple American Heart Association AMI guidelines, more than 80% of eligible patients do not receive appropriate CR and much of this is due to challenges in access to these programs. Recent innovations in technology allow us to passively monitor an individual's physical activity using wearable devices. Incentives designed using insights from behavioral economics have been demonstrated to motivate device engagement and behavior change. A remotely-monitored CR program could improve access for many individuals and potentially be more cost-effective because it is less resource- and personnel-intensive. The objective of this study is to use a randomized, controlled trial to test the effectiveness of a home-based, remotely monitored program using wearable devices and financial incentives to increase physical activity. Participants will go through four phases: baseline period (weeks 1-2), ramp-up period (weeks 3-10), maintenance period (weeks 11-18), and follow-up period (weeks 19-26).

2. Overall objectives

The objective of this study is to use a randomized, controlled trial to test the effectiveness of a home-based, remotely monitored program using wearable devices and financial incentives to increase physical activity

3. Aims

3.1 Primary outcome

The primary outcome variable is the change in mean daily step count from the baseline period (weeks 1-2) to the maintenance period (weeks 11-18).

3.2 Secondary outcome

Secondary outcomes include change in mean daily steps from baseline to follow-up period, change in time slept from baseline to maintenance period, change in six minute walk test from baseline to end of maintenance period (optional for participants), and healthcare utilization during the ramp-up and maintenance period as measured by number of hospitalizations and emergency department visits.

4. Background

Cardiovascular disease is the leading cause of mortality in the United States (1). Among patients that survive an acute myocardial infarction (AMI), cardiac rehabilitation (CR) has been demonstrated to effectively reduce risk of re-infarction, cardiac mortality, and all-cause mortality

(2). Patients completing CR have also been found to have improvements in blood pressure control, lipid levels, and a reduction in smoking (3).

Despite this, more than 80% of eligible patients do not receive cardiac rehabilitation (4). Access and affordability are some of the primary factors associated with the low compliance with CR (5). Since CR centers are often located in more urban areas, patients that live in more rural locations or without transportation may have difficulty reaching these centers.

Recent innovations in technology allow us to passively monitor an individual's physical activity using wearable devices (6). These devices have been demonstrated to be accurate for tracking step counts (7) and could be utilized to deploy a home-based intervention. Recently, the concept of a remotely-monitored, internet-based CR program has been shown to be safe and superior to usual care (in terms of reducing CVD risk) in a small Canadian pilot study (8). A remotely-monitored CR program would provide access for the many individuals that cannot reach a CR center and potentially, in the future, could be more cost-effective because it is less resource- and personnel-intensive. The optimal range of steps for secondary prevention of AMI is in the range of 6500-8500 steps/day (9).

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5. Study design

5.1 Design

We will conduct a two-arm randomized, controlled trial comparing a control group that uses a wearable devices to track physical activity and sleep data to an intervention group that uses the same wearable devices and receives a financial incentive to adhere to a step goal program. Patients will be randomized to one of the two arms using a block size of four. To account for

possible differences in reimbursement for CR among patients with and without Medicare, we will stratify the randomization by age (less than 65 years vs. 65 years and older). Since referral to a standard health system CR program is recommended for all patients after an acute myocardial infarction, we will not attempt to modify current referral and adherence patterns to these programs. However, data suggest that more than 80% will not actually obtain this type of cardiac rehabilitation. During the study, we will ask all patients whether or not they participated in a standard cardiac rehabilitation program.

All participants will receive $20 for enrolling and $30 for completing the 26 week study. All participants will be given the option to have an in-person visit with the study coordinator at the beginning and after the maintenance period to conduct the six minute walk test. If a participant chooses to participate they will receive $30 for each visit.

Participants in all arms will be informed of the CDC/federal recommendation guidelines for physical activity and receive additional interventions as follows:

Arm 1. Control: use a wearable device to track physical activity and sleep data. Receive reminders to use their device and sync their data.

Arm 2. Financial incentive-based program: Participants will be given a wearable device to monitor daily step counts and sleep patterns with automated feedback on physical activity goal attainment via text message, automated interactive voice call or email (based on participant communication choice). Based on recommendations for the optimal step count for secondary prevention of AMI, we will establish a baseline step count for each participant (weeks 1-2) and then recommend a 15 percentage point increase in daily step goal each week during the 8-week ramp-up phase (weeks 3-10) with a maximum goal of 10,000 steps. After the ramp-up phase, participants will be asked to maintain that daily step goal for the maintenance period (weeks 11-18). After 18 weeks, financial incentives will be stopped and the participants will be followed for an additional 8 weeks with the same step goal as the maintenance period (weeks 19-26). Participants will be given daily feedback on whether or not they achieved their daily step goal on the prior day, for the entire intervention and follow-up period. Participants will be told at the beginning of each week during the ramp-up and maintenance phases that $14 has been placed in a virtual account for them. Each day during the week that the participant does not meet their daily step goal, $2 will be removed from their account. Accrued winnings will be sent to the participant by check via US mail at the end of each month. There will be no financial incentive during the 2-week baseline period or the 8-week follow-up period.

5.2 Study duration

This is an 26-week study with rolling enrollment beginning in January 2016.

5.3 Target population

Adults age ≥ 18 years with a history of acute coronary syndrome or history of undergoing coronary catheterization for suspected coronary artery disease.

5.4 Accrual

The study population will be drawn from adults at one of the University of Pennsylvania Health System hospitals or clinics. We will aim to enroll 150 participants. We estimate that a sample size of at least 148 participants (74 per arm) will provide 80% power to detect a difference of 1000 steps in the change in mean daily step count from baseline to maintenance phase between intervention and control, using a 2-sided α of 0.05, assuming a baseline mean step count of 6000 steps in the control group with a standard deviation of 2000 steps, and accounting for a 15% dropout rate.

5.5 Key inclusion criteria

1) Age ≥18 years; 2) ability to read and provide informed consent to participate in the study; 3) history of a) acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction); or b) patients having undergone coronary catheterization for suspected coronary artery disease.

5.6 Key exclusion criteria

1) Inability to provide informed consent; 2) does not have daily access to a smartphone compatible with the wearable device and not willing to use a device that we can provide them; 3) unable or unwilling to participate in a 26-week physical activity program 4) already enrolled in an exercise cardiac rehabilitation program prior to hospital admission; 5) hemodynamic instability or NYHA III-IV heart failure; 6) any other medical conditions that would prohibit participation in an 26-week physical activity program; 7) if admitted and not being discharged to home.

6. Subject recruitment

Potentially eligible participants will be identified from data requests to Penn Data Store and EPIC, and from the cardiology services or clinics at one of the University of Pennsylvania Health System hospitals by the study coordinator. Participants will be recruited either in person or by phone. Interested participants will be directed to the online Way to Health study website to review and provide informed consent, complete eligibility and baseline questionnaires, and if eligible enroll in the study.

7. Subject compensation

All participants will receive $20 for enrolling and $30 for completing the 26-week study. Participants that choose to attend the optional in-person visit for the six minute walk test will receive $30 for each visit.

Participants randomized to Arm 2 (financial incentive program) will be told at the beginning of each week during the ramp-up and maintenance phases that $14 has been placed in a virtual account. Each day that the participant does not meet their daily step goal, $2 will be removed from their account. Accrued winnings will be sent to the participant by check via US mail at the end of each month. There will be no financial incentive during the 2-week baseline period or 8-week follow-up period.

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. 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. If participants are still interested in participating, the Way to Health portal will take them through an automated 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. After consenting, participants will complete an online questionnaire to determine their eligibility. Eligible participants will be randomized to one of the study arms and led through an automated description of the details specific to that arm. 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

Potentially eligible participants will be identified from data requests to Penn Data Store and EPIC, and from the cardiology services or clinics at one of the University of Pennsylvania Health System hospitals by the study coordinator. Participants will be recruited either in person or by phone. Interested participants will be directed to the online Way to Health study website to review and provide informed consent, complete eligibility and baseline questionnaires, and if eligible enroll in the study.

All participants will receive a wearable device from the study coordinator and be asked to authorize the device to electronically transmit de-identified data to the study database.

Participants in this arm will be told to wear the step tracking device for the next two weeks and get used to the device. They will be provided with the study coordinator's email and phone number to contact with any questions. Participants will be told that they need to sync their wearable device with their smartphone in order for data to be transmitted to the study team. Participants will receive regular reminders during the baseline period to wear and sync their devices. If the study coordinator notices that a participant is not transmitting data during this two-week baseline period, they will contact the participant to determine the reason and offer assistance on how to use the device. After the two-week baseline period is completed, a baseline step count will be calculated using the second week of step count data and ignoring days on which the individual had less than 1,000 steps. We use the second week of data rather than both weeks in case the individual has more activity during the first week simply because they got a new device. We ignore days on which less than 1,000 steps are recorded because prior research suggests that this is unlikely to be appropriate capture of physical activity (Rowe et al. *Pediatric Exercise Science*. 2004;16:1-12. Kang et al. *Measurement in Physical Education and Exercise Science*. 2004;9(4):233-250.) and including these values may inappropriately downward bias the baseline step level for that individual. If at least four days of data are not available to calculate th baseline step count, then the period will extend until at least four days of data are available.

Once a baseline step level has been determined, participants will be sent a message to log into Way to Health to receive further instructions on their arm design as described previously in section 5.1: design.

9. Analysis plan

To compare sample characteristics between arms we will use t-tests or Wilcoxon rank-sum tests (F-tests or Kruskal-Wallis test) for continuous variables and Pearson chi square tests or Fisher's exact tests for categorical variables. In our primary analyses, we will compare the change in mean daily step count from baseline to maintenance period. In secondary analyses, we will compare the change from baseline period to ramp-up and follow-up periods. We will also compare change in sleep patterns and for those that participants change in distance in the six minute walk test. All hypothesis tests will be two-sided using a two-sided alpha of 0.05 as our threshold for statistical significance. We will use Stata and/or SAS to analyze the data. We will use multiple imputation for missing data.

10. Investigators

Mitesh Patel, MD, MBA, MS is the Principal Investigator (PI) and is an Assistant Professor of Medicine and Health Care Management at the Perelman School of Medicine and The Wharton School at the University of Pennsylvania. He has past experience leading six clinical trials using the Way to Health Platform to deploy interventions using financial and social incentives to promote weight loss and increased physical activity. He currently spends 80% of his effort on research and 20% on clinical and teaching activities.

Neel Chokshi, MD, MBA (Co-PI) is an Assistant Clinical Professor of Medicine at the Perelman School of Medicine. He is a clinical faculty member in the Consultative Cardiology Program, Echocardiography Laboratory and the Cardiac Stress Testing Laboratory at the Hospital of the University of Pennsylvania. Clinically, he is involved in improving and facilitating physical activity in cardiac patients through the development of the Exercise and Sports Cardiology program at the University of Pennsylvania. He currently spends 90% of his effort in clinical and teaching activities.

Srinath Adusumalli, MD (Co-Investigator) is a Fellow in Cardiovascular Medicine in the Department of Medicine at the Hospital of the University of Pennsylvania. He has previously led projects using technology-based solutions to improve the appropriateness of care delivered in the inpatient and outpatient settings. He currently spends 95% of his effort on clinical and teaching activities.

The Clinical Research Coordinator has experience with administering studies involving behavioral interventions and financial incentives, and also has experience training Research Assistants to follow study protocols.

11. Human research protection

11.1 Data confidentiality

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are in place to ensure the data are secure by using passwords and encryption, because the research involves web-based surveys.

11.2 Subject confidentiality

Research material will be obtained from participant surveys, from the wearable devices, and from the 6-minute walk test. All participants will provide informed consent for access to these materials. The data to be collected include demographic data (e.g., age, sex, self-identified race), outcome data, and daily activity data collected by the wearable device. Research material that is obtained will be used for research purposes only. The same procedure used for the analysis of automated data sources to ensure protection of patient information will be used for the survey data, in that patient identifiers will be used only for linkage purposes or to contact patients. The study identification number, and not other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project and is where the Way to Health web portal is based. The PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the

Department of Pathology, and the Leonard Davis Institute. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. Among the IT projects currently managed by PMACS are: (1) the capture and organization of complex, longitudinal clinical data via web and clinical applications portals from cancer patients enrolled in clinical trials; (2) the integration of genetic array databases and clinical data obtained from patients with cardiovascular disease; (3) computational biology and cytometry database management and analyses; (4) economic and health policy research using Medicare claims from over 40 million Medicare beneficiaries. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. All data for this project will be stored on the secure/firewalled servers of the PMACS Data Center, in data files that will be protected by multiple password layers. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by University of Pennsylvania system managers. We will use highly secure methods of data encryption for all transactions involving participants' financial information using a level of security comparable to what is used in commercial financial transactions. We believe this multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy. In addition, risk of loss of confidentiality will be minimized by storing completed paper copies of the surveys and signed informed consent forms in locked file cabinets in locked offices accessible only to trained study staff. Each subject will be assigned a unique identifier without identifying information, and data will be entered into an electronic database using only the unique identifier. Only trained study staff will have access to the code that links the unique identifier to the subject's identity. Electronic data will be stored on secure, password-protected firewalled servers at the University of Pennsylvania.

11.3 Subject privacy

Interested participants will be directed to the Way to Health portal where they will be asked to enter data related to eligibility and their demographic characteristics. Enrollment will include a description of the voluntary nature of participation, the study procedures, risks and potential benefits in detail. The enrollment procedure will provide the opportunity for potential

participants to ask questions and review the consent form information with family and friends prior to making a decision to participate. Participants will be told that they do not have to answer any questions if they do not wish and can drop out of the study at any time, without affecting their medical care or the cost of their care. They will be told that they may or may not benefit directly from the study and that all information will be kept strictly confidential, except as required by law. Subjects will be given a copy of the consent document. All efforts will be made by study staff to ensure subject privacy.

11.4 Data disclosure

The following entities, besides the members of the research team, may receive protected health information (PHI) for this research study: -Wells Fargo, the company which processes study-related payments. Patient addresses and account balances will be stored on their secure computers. –P'unk Ave., LLC, a software development company designing the Way to Health website. P'unk Ave. will not store any of the patients' PHI, but they will have access to de-identified patient information, for the purposes of website administration and development. -Misfit Wearables, the company that designs and manufactures the wearable devices used in the study to track participant physical activity. -Twilio, Inc., the company which processes some study-related messages. Twilio will store patients' phone numbers on their secure computers. -Qualtrics, Inc., the company which processes most study-related surveys. Qualtrics will house de-identified answers to these surveys on their secure servers. -The Office of Human Research Protections at the University of Pennsylvania -Federal and state agencies (for example, the Department of Health and Human Services, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes.

11.5 Data safety and monitoring

At the time of discharge from the hospital, all patients are given anticipatory guidance on when to seek medical attention. In addition, participants will be asked to report to the study team any episodes of chest pain, shortness of breath or other changes during periods of exercise. They will be reminded of this at the end of each week of the study. They can either call the study team or send an email. The research coordinator will call the participant to collect information regarding the issue and then the PI will review and determine whether it is ok to proceed, further investigation is needed, or the participant should stop the study. If the participant happens to also enroll in a standard cardiac rehabilitation program and is told that they should be pursuing a different step count than in the study, they will be asked to report that to the study team and their study count goal may be adjusted.

11.6 Risk/benefit

11.6.1 Potential study risks

To minimize the chance for serious and unexpected adverse events, study participants will be screened through exclusion criteria for any health conditions that may be exacerbated by participating in a physical activity study. The home-based rehab program tries to motivate a gradual step count increase that should pose little health risk to participants. Participants are given guidance on when to seek medical attention and a reporting protocol is in place to capture any changes in symptoms with physical activity. Another potential risk of this study is a breach of participant confidentiality. We will minimize this risk by linking individual identifying information with participant ID numbers only in one single secure file that will only be accessed by the study team in the case of an adverse medical event, participant dropout, or if otherwise deemed necessary by the Principal Investigator. All other identifying information will be discarded after initial contact with the Study Coordinator. Due to the financial incentives in this study, we will be collecting social security numbers so that we can complete W-9 forms for participants. Social security numbers only will be used to generate W-9 forms and will be deleted once they are no longer needed. We will also collect home addresses to mail incentive payments. This will be done through a University of Pennsylvania approved partnership with Wells Fargo. Accidental disclosure of social security numbers could lead to identity theft. We will use commercial-grade encryption to protect social security information in transit. Names and addresses will be stored in encrypted databases. These data will be viewable only by the respective participants and the study coordinator. All other members of the research team will be able to view only participant ID numbers. There will be no functionality in the web application to export a dataset with identifiable information. Even the study arms will be identified by code letters until both the statistician and PI agree that analysis is complete.

11.6.2 Potential study benefits

Through participation in this study, each participant will have the potential to increase their physical activity, which could improve their health and reduce their risk for future cardiovascular disease or other conditions such as diabetes, hypertension, and osteoarthritis. If this approach is effective, it could have tremendous benefits for society if adopted on a wide scale to help individuals increase physical activity after discharge from the cardiology service. It is expected that other people will gain knowledge from this study and that participation could help understand how to effectively motivate people to become more physically active. Participants may also receive no benefit from their participation in the study.

11.6.3 Risk/benefit assessment

Anticipated risks of this study should be minimal and the risk/benefit ratio is very favorable. To minimize the chance for serious and unexpected adverse events, study participants will be screened through exclusion criteria for any health conditions that may be exacerbated by participating in a physical activity study. Participants that increase physical activity may improve their health and reduce their risk for future cardiovascular disease or other conditions such as diabetes, hypertension, and osteoarthritis.