

## Supplement

Automated Hovering to Improve Outcomes following Myocardial Infarction (HeartStrong):

A Randomized Control Trial

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## **Initial Protocol**

### **Abstract**

The goal of this proposal is to test the implementation of an innovative approach to improving health and lowering cost for a high risk population of patients with acute myocardial infarction (AMI) immediately post-hospitalization. We will implement a new service delivery approach that will provide a foundation for a payment system that rewards keeping high-risk patients healthy and that deploys technology and a health care workforce of the future to implement prevention, care coordination, care process re-engineering, team-based care, and the use of data to support new care delivery models. This program is focused on coronary artery disease (CAD), but we expect that a successful implementation of this model will demonstrate a sustainable pathway to the three-part aim not just for CAD, but for many other conditions whose outcomes are highly sensitive to post-discharge coordination.

Those randomized into the intervention arm will receive a compound set of approaches including: (1) provision of up to 4 Vitality GlowCaps, a remote monitoring and medication bottle reminder device, for aspirin, beta blockers, statins and, if they received a stent for Plavix or similar anti-platelet agents; (2) assignment of an engagement advisor from the study team; (3) enlisting a family member or friend (patient choice) as a support person for medication adherence; (4) engagement incentives that will use lotteries where winning will be dependent on medication adherence; and (5) self-service/customization of the Way to Health platform communication methods. Participants in the intervention arm will be offered all of these components; however, they are still able to participate even if they opt not to use any of the list above. Both the intervention and control groups will have their claims data analyzed for 12 months post enrollment to examine the rate of hospital readmission, new vascular events, or new cardiovascular procedures.

### **Objectives**

#### 1.1 Overall objectives

The specific aims of this study are to:

1. Test the effectiveness of a state-of-the-art web-based portal with home-based wireless medication adherence devices and behavioral economic feedback mechanisms in preventing vascular events or rehospitalization in the 12 months following hospital admission for AMI
2. Deploy a new model of evidence based evolutionary learning that uses rapid cycle innovation in 3 successive planning cycles over the 36 months of this proposal

#### 1.2 Primary outcome variable(s)

Primary outcomes will be vascular events (AMI, stroke, acute coronary syndrome admission, or death)

#### 1.3 Secondary outcome variable(s)

Secondary outcomes will be hospitalization, repeat or new cardiovascular procedures, medication possession/gap ratios (for those patients for whom we can link to CVS Caremark pharmacy benefits data) and total cost of care.

### **Background**

#### 1.1 Program Goals

There is widespread agreement that incentive approaches that reward improved patient health instead of increased volume need to be developed and rigorously tested. (references listed in full grant submission) The goal of this proposal is to test the implementation of an innovative

approach to improving health and lowering cost for a high risk population of patients with acute myocardial infarction (AMI) immediately post-hospitalization. We will implement a new service delivery approach that will provide a foundation for a payment system that rewards keeping high-risk patients healthy and that deploys technology and a health care workforce of the future to implement prevention, care coordination, care process re-engineering, team-based care, and the use of data to support new care delivery models. This program is focused on coronary artery disease (CAD), but we expect that a successful implementation of this model will demonstrate a sustainable pathway to the three-part aim not just for CAD, but for many other conditions whose outcomes are highly sensitive to post-discharge coordination.

Coronary artery disease (CAD) is the single leading cause of death in the United States. (references listed in full grant submission) Approximately 16 million Americans have a history of CAD. Moreover, an estimated 1.2 million each year have a new or recurrent myocardial infarction (AMI) and 38% of them die from it in a given year. Medications such as aspirin, beta blockers, statins, and clopidogrel (Plavix) significantly reduce the rate of cardiovascular events and repeat treatment procedures, (references listed in full grant submission) which increase morbidity, mortality, and cost (references listed in full grant submission.) Despite the proven benefits of such medications, rates of adherence to chronic cardioprotective medications are frustratingly low (references listed in full grant submission) For example, one year after hospitalization for an acute coronary syndrome, nearly half of patients prescribed statins stop taking them (references listed in full grant submission) Given the well-established effectiveness of these agents, and how generally well tolerated they are, these low rates of adherence are concerning, but they also reflect a considerable opportunity target for improvement. Reducing CAD-related morbidity, mortality, and cost will depend to a great degree on effective strategies to help patients improve medication adherence and other health behaviors.(references listed in full grant submission)

Poor adherence to cardioprotective medications leads to worse medical treatment outcomes, higher hospitalization and mortality rates, and increased health care costs among CAD patients (references listed in full grant submission.) Hence, medication adherence among such patients is an important modifiable factor that affects the triple aim of improved health care quality, improved health, and lower cost. As many as 33 to 69 percent of all medication-related hospital admissions in the United States may be due to poor medication adherence, which amounts to a cost of \$100 billion a year (references listed in full grant submission.) Many previous successful efforts to improve adherence to these medications have been too complex to be implemented in clinical practice, not easily packaged or standardized, or required tremendous resource expenditures, limiting their applicability to and sustainability in resource constrained environments (references listed in full grant submission.)

The insight that improved adherence will improve care and lower cost is not new. What is new is the recognition that earlier efforts involving intensive case management are expensive and unwieldy, not easily scaled, and might be replaced with simpler and cheaper approaches leveraging more contemporary technology and concepts of behavior change.

This proposal has three main principles:

1. Principles of behavioral economics that have been developed, refined, and tested over the past decade offer practical insights into health behaviors that were previously unavailable and are not reflected in existing care models.
2. New technology, typically wireless devices for pill bottles, and mobile telephones, make engagement with patients substantially easier and more immediate now than ever before.
3. While randomized clinical intervention trials provide exceptional confidence of

comparative effectiveness in narrow interventions, they are slow and rigid and don't reflect the urgency that health care transformation currently requires. Principles of rapid cycle innovation are gaining acceptance as an alternative to or supplement of these traditional methods in supporting evidence for implementation success.

Care provision in the US tends to be reactive, visit-based, and physician-centered, in part because the incentives embedded in current models of financing care provide compensation for visits and not efforts to keep people healthy. However, this RFA provides an opportunity to change that in deploying a new model of chronic disease management that is proactive rather than visit-based, utilizes automation through technology as both a quality improvement and cost reduction strategy, and creates new workforce roles for non-physician providers such as engagement advisors (clinical social workers), nurses who monitor and act on inputs from home-based wireless monitoring technologies, IT personnel who support the deployment of such systems, and consumer psychologists/behavioral economists who test refinements of engagement strategies aimed at increasing the rate of patient adherence to treatment recommendations.

Our plan for testing the implementation of a new model for care delivery builds on infrastructure that we have developed and tested with NIH Support (RC2 AG036592-01, Asch and Volpp, Multiple PIs). We aim to improve medication adherence in patients following hospital admission for acute myocardial infarction (AMI), leveraging insights from three major domains of thinking. First, we will take advantage of the promise offered by insights from behavioral economics (see 1.2.b.). Second, we combine these insights with technologies such as cell phones, home-based peripheral devices, and web-based social networking services to deploy state-of-the-art approaches for motivating healthy behavior. Such technologies, which are easily adoptable by other organizations, create new opportunities for connecting with patients, allowing for reinforcing feedback that is frequent and closely tied to the timing of health-related decisions in ways that were previously infeasible for large numbers of patients due to the cost of the required personnel. Indeed, while many patients will require the kind of intensive and expensive engagement provided by nurses or community health workers or promotor, those approaches are challenging and expensive and for many patients might be replaced by cheaper and more scalable approaches, some of which can involve patients own family and support networks. Third, through a process of rapid cycle innovation and testing we will make ongoing improvements in the intervention design with 3 product cycles within the timeframe of this proposal (see 1.2.g.). The main intervention will be informed by a series of side experiments that will test ways to improve patient engagement using tools from social networking, behavioral economics, and consumer marketing. We designed this process in response to this RFA and have labeled it evidence-based evolutionary learning a term that is meant to reflect both the sense of urgency health care transformation requires and the importance of strong evidentiary standards to get it right and to do so credibly.

Innovation is also reflected in the interdisciplinary team we have built for this project through partnership with the University of Pennsylvania Health System (UPHS) (which serves as a referral center for AMI care for patients throughout the Philadelphia metropolitan area and Southern New Jersey); Horizon Blue Cross Blue Shield, which provides services to 3.5 million New Jersey (NJ) residents including nearly 2,000 patients hospitalized with AMI per year throughout NJ; Independence Blue Cross, an insurer of approximately 2 million in Southeastern PA; Keystone Mercy, an insurer for approximately 320,000 Medicaid recipients in Southeastern PA; Aetna, one of the largest insurers in the United States; and HealthFirst, a Medicare managed plan in New York City with approximately 600,000 members and CVS Caremark, with 40 million members throughout the US. The external partners will be supported by a team of faculty members from the Departments of Operations and Information Management, Marketing, and Health Care Management at the Wharton School along with faculty from the Perelman School of Medicine at

the University of Pennsylvania (UPENN) and from the Center for Health Incentives and Behavioral Economics at the Leonard Davis Institute, 1 of 2 NIH-funded Centers in Behavioral Economics and Health in the US. Approximately 1,500 participants will be enrolled post-hospital admission for AMI from hospitals throughout NJ and, southeastern Pennsylvania for the main intervention study.

## **Statistical Considerations**

### 1.2 Power and sample size (from 4.1.b.i.of the full grant):

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%,<sup>60</sup> and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1500 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 500 control and 1000 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurer partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

### 1.3 Data analysis

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding<sup>96,97</sup> (references listed in full grant submission) or predictive ability. Models will be assessed using standard diagnostic techniques.<sup>98</sup> (references listed in full grant submission)

We expect to have nearly complete follow-up data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the

sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## **Study Design**

### 1.1 Design

Participants in this study will be identified in primarily 1 of 2 methods.

The first will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and the coordinator will work with hospital staff to meet with the patient in person and invited to participate. If the patient has already been discharged, they will be scheduled to receive a recruitment phone call to their home.

The second method involves patients who are hospitalized outside the UPHS health systems who are identified through our insurer partners. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreement (DUA) and/or Business Associates Agreement (BAA), as determined by negotiations between them and the Penn Medicine privacy officer, with that health insurer that allows for the receipt of PHI for screening and recruitment purposes for this study. The data will include principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2), name, address, phone number, insurance provider. Since all patient will have the same diagnosis code, we will just ask for the contact information and dates of hospital discharge minimizing the risk to participants of this waiver of authorization. These agreements will also include HIPAA waivers from each insurance provider to authorize the release of their PHI for use in screening and recruitment for this study.

For patients identified in the UPHS health system, a study coordinator will attempt to make contact with them 1 or 2 days before discharge from the hospital to discuss the study, confirm eligibility and enroll the patient if they are interested. Enrollment in person will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document.

For those patients not seen in the UPHS health system, or for those we were not able to contact before discharge from UPHS, the study coordinator will mail a recruitment packet containing a recruitment letter and a copy of the Consent/HIPAA document. In a few days, a coordinator will call the patient to conduct a recruitment telephone call. The coordinator will ask the patient if they are interested in answering some screening questions to confirm they are eligible to participate in this research study. If they are eligible, the coordinator will review the verbal Consent/HIPAA script to the patient over the phone and obtain verbal consent and HIPAA authorization. Remote enrollments will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal

consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document.

After confirming consent to participate, the coordinator begins entering basic demographic information for the patient into the WTH site, and the coordinator will use the Way to Health web platform to randomize patients into this study.

Patients will be randomized into 1 of the 2 study arms. After randomization occurs, the study coordinator will inform the patient of the randomization group they have been assigned into. The intervention group (1) will use the GlowCaps, a remote monitoring and reminder pill bottle; (2) will be assigned an engagement advisor from the study team; (3) asked to provide the study team with names and contact information of up to 3 family members or friends as support partners for medication adherence. The study team will contact these people in order listed until 1 agrees to serve in this role; (4) will select a 2-digit lucky number to be used as part of the sweepstakes-based engagement incentives in which eligibility to win will be conditional on medication adherence; and (5) will determine their preferences for Way to Health platform communication methods during the study.

The group receiving the program intervention will also have their claims data analyzed for the 12 months post-enrollment.

The control group will have the health insurance claims records analyzed over the next 12 months.

Instructions for control arm will read: Thank you for participating in this study. You have been randomized to the control arm of this study. Our study team will analyze health insurance claims records over the next 12 months and use any information gained about readmissions to the hospital or health related procedures you may undergo during this time. This information will be very helpful for the analysis of this study data and help us to understand whether the intervention is improving patient outcomes. (For full script, please see attached Control script uploaded with this submission)

Instructions for intervention arm will read: Thank you for participating in this study. You have been randomized to the intervention arm of this study. The study team will send you a study packet in the next few days to the mailing address you indicated in this enrollment process. The packet will include up to 4 Vitality GlowCaps, which is a remote monitoring and reminder pill bottle, you will use for the medications we are monitoring in this study.

As a participant in this study, you will have access to our study engagement advisors from the study team, who will assist with your transition from hospital to home and help you get started with this study. Another part of this study is naming a support person who can remind you about taking your medications. We are asking you to provide the names of up to 3 family members or friends, of your choice, as a support person for medication adherence. If you provide more than one name, the study team will contact these people in the order of your preference until 1 person agrees to serve in this role. This person will only receive a message from our study if you have not opened the study GlowCaps to take your medicine for 2 days in a row, or 2 days over a 72 hour time period. They will have the option of receiving a text, an email, or interactive voice recording (IVR). The report they receive will not contain your name or any identifying information. Your support friend/family member will receive a phone call from our study team if it appears that you have missed 5 days of medication in a row. Your primary care physician will receive a phone call from our study team if it appears that you have missed 7 days of medication in a row.

As a participant in this study, you are also eligible for daily sweepstakes that is based on whether or not you use the GlowCaps pill bottles as selected. Please select the 3 digit number to be used with in the daily sweepstakes incentives where eligibility to win will be conditional on medication adherence; Finally, there are certain customizations that you can make to the Way to Health platform. Would you prefer to receive sweepstakes messages via text message, email or automated phone call?

The group receiving the program intervention will also have claims data monitored for the above over the duration of the study

During the enrollment process the Coordinator collects:  
SSN for W-9 from intervention group participants and asks them to pick sweepstakes number to be used in the study.

### 1.2 Consent Process

We are not requesting a waiver of consent/HIPAA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

We are requesting a waiver of the requirement to document consent and HIPAA authorization with a signature for participants enrolled into this study since we believe the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. [45 CFR 46.117(c)(2)]

A majority of participants being enrolled in this study will be enrolled via a remote recruitment process; therefore we will read the IRB approved Consent/HIPAA script over the phone to each patient and ask them to provide verbal consent and verbal HIPAA authorization for use of their data in the study. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study. At this point, the participant is randomized into 1 of the 2 study groups. After randomization the coordinator will inform the participant of their assignment and read the instructions for their study group.

If the participant requests a copy of the consent form requests a copy of the consent form, the study coordinator will mail a copy to their home address.

For patients enrolled in person at UPHS, we are also requesting a waiver of documentation of signed consent and HIPAA authorization. For these enrollment visits, the study coordinator will visit the patient in the hospital 1 to 2 days before their scheduled discharge date. The coordinator will review the Consent/HIPAA script with the patient. If they consent to participate in the study, the coordinator will use a study laptop to access the WTH web platform for this study and will create a participant user account for the patient. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study and will explain the arm assignment to the participant as noted above.

The participant will be given a copy of the consent form upon request.

For participants enrolled into the intervention arm remotely, the coordinator will mail up to 4 GlowCaps to them for use in the study. Those enrolled while in the hospital will be given the GlowCaps to take home with them. A study coordinator will schedule a follow up call with all participants to facilitate setting up the GlowCap device and the transfer of their medications into the GlowCaps.

### **Study duration**

The duration of participation for each individual participant is expected to be 12 months. We expect the total duration of the study to last 36 months for the completion of all 3 versions of the study noted below.

We will recruit patients for version 1.0 from January 2013 September 2013 and version 2.0 from October 2013 June 2014. Patients will be followed for a 1 year period until the end of the grant in June 2015.

### **Resources necessary for human research protection**

The project will take place at the Leonard Davis Institute Center for Health Incentives and Behavioral

Economics (LDI CHIBE) at the University of Pennsylvania (UPENN). The team includes investigators experienced in clinical medicine, health behavior interventions, clinical trials, behavioral economics, cost-effectiveness analysis, and program evaluation. Our partnership combines the resources and capabilities of a major university (the Wharton School and the Perelman School of Medicine at the University of Pennsylvania), a major health care provider (UPHS), insurers (Horizon BCBS, Keystone Mercy, and Independence Blue Cross, Aetna, HealthFirst), and the largest Pharmacy Benefits Manager in the US (CVS Caremark).

Multiple PIs: Dr. Kevin Volpp directs the LDI CHIBE and the NIA-funded PENN-CMU Roybal P30 Center on Behavioral Economics and Health and is a Professor of Medicine at the Perelman School of Medicine (SOM) and Professor of Health Care Management at the Wharton School at UPENN. He has led numerous studies of patient financial incentives and behavioral economic interventions. David Asch, MD, MBA - Co-Project Director is Executive Director of the Penn Medicine Center for Innovation, Professor of Health Care Management and Economics and Professor of Operations and Information Management at Wharton and Professor of Medicine at Perelman. The financial analyses will be co-led by Dr. Shivan Mehta. Statistical Analysis: Dr. Andrea Troxel (Co-I, Statistician) is Director of Biostatistics for LDI CHIBE and a Professor of Biostatistics at UPENN. She has over 15 years of experience in the design, conduct, and analysis of clinical studies, including randomized trials that involve repeated measurements. There will be a project manager and research coordinator assigned to this study to facilitate enrollment, GlowCap distribution, follow up contacts and payment distributions.

This study will be supported on a secure web portal on the Way to Health platform, modified to the specifications of this study.

### **Target population**

Eligibility Criteria: Patients admitted to hospitals throughout New Jersey, Pennsylvania, New York or at the University of Pennsylvania Health System who are discharged(or scheduled to be discharged) with a principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2)

and a length of stay of 1 to 180 days will be considered eligible for the study and randomized to either the control arm, receiving standard care and having records analyzed for this study or into our new model of evidence-based evolutionary care.

The total target enrollment will be 1500 participants. 500 will be enrolled into the control arm and 1,000 will be enrolled into the program intervention arm.

### **Subjects enrolled by Penn Researchers**

1500

### **Subjects enrolled by Collaborating Researchers**

0

### **Accrual**

Participants in this study will be identified in primarily 1 of 2 methods.

Participants will be recruited either at the time of hospital discharge from an admission with AMI or immediately thereafter from UPHS hospitals or hospitals throughout Pennsylvania (PA), New Jersey (NJ), or New York (NY) through our partnerships with Horizon, Independence Blue Cross, Aetna, Keystone Mercy, and HealthFirst.

The first method will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS to create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and contacted in person for a screening and enrollment interview. If these patients are discharged before we can contact them, they will be scheduled to receive a recruitment phone call in their home.

The second method involves patients who are seen outside the UPHS health systems. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreement (DUA) and/or Business Associates Agreement (BAA), as determined by negotiations between them and the Penn Medicine privacy officer, with that health insurer that allows for the receipt of PHI for screening and recruitment purposes for this study. The agreements with these insurance partners will include Business Associates Agreements/HIPAA waivers from each partner authorizing release of their patient data to University of Pennsylvania for screening and recruitment activities.

### **Key inclusion criteria**

Eligibility Criteria: Patients admitted to hospitals throughout New Jersey or at the University of Pennsylvania Health System who are discharged(or scheduled to be discharged) to their homes with a principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2) and a length of stay of 1 to 180 days will be considered eligible for the study and randomized to either standard care or our new model of evidence-based evolutionary care. Patients must be over the age of 18 and be discharged to home.

**Key exclusion criteria**

Exclusion criteria: Patients will be excluded if they are less than 18 years old, will not or cannot give consent, or have a markedly shortened life expectancy (diagnosis of metastatic cancer, end-stage renal disease on dialysis, or dementia). Patients who have a known allergy or history of side effects to any of the 3 targeted classes of medications will be enrolled but provided GlowCaps only for the remaining medications.

**Vulnerable Populations**

No vulnerable populations are included in the research study

**Populations vulnerable to undue influence or coercion**

Subjects will be given consent forms and reminded their participation is voluntary and they will be informed that their decision to participate or not participate will in no way affect their medical care.

**Subject recruitment**

Participants in this study will be identified in primarily 1 of 2 methods.

Participants will be recruited either at the time of hospital discharge from an admission with AMI or immediately thereafter from UPHS hospitals or hospitals throughout Pennsylvania (PA), New Jersey (NJ), or New York (NY) through our partnerships with Horizon, Independence Blue Cross, Aetna, Keystone Mercy, and HealthFirst.

The first method will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS to create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and contacted in person for a screening and enrollment interview. If these patients are discharged before we can contact them, they will be scheduled to receive a recruitment phone call in their home.

The second recruitment method involves patients who are seen outside the UPHS health systems. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreements (DUA) and/or Business Associates Agreement (BAA) with that health insurance provider, as determined by negotiations between them and the Penn Medicine privacy officer, that allows for the receipt of PHI for screening and recruitment purposes for this study. The agreements with each insurer partner will include HIPAA waivers from each partner authorizing release of their patient data to University of Pennsylvania for screening and recruitment activities.

Remote enrollments will be conducted via a phone call from the study staff. We will contact patients by phone after hospital discharge to confirm eligibility and to see if they are interested in participating in the study. If participants are interested, the coordinator will complete an intake form and consent via the remote enrollment process over the phone. The coordinator will enter patient information directly into the Way to Health web portal for this study.

After providing consent, the patient will be randomized into 1 of the 2 study arms and will be read the script for either the control or the intervention arm of the study.

**Subject compensation**

Subjects will be financially compensated for their participation.

The 500 participants randomized into the control arm will not receive financial compensation for this study.

The 1,000 participants randomized into the intervention arm will receive an average expected sweepstakes payment of \$1.40/day if they are adherent in using the GlowCap electronic pill bottles.

**Procedures**

The study staff will screen and identify eligible participants in 1 of 2 methods. First, through UPHS Medview medical record review for UPHS patients. Second, via data feeds sent in daily data feeds from our insurance partners for patients hospitalized outside the UPHS healthcare system.

For patients identified in the UPHS health system, a study coordinator will attempt to make contact with them 1 or 2 days before discharge from the hospital to discuss the study, confirm eligibility and conduct the enrollment visit with the patient if they are interested. In-person enrollments will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. For in person enrollments, we would like to have the participants confirm consent with the coordinator who will indicate their consent in the Way to Health system by clicking the consent to participate study on the Way to Health web portal for this study.

For those patients not seen in the UPHS health system, or for those we were not able to contact before discharge from UPHS, the study coordinator will contact via telephone to conduct the screening and enrollment visit remotely with interested patients.

In both cases, the coordinator will ask the patient if they are willing to answer some screening questions to confirm they are eligible. If they agree, the coordinator will read through a brief screening survey to confirm they meet the criteria of having had a heart attack, have been prescribed a statin, beta-blocker, anti-platelet and aspirin and are living at home and not a long-term care facility.

After confirming eligibility, the coordinator will read the verbal Consent/HIPAA script to the patient over the phone and obtain verbal consent and HIPAA authorization. Remote enrollments will be facilitated by the coordinator accessing the Way to Health web portal for this study so they can direct enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document with the initial recruitment letter mailed to their home.

At this time, patients will be randomized into either the control or intervention arms at a ratio of 1(control):2(intervention).

The control group will simply have their claims data analyzed for a 12 month period. We will be examining these data for hospital admissions, new vascular events (AMI, stroke, acute coronary syndrome admission), or repeat or new cardiovascular procedures.

Participants randomized into this group will have the Control group script read to them at this point.

Those randomized into the intervention arm will receive a compound set of approaches including: (1) provision of up to 4 Vitality GlowCaps, a remote monitoring and reminder pill bottle, to use for the cardiovascular medications aspirin, statins, and beta blockers (and Plavix or prasugel if they received a stent); (2) assignment of an engagement advisor from the study team; (3) enlisting a family member or friend (patient choice) as a support person for medication adherence (participants will be asked to identify up to 3 in descending order of preference); (4) engagement incentives that will use lotteries where eligibility to win will be dependent on medication adherence; and (5) self service/customization of the Way to Health platform communication methods. Participants in the intervention arm will be offered all of these components, however, they are still able to participate even if they opt not to use any of the list above. The group receiving the program intervention will also have their claims data analyzed for the 12 months in the study to examine rates of hospital admissions, new vascular events (AMI, stroke, acute coronary syndrome admission), or repeat or new cardiovascular procedures.

Participants randomized into this group will have the Intervention group script read to them at this point.

The Study Coordinator will collect the SSN to enter into the W-9 webpage on the Way to Health web port for intervention group participants only for this study to facilitate participant incentive payments. The coordinator will ask the participant to provide details about medications they have been prescribed, contact information for the person (s) they want us to contact to serve as the support person for medication adherence, and their preferences for receiving communications from the Way to Health system.

After collecting this information, the study coordinator will configure a set of up to 4 GlowCaps to send via express shipping to the participants for use with the indicated medications.

On the day the participant is expected to receive the GlowCap package sent by the study staff, they will receive a phone call from the study coordinator/engagement advisor to provide them with assistance in transferring their medications into the GlowCaps. The study coordinator/engagement advisor will confirm medications and make sure the alarm is set to the desired time for individual medications, based on the times provided by the participant on the phone call.

The schedule of Alarms for participants and Feedback Partners in the intervention arm is as follows:

*Daily message*- all intervention group participants will receive a daily message about their use of the GlowCaps in the last 24 hour period and whether or not their study sweepstakes number was drawn on the study sweepstakes system. The messages will be similar to the following: A. Congratulations, you used your glowcaps correctly yesterday and your study number was drawn. You won (\$5 or \$50, depending on number of digits that were drawn for participant) B. We are sorry, you did not use your glowcaps correctly yesterday and your study number was drawn. You could have won (\$5 or \$50, depending on number of digits that were drawn for participant) C. You used your glowcaps correctly yesterday but your study number was not drawn, keep up the good work D. You did not use your glowcaps correctly yesterday. You never know when your study number may be drawn, please remember to use your GlowCaps each day you are scheduled to take your medicine.

*Feedback Partners* - If the participant identifies a feedback partner and they agree to serve in this role, they will also have an account created for them on the Way to Health platform for this study. This person will receive a notification starting at 48 hours, or if there are 2 of 3 days (and then daily through 7 days) without feedback adherence messages from the participants GlowCaps. The interactions that the feedback partner has with the participant are up to their discretion. This role is not supposed to provide trained assistance to the participant, but rather serve the role of providing social support around their medication adherence. Both the participant and their feedback partner will be notified at study outset that they will automatically be sent these alerts. Numerous studies, including our own, have shown that peer mentoring and social support are helpful in improving adherence and patient outcomes. This reflects engagement of a powerful social force: the ability of peers and family to help one another that can be used to augment other ways of helping patients improve their medication adherence. The feedback partner will let the study team know their desired method of receiving these notifications from the Way to Health program. The available options are text, email or interactive voice recording.

*Engagement Advisors* - The primary role of the Study Coordinator/Engagement Advisors will be to assist patients in getting started in the intervention, to monitor the patients medication adherence using the daily Vitality GlowCaps information, and to serve as a resource for patients who are struggling to stay adherent to their medications. While this will help to quickly spot gaps in adherence and intervene, the role of this engagement advisor is to get involved only when automated feedback on adherence through the WTH system (including incentives) proves insufficient. After 4 days without feedback adherence messages from the participants GlowCaps, the Study Coordinator/Engagement Advisors will contact the participants to inquire about the reasons they have not used the GlowCaps for this time period and to offer to provide assistance. The coordinator/engagement advisor will continue to receive daily alerts on non-adherent patients and on day 5 will contact the support friend/family member to enlist their support. On day 7 without medication, the engagement advisor will attempt to reach the primary

care providers office designated by the patient on enrollment to enlist their support.

3 months post enrollment an automated message will be sent to the participant for a reminder that if they have any questions about the GlowCaps or any medication updates to make they should contact the study team.

5 1/2 months post enrollment - the study platform will send an alert to the participant to let them know that they will be receiving a replacement set of GlowCaps because the batteries in the existing GlowCaps will begin to lose power. Once the new set of GlowCaps are received by the participant, a Study Coordinator/Engagement Advisor will call the participant to talk through the process of getting rid of the old GlowCaps and replacing them with the new GlowCaps.

12 months post enrollment the participant will receive automated message 2 weeks before end of study that program is ending, should tell them to not use GlowCaps anymore since they will no longer be monitored by the study team.

## **Analysis Plan**

### **1.1 Power and sample size**

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%,<sup>60</sup> (reference from full grant proposal) and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1500 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 500 control and 1000 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurance partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health and be available 24/7. The trial design combines the best elements of

standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

## 1.2 Data analysis

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding<sup>96,97</sup> (refs from original submission) or predictive ability. Models will be assessed using standard diagnostic techniques.<sup>98</sup> (ref from original submission)

We expect to have nearly complete follow-up data since our primary outcomes will be analyzed using claims data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

### **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. Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. Wherever feasible, identifiers will be removed from study-related information. Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

### **Subject Confidentiality**

The long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data.

We are not requesting a waiver of consent/HIPPA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

The initial patient information collected for screening and recruitment will consist of name, address, phone number, information about medical condition indicating heart attack. For patients from UPHS this information will come from Electronic Chart reviews. For patients outside the UPHS healthcare system, this information will be provided by our insurance

partners.

### 1.1 Database Security/Protection against Risk

To assure that patient, physician and other informant confidentiality is preserved, individual identifiers (such as name and medical record number/physician billing identifier) are stored in a single password protected system that is accessible only to study research, analysis and IT staff. This system is hosted on site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is in this system, they will be given a unique study identification number (ID). Any datasets and computer files that leave the firewall will be stripped of all identifiers and individuals will be referred to by their study ID. The study ID will also be used on all analytical files. Please see attached document (WTH database security grant-protocol text FINAL (2)) for full database security details.

The GlowCaps adherence monitoring devices will provide adherence data from each participant. This information is transmitted via cellular signal without any subject identifiers.

### 1.2 Vitality GlowCaps data security

Vitality's GlowCaps measure adherence with prescription drug regimens (i.e. whether the drug was taken as prescribed). In most cases the data is de-identified and Vitality is provided only with a study ID and a "cap ID(s)" for each participant. However some projects may use additional GlowCap functionality in which case participant phone number, e-mail address and medication dosing schedule may be entered onto Vitality's secure server. Data transfer from Vitality to Way to Health takes place via a secure connection (https). A HIPAA Business Associate Agreement is in place

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, adherence data (from the GlowCaps), and medical conditions and medications. 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 no 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 UPENN Biomedical Informatics Consortium (BMIC) will be the hub for the hardware and database infrastructure that will support the project and where the Way to Health web portal is based. The BMIC 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 BMIC 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 BMIC 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. BMIC requires all users of data or applications on BMIC servers to complete a BMIC-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. Curriculum includes 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 Health Insurance Portability and Accountability Act certification in accordance with University of Pennsylvania regulations. All data for this project will be stored on the secure/firewalled servers of the BMIC 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. 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 UPENN.

Please see the attached documents for more detail about data security uploaded in the procedures section:

1. Way to Health Database Security/Protection against Risk.
2. Way to Health External Partner Privacy
3. Way to Health global privacy

### **Sensitive Research Information**

This Research does not involve collection of sensitive information about the subjects that should be excluded from the electronic medical record

### **Subject Privacy**

At the time the University of Pennsylvania IT study staff receives patient data, they will upload the patient data into the secure, web based data base (RedCap) and a study identification number will be generated for each patient. A link between the study ID number and the patient PHI will need to be maintained to ensure the study staff can track recruitment efforts to potential participants and to avoid contacting any patients who have previously declined to participate.

To assure that patient confidentiality is preserved, individual identifiers (such as name and plan ID#) are stored in a single password protected system that is accessible only to study research, analysis and IT staff. This system is hosted on site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is in this system, they will be given a unique study identification number (ID). Any datasets and computer files that leave the firewall will be stripped of all identifiers besides the study ID and individuals will be referred to only by their study ID. The study ID will also be used on all analytical files.

REDCap is a secure web application for building and managing online surveys and databases. The institution installing REDCap will store all data captured in REDCap on its own servers. Therefore all project data is stored and hosted there at the local institution (University of Pennsylvania), and no project data is ever transmitted at any time by REDCap from that institution to another institution or organization.

Privacy of all study data will be maintained by restricting access to the identifiable information only to approved study staff who have received subject confidentiality and privacy training.

Study coordinators will access patient contact information from the data base to conduct recruitment visits in person, for UPHS patients, and via phone call, for remote patients. The study coordinator will review the consent script, which will include a description of the voluntary nature of participation, the study procedures, risks and potential benefits in detail. Participants will be told 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.

Enrollment visits will be conducted by the study coordinators who will enter patient information directly into the Way to Health website once a participant has consented to participate. This database is hosted on a secure server as detailed in the subject confidentiality section. Study coordinators may have to contact patients and feedback partners during the course of the study and will use the WTH database to access contact information to facilitate this contact. For participants in the intervention arm, if the rate of non-adherence, as recorded by the GlowCaps, rises above a certain threshold, the study team may also contact the participants Primary Care Physician. This will be explained to the participant in the consent process and again when the details of the intervention arm are explained by the coordinator. Participants will be asked to provide the name of their PCP during the enrollment process.

PHI will not be shared with anyone outside the parameters of the study as detailed in the Consent/HIPAA process

### **Data Disclosure**

The following entities, besides the members of the research team, may receive PHI for this research study: Vitality, Inc., the company which records the responses from the GlowCap. Daily adherence information will be stored on their secure computers. 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 A data and safety monitoring board organized to oversee this research.

Limited participant information will be shared with insurers of the participant in order to track the Primary and Secondary outcomes of the study.

## **Protected Health Information/ Data Protection**

- Name
- Street address, city, county, precinct, zip code, and equivalent geocodes
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone and fax number
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan ID numbers
- Account numbers

## **Consent Process**

### 1.1 Overview

We are not requesting a waiver of consent/HIPAA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

We are requesting a waiver of the requirement to document consent and HIPAA authorization with a signature for participants enrolled into this study since we believe the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. [45 CFR 46.117(c)(2)]

A majority of participants being enrolled in this study will be enrolled via a remote recruitment process, therefore we will read the IRB approved Consent/HIPAA script over the phone to each patient and ask them to provide verbal consent and verbal HIPAA authorization for use of their data in the study. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study. At this point, the participant is randomized into 1 of the 2 study groups. After randomization the coordinator will inform the participant of their assignment and read the instructions for their study group.

If the participant requests a copy of the consent form requests a copy of the consent form, the study coordinator will mail a copy to their home address.

For patients enrolled in person at UPHS, we are also requesting a waiver of documentation of signed consent and HIPAA authorization. For these enrollment visits, the study coordinator will visit the patient in the hospital 1 to 2 days before their scheduled discharge date. The coordinator will review the Consent/HIPAA script with the patient. If they consent to participate in the study, the coordinator will use a study laptop to access the WTH web platform for this study and will create a participant user account for the patient. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study and will explain the arm assignment to the participant as noted above.

A copy of the Consent/HIPAA document will be included in the recruitment mailings sent to all patients before being called by the study team.

For participants enrolled into the intervention arm remotely, the coordinator will mail up to 4 GlowCaps to them for use in the study. Those enrolled while in the hospital will be given the GlowCaps to take home with them. A study coordinator will schedule a follow up call with all participants to facilitate setting up the GlowCap device and the transfer of their medications into the GlowCaps.

#### 1.2 Children and Adolescents

Not applicable. We are only enrolling subjects 18 years of age and older.

#### 1.3 Adult Subjects Not Competent to Give Consent

We plan to enroll only those patients who are competent to provide consent for themselves.

#### 1.4 Written Statement of Research

All patients recruited through remote procedures will be mailed a Recruitment Letter and a copy of the Combined Consent/HIPAA authorization for this study. For in person enrollments at UPHS, the study coordinator will have copies of the written statement of the research on hand to provide to all participants.

#### **Potential Study Risks**

As this study does not involve any medical decision making and only tests the use of social behavioral approaches to encouraging patients to use evidence-based treatments that their providers have prescribed following a heart attack, we consider this study minimal risk. The primary risk would be from a breach of confidentiality involving medical records reviews and monitoring of statin adherence with GlowCaps, which will be maintained on the Way to Health platform. This risk has been mitigated by extensive privacy protection protocols, a highly secure data storage system, and a plan to remove identifiers from the data wherever possible. In addition, all personnel will be held to high standards of upholding confidentiality and safeguarding patient privacy.

#### **Potential Study Benefits**

The immediate benefits of this study for participants may include an improvement in adherence to medications that have been proven to be effective in improving patient outcomes. It is

possible that the benefits for many participants will be minimal. However, as mentioned, we believe the risks are also minimal. Overall the risk to benefit ratio is favorable given the long term potential of on health and health related behaviors Database Security/Protection against Risk. Participants in this study may not receive any direct benefits. Some may benefit directly by improving their adherence to the medications and thus lower their risk for future heart attacks, strokes and death, improve their quality of life, and reduce future medical care costs. The control group is unlikely to directly benefit, as this group will continue to simply receive usual care.

Knowledge gained from the study will assist in development of interventions in other high-risk patient populations in which non-adherence rates are high. The potential public health impact of a successful intervention to improve adherence to statin medications is enormous and could reduce the number of deaths from heart attacks and strokes by tens of thousands in the United States each year.

The risks of loss of confidentiality are minimal in this study. Thus, the benefits of this research to the participants studied, and to society at large, far surpass the risks.

#### **Alternatives to Participation (optional)**

Patients are free not to participate in this study and will thereby receive no reduction in the usual care received from their health care providers or insurers for this condition.

#### **Data and Safety Monitoring**

While we consider this study of minimal risk to participants, we have set up an external DSMB. This DSMB is scheduled to meet every 6 months to review study progress and ensure patient safety is maintained.

The members making up this board are a highly experienced group that includes Donald Lloyd Jones, MD, Chairman of Preventive Medicine at Northwestern and one of the leading cardiology clinical researchers nationally; Eugene Oddone MD, Chief of the Durham VA Health Services Research Center of Excellence and a leading health services researcher; and Constantine Gatsonis, Henry Ledyard Goddard University Professor of Biostatistics and Chair of the Department of Biostatistics at Brown University.

#### **Risk/ Benefit Assessment**

Poor medication adherence following AMI events is a major public health problem with few scalable, cost-effective solutions. This study is designed to test an intervention that incorporates many components that have previously demonstrated improvement in past studies. We believe the combination of these approaches in this study will provide the research and public health communities with important information that can lead to broad generalizability in treating people at risk for coronary events and death nationally, as these types of interventions could be set up by insurers and healthcare systems to be broadly utilized.

## Final Protocol

**\*\*New changes from initial protocol notated in bold, parts removed from initial protocol notated in strikethrough**

### Abstract

The goal of this proposal is to test the implementation of an innovative approach to improving health and lowering cost for a high risk population of patients with acute myocardial infarction (AMI) immediately post-hospitalization. We will implement a new service delivery approach that will provide a foundation for a payment system that rewards keeping high-risk patients healthy and that deploys technology and a health care workforce of the future to implement prevention, care coordination, care process re-engineering, team-based care, and the use of data to support new care delivery models. This program is focused on coronary artery disease (CAD), but we expect that a successful implementation of this model will demonstrate a sustainable pathway to the three-part aim not just for CAD, but for many other conditions whose outcomes are highly sensitive to post-discharge coordination.

Those randomized into the intervention arm will receive a compound set of approaches including: (1) provision of up to 4 Vitality GlowCaps (**or MedSignal device**), a remote monitoring and medication bottle reminder device, for aspirin, beta blockers, statins and, if they received a stent, for Plavix or similar anti-platelet agents; (2) assignment of an engagement advisor from the study team; (3) enlisting a family member or friend (patient choice) as a support person for medication adherence; (4) engagement incentives that will use lotteries where winning will be dependent on medication adherence; and (5) self-service/customization of the Way to Health platform communication methods. Participants in the intervention arm will be offered all of these components; however, they are still able to participate even if they opt not to use any of the lists above. Both the intervention and control groups will have their claims data analyzed for 12 months post enrollment to examine the rate of hospital readmission, new vascular events, or new cardiovascular procedures.

### Objectives

#### 1.1 Overall objectives

The specific aims of this study are to:

1. Test the effectiveness of a state-of-the-art web-based portal with home-based wireless medication adherence devices and behavioral economic feedback mechanisms in preventing vascular events or rehospitalization in the 12 months following hospital admission for AMI
2. Deploy a new model of evidence based evolutionary learning that uses rapid cycle innovation in 3 successive planning cycles over the 36 months of this proposal

#### 1.2 Primary outcome variable

Primary outcomes will be vascular events (AMI, stroke, acute coronary syndrome admission, or death)

#### 1.3 Secondary outcome variables

Secondary outcomes will be hospitalization, repeat or new cardiovascular procedures, medication possession/gap ratios (for those patients for whom we can link to CVS Caremark pharmacy benefits data) and total cost of care.

## **Background**

### **1.1 Program Goals**

There is widespread agreement that incentive approaches that reward improved patient health instead of increased volume need to be developed and rigorously tested (references listed in full grant submission) The goal of this proposal is to test the implementation of an innovative approach to improving health and lowering cost for a high risk population of patients with acute myocardial infarction (AMI) immediately post-hospitalization. We will implement a new service delivery approach that will provide a foundation for a payment system that rewards keeping high-risk patients healthy and that deploys technology and a health care workforce of the future to implement prevention, care coordination, care process re-engineering, team-based care, and the use of data to support new care delivery models. This program is focused on coronary artery disease (CAD), but we expect that a successful implementation of this model will demonstrate a sustainable pathway to the three-part aim not just for CAD, but for many other conditions whose outcomes are highly sensitive to post-discharge coordination.

Coronary artery disease (CAD) is the single leading cause of death in the United States. (references listed in full grant submission) Approximately 16 million Americans have a history of CAD. Moreover, an estimated 1.2 million each year have a new or recurrent myocardial infarction (AMI) and 38% of them die from it in a given year. Medications such as aspirin, beta blockers, statins, and clopidogrel (Plavix) significantly reduce the rate of cardiovascular events and repeat treatment procedures, (references listed in full grant submission) which increase morbidity, mortality, and cost (references listed in full grant submission.) Despite the proven benefits of such medications, rates of adherence to chronic cardio protective medications are frustratingly low (references listed in full grant submission) For example, one year after hospitalization for an acute coronary syndrome, nearly half of patients prescribed statins stop taking them (references listed in full grant submission) Given the well-established effectiveness of these agents, and how generally well tolerated they are, these low rates of adherence are concerning, but they also reflect a considerable opportunity target for improvement. Reducing CAD-related morbidity, mortality, and cost will depend to a great degree on effective strategies to help patients improve medication adherence and other health behaviors.(references listed in full grant submission)

Poor adherence to cardio protective medications leads to worse medical treatment outcomes, higher hospitalization and mortality rates, and increased health care costs among CAD patients (references listed in full grant submission.) Hence, medication adherence among such patients is an important modifiable factor that affects the triple aim of improved health care quality, improved health, and lower cost. As many as 33 to 69 percent of all medication-related hospital admissions in the United States may be due to poor medication adherence, which amounts to a cost of \$100 billion a year (references listed in full grant submission.) Many previous successful efforts to improve adherence to these medications have been too complex to be implemented in clinical practice, not easily packaged or standardized, or required tremendous resource expenditures, limiting their applicability to and sustainability in resource constrained environments (references listed in full grant submission.)

The insight that improved adherence will improve care and lower cost is not new. What is new is the recognition that earlier efforts involving intensive case management are expensive and unwieldy, not easily scaled, and might be replaced with simpler and cheaper approaches leveraging more contemporary technology and concepts of behavior change.

This proposal has three main principles:

1. Principles of behavioral economics that have been developed, refined, and tested over the past decade offer practical insights into health behaviors that were previously unavailable and are not reflected in existing care models.
2. New technology, typically wireless devices for pill bottles, and mobile telephones, make engagement with patients substantially easier and more immediate now than ever before.
3. While randomized clinical intervention trials provide exceptional confidence of comparative effectiveness in narrow interventions, they are slow and rigid and don't reflect the urgency that health care transformation currently requires. Principles of rapid cycle innovation are gaining acceptance as an alternative to or supplement of these traditional methods in supporting evidence for implementation success.

Care provision in the US tends to be reactive, visit-based, and physician-centered, in part because the incentives embedded in current models of financing care provide compensation for visits and not efforts to keep people healthy. However, this RFA provides an opportunity to change that in deploying a new model of chronic disease management that is proactive rather than visit-based, utilizes automation through technology as both a quality improvement and cost reduction strategy, and creates new workforce roles for non-physician providers such as engagement advisors (clinical social workers), nurses who monitor and act on inputs from home-based wireless monitoring technologies, IT personnel who support the deployment of such systems, and consumer psychologists/behavioral economists who test refinements of engagement strategies aimed at increasing the rate of patient adherence to treatment recommendations.

Our plan for testing the implementation of a new model for care delivery builds on infrastructure that we have developed and tested with NIH Support (RC2 AG036592-01, Asch and Volpp, Multiple PIs). We aim to improve medication adherence in patients following hospital admission for acute myocardial infarction (AMI), leveraging insights from three major domains of thinking. First, we will take advantage of the promise offered by insights from behavioral economics (see 1.2.b.). Second, we combine these insights with technologies such as cell phones, home-based peripheral devices, and web-based social networking services to deploy state-of-the-art approaches for motivating healthy behavior. Such technologies, which are easily adoptable by other organizations, create new opportunities for connecting with patients, allowing for reinforcing feedback that is frequent and closely tied to the timing of health-related decisions in ways that were previously infeasible for large numbers of patients due to the cost of the required personnel. Indeed, while many patients will require the kind of intensive and expensive engagement provided by nurses or community health workers or promoters, those approaches are challenging and expensive and for many patients might be replaced by cheaper and more scalable approaches, some of which can involve patients own family and support networks. Third, through a process of rapid cycle innovation and testing we will make ongoing improvements in the intervention design with 3 product cycles within the timeframe of this proposal (see 1.2.g.). The main intervention will be informed by a series of side experiments that will test ways to improve patient engagement using tools from social networking, behavioral economics, and consumer marketing. We designed this process in response to this RFA and have labeled it evidence-based evolutionary learning a term that is meant to reflect both the sense of urgency health care transformation requires and the importance of strong evidentiary standards to get it right and to do so credibly.

Innovation is also reflected in the interdisciplinary team we have built for this project through partnership with the University of Pennsylvania Health System (UPHS) (which serves as a referral center for AMI care for patients throughout the Philadelphia metropolitan area and Southern New Jersey); Horizon Blue Cross Blue Shield, which provides services to 3.5 million New Jersey (NJ)

residents including nearly 2,000 patients hospitalized with AMI per year throughout NJ; Independence Blue Cross, an insurer of approximately 2 million in Southeastern PA; Keystone Mercy, an insurer for approximately 320,000 Medicaid recipients in Southeastern PA; Aetna, one of the largest insurers in the United States; and HealthFirst, a Medicare managed plan in New York City with approximately 600,000 members and CVS Caremark, with 40 million members throughout the US. The external partners will be supported by a team of faculty members from the Departments of Operations and Information Management, Marketing, and Health Care Management at the Wharton School along with faculty from the Perelman School of Medicine at the University of Pennsylvania (UPENN) and from the Center for Health Incentives and Behavioral Economics at the Leonard Davis Institute, 1 of 2 NIH-funded Centers in Behavioral Economics and Health in the US. Approximately 1,500 participants will be enrolled post-hospital admission for AMI from hospitals throughout NJ and, southeastern Pennsylvania for the main intervention study.

## **Statistical Considerations**

### 1.2 Power and sample size (from 4.1.b.i. of the full grant):

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%, 60 and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue ~~4500~~ **1520** patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield ~~500~~ **506** control and ~~4000~~ **1014** intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurer partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

### 1.3 Data analysis

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial

admission), retaining these given evidence of confounding 96,97 (references listed in full grant submission) or predictive ability. Models will be assessed using standard diagnostic techniques.98 (references listed in full grant submission)

We expect to have nearly complete follow-up data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## **Study Design**

### **1.1 Design**

Participants in this study will be identified in primarily 1 of 2 methods.

The first will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and the coordinator will work with hospital staff to meet with the patient in person and invited to participate. If the patient has already been discharged, they will be scheduled to receive a recruitment phone call to their home.

The second method involves patients who are hospitalized outside the UPHS health systems who are identified through our insurer partners. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreement (DUA) and/or Business Associates Agreement (BAA), as determined by negotiations between them and the Penn Medicine privacy officer, with that health insurer that allows for the receipt of PHI for screening and recruitment purposes for this study. The data will include principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2), name, address, phone number, insurance provider. Since all patients will have the same diagnosis code, we will just ask for the contact information and dates of hospital discharge minimizing the risk to participants of this waiver of authorization. These agreements will also include HIPAA waivers from each insurance provider to authorize the release of their PHI for use in screening and recruitment for this study.

**The study coordinator will mail a recruitment packet containing a recruitment letter and a copy of the Consent/HIPAA document. In a few days, a coordinator will call the patient to conduct a recruitment telephone call. The coordinator will ask the patient if they are interested in answering some screening questions to confirm they are eligible to participate in this research study. A competency screening tool will be administered to anyone 75 years or older to ensure they are competent enough to consent and enroll in the study. We have chosen the Ottawa 3DY and the AD8 Dementia Screening Tool to assess for competency during our enrollment phase of our program. The Ottawa 3DY is a four question tool designed to screen for cognitive impairment in the elderly. The AD8 Dementia Screening Tool is sensitive to detecting early cognitive changes associated with many common dementing illnesses. If a patient answers one or more questions incorrect on the Ottawa 3DY then the AD8 Dementia Screening Tool can be administered to an available**

caregiver to determine whether the patient is eligible for participation in the program. These tools were both shown to be effective in screening for cognitive impairment, are brief to administer and can be administered by non-clinicians. If they are eligible, the coordinator will review the verbal Consent/HIPAA script to the patient over the phone and obtain verbal consent and HIPAA authorization. Remote enrollments will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document.

~~For patients identified in the UPHS health system, a study coordinator will attempt to make contact with them 1 or 2 days before discharge from the hospital to discuss the study, confirm eligibility and enroll the patient if they are interested. Enrollment in person will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document.~~

~~For those patients not seen in the UPHS health system, or for those we were not able to contact before discharge from UPHS, the study coordinator will mail a recruitment packet containing a recruitment letter and a copy of the Consent/HIPAA document. In a few days, a coordinator will call the patient to conduct a recruitment telephone call. The coordinator will ask the patient if they are interested in answering some screening questions to confirm they are eligible to participate in this research study. If they are eligible, the coordinator will review the verbal Consent/HIPAA script to the patient over the phone and obtain verbal consent and HIPAA authorization. Remote enrollments will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document.~~

After confirming consent to participate, the coordinator begins entering basic demographic information for the patient into the WTH site, and the coordinator will use the Way to Health web platform to randomize patients into this study.

Patients will be randomized into 1 of the 2 study arms. After randomization occurs, the study coordinator will inform the patient of the randomization group they have been assigned into. **We plan to ask a 2 question survey called the PHQ-2 to participants in both the control and intervention arms. We will also ask participants in the intervention group these same questions at the end of their participation in the study. All participants will be encouraged to follow up with their primary care doctor about the results of the survey. In efforts to give extra attention to participants scoring at the range of 5 or 6 on this questionnaire, participants scoring in this range will be given the opportunity to be contacted by one of our 2 Research Coordinators who are also Social Workers. The Social Workers will reach out to these participants within 24 hours and can link these participants to resources and supports to meet their expressed needs.**

The intervention group (1) will use the GlowCaps, a remote monitoring and reminder pill bottle; (2) will be assigned an engagement advisor from the study team; (3) asked to provide the study team with names and contact information of up to 3 family members or friends as support partners for medication adherence. The study team will contact these people in order listed until 1 agrees to serve in this role; (4) will select a 2-digit lucky number to be used as part of the sweepstakes-based engagement incentives in which eligibility to win will be conditional on medication adherence; and (5) will determine their preferences for Way to Health platform communication methods during the study.

The group receiving the program intervention will also have their claims data analyzed for the 12 months post-enrollment.

The control group will have the health insurance claims records analyzed over the next 12 months.

Instructions for control arm will read: Thank you for participating in this study. You have been randomized to the control arm of this study. Our study team will analyze health insurance claims records over the next 12 months and use any information gained about readmissions to the hospital or health related procedures you may undergo during this time. This information will be very helpful for the analysis of this study data and help us to understand whether the intervention is improving patient outcomes. (For full script, please see attached Control script uploaded with this submission)

Instructions for intervention arm will read: Thank you for participating in this study. You have been randomized to the intervention arm of this study. The study team will send you a study packet in the next few days to the mailing address you indicated in this enrollment process. The packet will include up to 4 Vitality GlowCaps, which is a remote monitoring and reminder pill bottle, you will use for the medications we are monitoring in this study.

As a participant in this study, you will have access to our study engagement advisors from the study team, who will to assist with your transition from hospital to home and help you get started with this study. Another part of this study is naming a support person who can remind you about taking your medications. We are asking you to provide the names of up to 3 a family members or friends, of your choice, as a support person for medication adherence. If you provide more than one name, the study team will contact these people in the order of your preference until 1 person agrees to serve in this role. This person will only receive a message from our study if you have not opened the study GlowCaps to take your medicine for 2 days in a row, or 2 days over a 72 hour time period. They will have the option of receiving a text, an email, or interactive voice recording (IVR). The report they receive will not contain your name or any identifying information. ~~Your support friend/family member will receive a phone call from our study team if it appears that you have missed 5 days of medication in a row. Your primary care physician will receive a phone call from our study team if it appears that you have missed 7 days of medication in a row.~~ **After the 4th day with no GlowCap openings, the Engagement Advisors will attempt to contact you by phone to inquire about the reasons you have not used the GlowCaps for this time period and to offer to provide assistance. On the 6th day with no GlowCap openings, a Text/email/IVR message is sent to you by your advisor saying we will be reaching out to your feedback partner (if named) if we do not hear back from them by tomorrow. On the 7th day with not GlowCap openings, the Feedback partner will be called to be informed that the participant has not opened their GlowCaps for some time. On the 8th day without GlowCap openings, the study team will mail a letter to the participant reminding them our next step**

**is to contact the physician (If named during enrollment) to let them know you have not opened your GlowCaps for some time. On day 14 without GlowCap openings and no contact from the participant, the engagement advisor will attempt to reach the primary care providers office designated by the patient on enrollment to enlist their support.**

As a participant in this study, you are also eligible for daily sweepstakes that is based on whether or not you use the GlowCaps pill bottles as selected. Please select the 3 digit number to be used with in the daily sweepstakes incentives where eligibility to win will be conditional on medication adherence; Finally, there are certain customizations that you can make to the Way to Health platform. Would you prefer to receive sweepstakes messages via text message, email or automated phone call?

The group receiving the program intervention will also have claims data monitored for the above over the duration of the study

During the enrollment process the Coordinator collects:  
SSN for W-9 from intervention group participants and asks them to pick sweepstakes number to be used in the study.

### 1.2 Consent Process

We are not requesting a waiver of consent/HIPAA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

We are requesting a waiver of the requirement to document consent and HIPAA authorization with a signature for participants enrolled into this study since we believe the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. [45 CFR 46.117(c)(2)]

~~A majority of~~ Participants being enrolled in this study will be enrolled via a remote recruitment process; therefore we will read the IRB approved Consent/HIPAA script over the phone to each patient and ask them to provide verbal consent and verbal HIPAA authorization for use of their data in the study. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study. At this point, the participant is randomized into 1 of the 2 study groups. After randomization the coordinator will inform the participant of their assignment and read the instructions for their study group.

If the participant requests a copy of the consent form requests a copy of the consent form, the study coordinator will mail a copy to their home address.

~~For patients enrolled in person at UPHS, we are also requesting a waiver of documentation of signed consent and HIPAA authorization. For these enrollment visits, the study coordinator will visit the patient in the hospital 1 to 2 days before their scheduled discharge date. The coordinator will review the Consent/HIPAA script with the patient. If they consent to participate in the study, the coordinator will use a study laptop to access the WTH web platform for this study and will create a participant user account for the patient. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study~~

~~and will explain the arm assignment to the participant as noted above.~~

~~The participant will be given a copy of the consent form upon request.~~

For participants enrolled into the intervention arm remotely, the coordinator will mail up to 4 GlowCaps to them for use in the study. Those enrolled while in the hospital will be given the GlowCaps to take home with them. A study coordinator will schedule a follow up call with all participants to facilitate setting up the GlowCap device and the transfer of their medications into the GlowCaps.

**At the end of participation, there is a transition process to help participants in the intervention group phase out of the program. Participants are made aware their participation is ending; the GlowCaps will no longer function as they have during the study, and the Program Advisors will no longer be monitoring their adherence (GlowCap openings) or reaching out to them as they have during their enrollment period. Participants will have the opportunity to complete a study end survey at this time as well.**

### **Study duration**

The duration of participation for each individual participant is expected to be 12 months. We expect the total duration of the study to last 36 months for the completion of all 3 versions of the study noted below. **We will recruit patients for version 1.0 from January 2013 until December 2014. Patients will be followed for a 1 year period until the end of the grant in June 2015.**

~~We will recruit patients for version 1.0 from January 2013 – September 2013 and version 2.0 from October 2013 – June 2014. Patients will be followed for a 1 year period until the end of the grant in June 2015.~~

### **Resources necessary for human research protection**

The project will take place at the Leonard Davis Institute Center for Health Incentives and Behavioral

Economics (LDI CHIBE) at the University of Pennsylvania (UPENN). The team includes investigators experienced in clinical medicine, health behavior interventions, clinical trials, behavioral economics, cost-effectiveness analysis, and program evaluation. Our partnership combines the resources and capabilities of a major university (the Wharton School and the Perelman School of Medicine at the University of Pennsylvania), a major health care provider (UPHS), insurers (Horizon BCBS, Keystone Mercy, and Independence Blue Cross, Aetna, HealthFirst), and the largest Pharmacy Benefits Manager in the US (CVS Caremark).

Multiple PIs: Dr. Kevin Volpp directs the LDI CHIBE and the NIA-funded PENN-CMU Roybal P30 Center on Behavioral Economics and Health and is a Professor of Medicine at the Perelman School of Medicine (SOM) and Professor of Health Care Management at the Wharton School at UPENN. He has led numerous studies of patient financial incentives and behavioral economic interventions. David Asch, MD, MBA - Co-Project Director is Executive Director of the Penn Medicine Center for Innovation, Professor of Health Care Management and Economics and Professor of Operations and Information Management at Wharton and Professor of Medicine at Perelman. The financial analyses will be co-led by Dr. Shivan Mehta. Statistical Analysis: Dr. Andrea Troxel (Co-I, Statistician) is Director of Biostatistics for LDI CHIBE and a Professor of Biostatistics at UPENN. She has over 15 years of experience in the design, conduct, and analysis of clinical studies, including randomized trials that involve repeated measurements. There will be a

project manager and research coordinator assigned to this study to facilitate enrollment, GlowCap distribution, follow up contacts and payment distributions.

This study will be supported on a secure web portal on the Way to Health platform, modified to the specifications of this study.

### **Target population**

Eligibility Criteria: Patients admitted to hospitals throughout the **United States** ~~New Jersey, Pennsylvania, New York or at the University of Pennsylvania Health System~~ who are discharged (or scheduled to be discharged) with a principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2) and a length of stay of 1 to 180 days will be considered eligible for the study and randomized to either the control arm, receiving standard care and having records analyzed for this study or into our new model of evidence-based evolutionary care, **3) Patients are only eligible to enroll in the study for up to 60 days after their hospital discharge for a heart attack**

The total target enrollment will be ~~4500~~ **1520** participants. ~~500~~ **506** will be enrolled into the control arm and ~~4040~~ **1,014** will be enrolled into the program intervention arm.

### **Subjects enrolled by Penn Researchers**

~~4500~~ **1520**

### **Subjects enrolled by Collaborating Researchers**

0

### **Accrual**

Participants in this study will be identified in primarily 1 of 2 methods.

Participants will be recruited either at the time of hospital discharge from an admission with AMI or immediately thereafter from UPHS hospitals or hospitals throughout Pennsylvania (PA), New Jersey (NJ), or New York (NY) through our partnerships with Horizon, Independence Blue Cross, Aetna, ~~Keystone Mercy, and HealthFirst~~ **and Humana**

The first method will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS to create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and contacted in person for a screening and enrollment interview. If these patients are discharged before we can contact them, they will be scheduled to receive a recruitment phone call in their home.

The second method involves patients who are seen outside the UPHS health systems. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreement (DUA) and/or Business Associates Agreement (BAA), as determined by negotiations between them and the Penn Medicine privacy officer, with that health insurer that allows for the receipt of PHI for screening and recruitment purposes for this study. The agreements with these insurance partners will include Business Associates Agreements/HIPAA waivers from each partner

authorizing release of their patient data to University of Pennsylvania for screening and recruitment activities.

### **Key inclusion criteria**

Eligibility Criteria: Patients admitted to hospitals throughout the **United States** ~~New Jersey or at the University of Pennsylvania~~ who are discharged (or scheduled to be discharged) to their homes with a principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2) and a length of stay of 1 to 180 days will be considered eligible for the study and randomized to either standard care or our new model of evidence-based evolutionary care. Patients must be over the age of 18 and be discharged to home, **3) Patients are only eligible to enroll in the study for up to 60 days after their hospital discharge for a heart attack, and 4) Patients must receive their health benefits from one of our insurer partners (Horizon, Independence Blue Cross, Aetna, Health First, or Humana, or CMS).**

### **Key exclusion criteria**

Exclusion criteria: Patients will be excluded if they are less than 18 years old, will not or cannot give consent, or have a markedly shortened life expectancy (diagnosis of metastatic cancer, end-stage renal disease on dialysis, or dementia). Patients who have a known allergy or history of side effects to any of the 4 targeted classes of medications will be enrolled but provided GlowCaps only for the remaining medications. **We are excluding patients who are enrolled in any other medication management studies that incorporate the GlowCap electronic pill bottles.**

**(Please note patients who are prescribed the anti-platelet Effient® (prasugrel) will not be given a GlowCap to use for this medication due to specific guidance about pill maintenance. The package insert for Effient® (prasugrel) (<http://pi.lilly.com/us/effient-ppi.pdf>) indicates the medication should remain in the original bottle, it should be kept at room temperature between 59°F to 86°F (15°C to 30°C) and the container should be closed tightly with the gray cylinder inside and be protected from moisture. This does not necessarily exclude these patients from participation in the study; they will still be eligible as long as they have been prescribed at least 2 of the remaining 3 medications being observed in this study. Also, those who are taking an anti-platelet other than Effient® (prasugrel) (i.e., Plavix) will be given a GlowCap to use to take that medication.)**

### **Vulnerable Populations**

No vulnerable populations are included in the research study

### **Populations vulnerable to undue influence or coercion**

Subjects will be given consent forms and reminded their participation is voluntary and they will be informed that their decision to participate or not participate will in no way affect their medical care.

### **Subject recruitment**

Participants in this study will be identified in primarily 1 of 2 methods.

Participants will be recruited either at the time of hospital discharge from an admission with AMI or immediately thereafter from UPHS hospitals or hospitals throughout Pennsylvania (PA), New

Jersey (NJ), or New York (NY) the United States through our partnerships with Horizon, Independence Blue Cross, Aetna, ~~Keystone Mercy,~~ and **HealthFirst, and Humana.**

The first method will be for patients being treated within the UPHS health system. They will be identified via daily electronic medical records review by our study staff. The study staff will work with UPHS to create a filter for the electronic medical record system that will generate a daily list of patients who may meet the study criteria. A study coordinator will review the list of patients to determine eligibility. If patients meet the minimal requirements they will be added to the study screening data base and **will be scheduled to receive a recruitment phone call in their home.** ~~Contacted in person for a screening and enrollment interview. If these patients are discharged before we can contact them, they will be scheduled to receive a recruitment phone call in their home.~~

The second recruitment method involves patients who are seen outside the UPHS health systems. Before recruitment with patients from any insurer partner begins, we will have a Data Use Agreements (DUA) and/or Business Associates Agreement (BAA) with that health insurance provider, as determined by negotiations between them and the Penn Medicine privacy officer that allows for the receipt of PHI for screening and recruitment purposes for this study. The agreements with each insurer partner will include HIPAA waivers from each partner authorizing release of their patient data to University of Pennsylvania for screening and recruitment activities.

~~Remote enrollments will be conducted via a phone call from the study staff. We will contact patients by phone after hospital discharge to confirm eligibility and to see if they are interested in participating in the study. If participants are interested, the coordinator will complete an intake form and consent via the remote enrollment process over the phone. The coordinator will enter patient information directly into the Way to Health web portal for this study.~~

~~After providing consent, the patient will be randomized into 1 or 2 study arms and will be read the script for either the control or the intervention arm of the study.~~

#### **Remote recruitment methods:**

**We plan on incorporating 3 different mailing methods to send recruitment materials to participants to determine which the most effective method is. All recruitment mailings will contain the same study materials (Recruitment letter; Informed Consent/HIPAA document). The only differences will be in the mode used for mailing materials to patients. We plan to randomly assign patients to 1 of the following 3 mailing methods. 1) The first method will be a hand addressed envelope, sent via standard USPS mail. 2) The second method will be a hand addressed envelope, sent via standard USPS mail, but will also include a \$5 bill for patients to keep regardless of whether or not they choose to enroll in the study. 3) The third method will be to send the recruitment materials via UPS, 2-day express mailing. After testing these methods, we have decided to send the recruitment materials via USPS priority mail, with tracking.**

**We are also including a few promotional materials into the mailings, to help increase the rate at which patients open our letters. We plan to include the following promotional items: pens with study contact information, a magnetic pad of paper that includes study information and a checklist for better health (see attached for text), bracelets with our contact information, and notecards with our contact information (see text attached).**

**After the recruitment materials are mailed, remote enrollments will be conducted via a**

phone call from the study staff. We will contact patients by phone after hospital discharge to confirm eligibility and to see if they are interested in participating in the study. If participants are interested, the coordinator will complete an intake form and consent via the remote enrollment process over the phone. The coordinator will enter patient information directly into the Way to Health web portal for this study.

After providing consent, the patient will be randomized into 1 of the 2 study arms and will be read the script for either the control or the intervention arm of the study. For patients whose emails we have on file, we also plan to send a follow up email to them one week after the letter is sent, as an alternate way to reach them. The email template is attached to the application,

### **Subject compensation**

Subjects will be financially compensated for their participation.

**All participants will receive participation payment of \$25 for time and effort during enrollment, regardless of the study arm they are randomized into.**

~~The 500 participants randomized into the control arm will not receive financial compensation for this study.~~

**In addition to this, we are providing participation payment of \$25 to participants randomized into the intervention arm, for completing the setup process of their GlowCap device and successfully transmitting a signal to the study platform. This is intended to pay participants for the effort of completing the device setup call and setting up their device for use**

The 1,000 participants randomized into the intervention arm will receive an average expected sweepstakes payment of \$1.40/day if they are adherent in using the GlowCap electronic pill bottles.

### **1.1 Payment Method Comparison Test**

**We would like incorporate a test of two different methods of distributing the initial payment to participants who complete the enrollment and randomization process.**

**a. The proposed test would involve 350 participant mailings divided into the following groups:**

**Group 1: 175 mailings with payment for enrolling in the study via typical method of processing a \$25 check, through the Way to Health platform, mailed to the participants home.**

**Group 2: 175 mailings with a \$25 Visa gift card included in the recruitment mailing. The letter would explain that the gift cards will be activated once the participant completes the enrollment process.**

**To facilitate the gift card activations, we have an agreement with the gift card vendor in which we have purchased gift cards with no balance, which can be activated and loaded with \$25 by our program advisors when participants in this mailing group are randomized**

into the study. No patient PHI will need to be provided to this vendor. After the test of 350 mailings is complete, we will use the typical method of processing a \$25 check, through the Way to Health platform to distribute the enrollment incentives. If the analysis reveals obvious benefit to using the gift card for the initial payment, we will incorporate this method for all future recruitment efforts.

## Procedures

The study staff will screen and identify eligible participants in 1 of 2 methods. First, through UPHS Medview medical record review for UPHS patients. Second, via data feeds sent in daily data feeds from our insurance partners for patients hospitalized outside the UPHS healthcare system.

~~For patients identified in the UPHS health system, a study coordinator will attempt to make contact with them 1 or 2 days before discharge from the hospital to discuss the study, confirm eligibility and conduct the enrollment visit with the patient if they are interested. In person enrollments will be facilitated by the coordinator with a study laptop in order to access the Way to Health platform for this study and directly enter the patient information into the Way to Health website and create their study account. For in person enrollments, we would like to have the participants confirm consent with the coordinator who will indicate their consent in the Way to Health portal for this study.~~

~~For those patients not seen in the UPHS health system, or for those we were not able to contact before discharge from UPHS, the study coordinator will contact via telephone to conduct the screening and enrollment visit remotely interested patients.~~ **For all patients, the study coordinator will contact via telephone to conduct the screening and enrollment visit remotely with interested patients.**

In both cases, the coordinator will ask the patient if they are willing to answer some screening questions to confirm they are eligible. If they agree, the coordinator will read through a brief screening survey to confirm they meet the criteria of having had a heart attack, have been prescribed a statin, beta-blocker, anti-platelet and aspirin and are living at home and not a long-term care facility. **Please note, patients who are prescribed the anti-platelet Effient® (prasugrel) will not be given a GlowCap to use for this medication due to specific guidance about pill maintenance. The package insert for Effient® (prasugrel) (<http://pi.lilly.com/us/effient-ppi.pdf>) indicates the medication should remain in the original bottle, it should be kept at room temperature between 59°F to 86°F (15°C to 30°C), and the container should be closed tightly with the gray cylinder inside and be protected from moisture. This does not necessarily exclude these patients from participation in the study, they will still be eligible as long as they have been prescribed at least 2 of the remaining 3 medications being observed in this study. Also, those who are taking an anti-platelet other than Effient® (prasugrel) (i.e., Plavix) will be given a GlowCap to use to take that medication. A competency screening tool will be administered to anyone 75 years or older to ensure they are competent enough to consent and enroll in the study. We have chosen the Ottawa 3DY and the AD8 Dementia Screening Tool to assess for competency during our enrollment phase of our program. The Ottawa 3DY is a four question tool designed to screen for cognitive impairment in**

**the elderly. The AD8 Dementia Screening Tool is sensitive to detecting early cognitive changes associated with many common dementing illnesses. If a patient answers one or more questions incorrect on the Ottawa 3DY then the AD8 Dementia Screening Tool can be administered to an available caregiver to determine whether the patient is eligible for participation in the program. These tools were both shown to be effective in screening for cognitive impairment, are brief to administer and can be administered by non-clinicians.**

After confirming eligibility, the coordinator will read the verbal Consent/HIPAA script to the patient over the phone and obtain verbal consent and HIPAA authorization. Remote enrollments will be facilitated by the coordinator accessing the Way to Health web portal for this study so they can direct enter the patient information into the Way to Health website and create their study account. If, after reviewing the Consent/HIPAA document with the patient they want to participate, the coordinator will indicate that the patient provided verbal consent to participate by selecting this option on the Way to Health platform. The patient will be given a copy of the consent document with the initial recruitment letter mailed to their home.

At this time, patients will be randomized into either the control or intervention arms at a ratio of 1(control):2(intervention). **We plan to ask a 2-question survey called the PHQ-2 to participants in both the control and intervention arms. Participants scoring 3 or greater will be recommended to follow up with their primary care doctor about the results of the survey.**

The control group will simply have their claims data analyzed for a 12-month period. We will be examining these data for hospital admissions, new vascular events (AMI, stroke, acute coronary syndrome admission), or repeat or new cardiovascular procedures.

Participants randomized into this group will have the control group script read to them at this point.

Those randomized into the intervention arm will receive a compound set of approaches including: (1) provision of up to 4 Vitality GlowCaps (**or MedSignal device**), a remote monitoring and reminder pill bottle, to use for the cardiovascular medications aspirin, statins, and beta blockers (and Plavix or prasugel if they received a stent); (2) assignment of an engagement advisor from the study team; (3) enlisting a family member or friend (patient choice) as a support person for medication adherence (participants will be asked to identify up to 3 in descending order of preference); (4) engagement incentives that will use lotteries where eligibility to win will be dependent on medication adherence; and (5) self-service/customization of the Way to Health platform communication methods. Participants in the intervention arm will be offered all of these components, however, they are still able to participate even if they opt not to use any of the list above. The group receiving the program intervention will also have their claims data analyzed for the 12 months in the study to examine rates of hospital admissions, new vascular events (AMI, stroke, acute coronary syndrome admission), or repeat or new cardiovascular procedures.

Participants randomized into this group will have the Intervention group script read to them at this point.

The Study Coordinator will collect the SSN to enter into the W-9 webpage on the Way to Health web port for intervention group participants only for this study to facilitate participant incentive payments. The coordinator will ask the participant to provide details about medications they have been prescribed, contact information for the person (s) they want us to contact to serve as the support person for medication adherence, and their preferences for receiving communications from the Way to Health system.

After collecting this information, the study coordinator will configure a set of up to 4 GlowCaps to send via express shipping to the participants for use with the indicated medications.

On the day the participant is expected to receive the GlowCap package sent by the study staff, they will receive a phone call from the study coordinator/engagement advisor to provide them with assistance in transferring their medications into the GlowCaps. The study coordinator/engagement advisor will confirm medications and make sure the alarm is set to the desired time for individual medications, based on the times provided by the participant on the phone call.

The schedule of Alarms for participants and Feedback Partners in the intervention arm is as follows:

*Daily message*- all intervention group participants will receive a daily message about their use of the GlowCaps in the last 24 hour period and whether or not their study sweepstakes number was drawn on the study sweepstakes system. The messages will be similar to the following: A. Congratulations, you used your glowcaps correctly yesterday and your study number was drawn. You won (\$5 or \$50, depending on number of digits that were drawn for participant) B. We are sorry, you did not use your glowcaps correctly yesterday and your study number was drawn. You could have won (\$5 or \$50, depending on number of digits that were drawn for participant) C. You used your glowcaps correctly yesterday but your study number was not drawn, keep up the good work D. You did not use your glowcaps correctly yesterday. You never know when your study number may be drawn; please remember to use your GlowCaps each day you are scheduled to take your medicine.

*Feedback Partners* - If the participant identifies a feedback partner and they agree to serve in this role, they will also have an account created for them on the Way to Health platform for this study. This person will receive a notification starting at 48 hours, or if there are 2 of 3 days (and then daily through 7 days) without feedback adherence messages from the participants GlowCaps. The interactions that the feedback partner has with the participant are up to their discretion. This role is not supposed to provide trained assistance to the participant, but rather serve the role of providing social support around their medication adherence. Both the participant and their feedback partner will be notified at study outset that they will automatically

be Sent these alerts. Numerous studies, including our own, have shown that peer mentoring and social support are helpful in improving adherence and patient outcomes. This reflects engagement of a powerful social force: the ability of peers and family to help one another that can be used to augment other ways of helping patients improve their medication adherence. The feedback partner will let the study team know their desired method of receiving these notifications from the Way to Health program. The available options are text, email or interactive voice recording.

*Engagement Advisors* - The primary role of the Study Coordinator/Engagement Advisors will be to assist patients in getting started in the intervention, to monitor the patients medication adherence using the daily Vitality GlowCaps **(or MedSignals)** information, and to serve as a resource for patients who are struggling to stay adherent to their medications. While this will help to quickly spot gaps in adherence and intervene, the role of this engagement advisor is to get involved only when automated feedback on adherence through the WTH system (including incentives) proves insufficient. After 4 days without feedback adherence messages from the participants GlowCaps, the Study Coordinator/Engagement Advisors will contact the participants to inquire about the reasons they have not used the GlowCaps for this time period and to offer to provide assistance. The coordinator/engagement advisor will continue to receive daily alerts on non-adherent patients and on day 5 will contact the support friend/family member to enlist their support. **On day 7 without medication, the engagement advisor will attempt to reach the feedback partner. On the 8th day without GlowCap openings, the study team will mail a letter to the participant reminding them our next step is to contact the physician (If named during enrollment) to let them know you have not opened your GlowCaps for some time. On day 14 without GlowCap openings and no contact from the participant, the engagement advisor will attempt to reach the primary care providers office designated by the patient on enrollment to enlist their support.** ~~On day 7 without medication, the engagement advisor will attempt to reach the primary care providers office designated by the patient on enrollment to enlist their support.~~

3 months post enrollment an automated message will be sent to the participant for a reminder that if they have any questions about the GlowCaps or any medication updates to make they should contact the study team.

5 1/2 months post enrollment - the study platform will send an alert to the participant to let them know that they will be receiving a replacement set of GlowCaps because the batteries in the existing GlowCaps will begin to lose power. Once the new set of GlowCaps are received by the participant, a Study Coordinator/Engagement Advisor will call the participant to talk through the process of getting rid of the old GlowCaps and replacing them with the new GlowCaps.

~~12 months post enrollment the participant will receive automated message 2 weeks before end of study that program is ending, should tell them to not use GlowCaps anymore since they will no longer be monitored by the study team.~~

**In an effort to reach participants who have enrolled in the program, but who have not set**

up their GlowCaps, we have developed a set of procedures, which we call Hotspotting, to try and re-engage these participants. After a participant has consented to be in the study and been randomized, the program advisors attempt to set the participant up with their GlowCap devices. Some participants never get set up on the GlowCap, so with this effort, the PAs will attempt to get them set up. Within 6 weeks of enrollment, the PAs will try and call the participant, and if unsuccessful, will send them a letter (Hotspotting Letter 1). If there is no response, then from 6 weeks until about 4 months after enrollment, the PAs will attempt to call the patient again and if we cannot reach them by phone, the PAs will send them another letter (Hotspotting Letter 2). If the PAs still do not get in contact with them, they will try to re-engage with them at 8 months with additional phone calls and a final letter (Hotspotting Letter 3). These various forms of contact were created in an effort to reach participants that may have moved, have alternative phone numbers or have experienced some other changes that may hinder reaching them. Our hope is that these efforts encourage and allow renewed participation from those individuals who have already enrolled in the program and have been assigned to the intervention group.

At the end of participation, there is a transition process to help participants in the intervention group phase out of the program. Participants are made aware their participation is ending, the GlowCaps will no longer function as they have during the study, and the Program Advisors will no longer be monitoring their adherence (GlowCap openings) or reaching out to them as they have during their enrollment period.

When mailing out the End of program letter we also will include a brief End of Study Survey to collect participant feedback about the program to use for improving the current study, as well as future studies.

The timeline for the transition communications is as follows:

**2 months before last day in the program:**

- The End of Program Letter will be mailed to Participants along with the End of Program Survey. A return envelope will be included to mail completed surveys back to the study team
- An Automated Message will be sent to the Feedback Partner, as well, so they are aware participation in this study will be ending in 2 months.

**1 month before last day in the program**

- The text for the Automated Message will be sent to the Participant to let them know participation in this study will be ending in 1 month
- A follow up Phone Call will be made to the Participant as well. At this time, if the participant has not returned the survey, the Program Advisor will ask the participant if they would like to complete End of Program Survey over the phone.

**Last day in the program**

- The End of Program Automated Message is sent to Participants

## **Analysis Plan**

### **1.1 Power and sample size**

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%, 60 (reference from full grant proposal) and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1520 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 500 control and 1000 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurance partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health and be available 24/7. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

### **1.2 Data analysis**

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding<sup>96,97</sup> (refs from original submission) or predictive ability. Models will be assessed using standard diagnostic techniques.<sup>98</sup> (ref from original submission)

We expect to have nearly complete follow-up data since our primary outcomes will be analyzed

using claims data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

### **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. Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. Wherever feasible, identifiers will be removed from study-related information. Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

### **Subject Confidentiality**

The long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data.

We are not requesting a waiver of consent/HIPPA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

The initial patient information collected for screening and recruitment will consist of name, address, phone number, information about medical condition indicating heart attack. For patients from UPHS this information will come from Electronic Chart reviews. For patients outside the UPHS healthcare system, this information will be provided by our insurance partners.

#### 1.1 Database Security/Protection against Risk

To assure that patient, physician and other informant confidentiality is preserved, individual identifiers (such as name and medical record number/physician billing identifier) are stored in a single password protected system that is accessible only to study research, analysis and IT staff. This system is hosted on site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is in this system, they will be given a unique study identification number (ID). Any datasets and computer files that leave the firewall will be stripped of all identifiers and individuals will be referred to by their study ID. The study ID will also be used on all analytical files. Please see attached document (WTH database security grant-protocol text FINAL (2)) for full database security details.

The GlowCaps adherence monitoring devices will provide adherence data from each participant. This information is transmitted via cellular signal without any subject identifiers.

## 1.2 Vitality GlowCaps data security

Vitality's GlowCaps measure adherence with prescription drug regimens (i.e. whether the drug was taken as prescribed). In most cases the data is de-identified and Vitality is provided only with a study ID and a "cap ID(s)" for each participant. However, some projects may use additional GlowCap functionality in which case participant phone number, e-mail address and medication dosing schedule may be entered onto Vitality's secure server. Data transfer from Vitality to Way to Health takes place via a secure connection (https). A HIPAA Business Associate Agreement is in place

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, adherence data (from the GlowCaps), and medical conditions and medications. 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 no 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 UPENN Biomedical Informatics Consortium (BMIC) will be the hub for the hardware and database infrastructure that will support the project and where the Way to Health web portal is based. The BMIC 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 BMIC 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 BMIC 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. BMIC requires all users of data or applications on BMIC servers to complete a BMIC-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. Curriculum includes 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 Health Insurance Portability and Accountability Act certification in accordance with University of Pennsylvania regulations. All data for this project will be stored on the secure/firewalled servers of the BMIC 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. 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 UPENN.

Please see the attached documents for more detail about data security uploaded in the procedures section:

1. Way to Health Database Security/Protection against Risk.
2. Way to Health External Partner Privacy
3. Way to Health global privacy

### **Sensitive Research Information**

This Research does not involve collection of sensitive information about the subjects that should be excluded from the electronic medical record

### **Subject Privacy**

At the time the University of Pennsylvania IT study staff receives patient data, they will upload the patient data into the secure, web based data base (RedCap) and a study identification number will be generated for each patient. A link between the study ID number and the patient PHI will need to be maintained to ensure the study staff can track recruitment efforts to potential participants and to avoid contacting any patients who have previously declined to participate.

To assure that patient confidentiality is preserved, individual identifiers (such as name and plan ID#) are stored in a single password protected system that is accessible only to study research, analysis and IT staff. This system is hosted on site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is in this system, they will be given a unique study identification number (ID). Any datasets and computer files that leave the firewall will be stripped of all identifiers besides the study ID and individuals will be referred to only by their study ID. The study ID will also be used on all analytical files.

REDCap is a secure web application for building and managing online surveys and databases. The institution installing REDCap will store all data captured in REDCap on its own servers. Therefore all project data is stored and hosted there at the local institution (University of Pennsylvania), and no project data is ever transmitted at any time by REDCap from that institution to another institution or organization.

Privacy of all study data will be maintained by restricting access to the identifiable information only to approved study staff who have received subject confidentiality and privacy training.

Study coordinators will access patient contact information from the data base to conduct recruitment visits in person, for UPHS patients, and via phone call, for remote patients. The study coordinator will review the consent script, which will include a description of the voluntary nature of participation, the study procedures, risks and potential benefits in detail. Participants will be told 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.

Enrollment visits will be conducted by the study coordinators who will enter patient information directly into the Way to Health website once a participant has consented to participate. This database is hosted on a secure server as detailed in the subject confidentiality section. Study coordinators may have to contact patients and feedback partners during the course of the study and will use the WTH database to access contact information to facilitate this contact. For participants in the intervention arm, if the rate of non-adherence, as recorded by the GlowCaps, rises above a certain threshold, the study team may also contact the participants Primary Care Physician. This will be explained to the participant in the consent process and again when the details of the intervention arm are explained by the coordinator. Participants will be asked to provide the name of their PCP during the enrollment process.

PHI will not be shared with anyone outside the parameters of the study as detailed in the Consent/HIPAA process

### **Data Disclosure**

The following entities, besides the members of the research team, may receive PHI for this research study: Vitality, Inc., the company which records the responses from the GlowCap. Daily adherence information will be stored on their secure computers. 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 A data and safety monitoring board organized to oversee this research.

Limited participant information will be shared with insurers of the participant in order to track the Primary and Secondary outcomes of the study.

### **Protected Health Information/ Data Protection**

- Name
- Street address, city, county, precinct, zip code, and equivalent geocodes
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone and fax number

- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan ID numbers
- Account numbers

## Consent Process

### 1.1 Overview

We are not requesting a waiver of consent/HIPAA authorization for the main intervention. However, we are requesting a limited waiver for the purposes of receiving contact information and discharge dates from the insurer partners that will allow us to contact potentially eligible study participants. We will forward documentation of the individual waiver approvals as they are received from the insurer partners.

We are requesting a waiver of the requirement to document consent and HIPAA authorization with a signature for participants enrolled into this study since we believe the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. [45 CFR 46.117(c)(2)]

~~A majority of participants being enrolled in this study will be enrolled via a remote recruitment process, therefore we will read the IRB approved Consent/HIPAA script over the phone to each patient ask them to provide verbal consent and verbal HIPAA authorization for use of their data in the study. Once a patient provides verbal consent, the research coordinator will select this opt in on the Consent/HIPAA screen on the participant dashboard that was just created for participation the WTH health web platform for this study. At this point, the participant is randomized into 1 of the 2 study groups. After randomization the coordinator will inform the participant of their assignment and read the instructions for their study group.~~

**Participants being enrolled in this study will be enrolled via a remote recruitment process, therefore we will read the IRB approved Consent/HIPAA script over the phone to each patient and ask them to provide verbal consent and verbal HIPAA authorization for use of their data in the study. A competency screening tool will be administered to anyone 75 years or older to ensure they are competent enough to consent and enroll in the study. We have chosen the Ottawa 3DY and the AD8 Dementia Screening Tool to assess for competency during our enrollment phase of our program. The Ottawa 3DY is a four question tool designed to screen for cognitive impairment in the elderly. The AD8 Dementia Screening Tool is sensitive to detecting early cognitive changes associated with many common dementing illnesses. If a patient answers one or more questions incorrect on the Ottawa 3DY then the AD8 Dementia Screening Tool can be administered to an available caregiver to determine whether the patient is eligible for participation in the program. These tools were both shown to be effective in screening for cognitive impairment, are brief to administer and can be administered by non-clinicians. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation on the WTH health web platform for this study. At this point, the participant is randomized into 1 of the 2 study groups. After randomization the coordinator will inform the participant of their assignment and read the instructions for their study group.**

If the participant requests a copy of the consent form requests a copy of the consent form, the study coordinator will mail a copy to their home address.

~~For patients enrolled in person at UPHS, we are also requesting a waiver of documentation of signed consent and HIPAA authorization. For these enrollment visits, the study coordinator will visit the patient in the hospital 1 to 2 days before their scheduled discharge date. The coordinator will review the Consent/HIPAA script with the patient. If they consent to participate in the study, the coordinator will use a study laptop to access the WTH web platform for this study and will create a participant user account for the patient. Once a patient provides verbal consent, the research coordinator will select this option on the Consent/HIPAA screen on the participant dashboard that was just created for participation as noted above.~~

A copy of the Consent/HIPAA document will be included in the recruitment mailings sent to all patients before being called by the study team.

For participants enrolled into the intervention arm remotely, the coordinator will mail up to 4 GlowCaps to them for use in the study. Those enrolled while in the hospital will be given the GlowCaps to take home with them. A study coordinator will schedule a follow up call with all participants to facilitate setting up the GlowCap device and the transfer of their medications into the GlowCaps.

## 1.2 Children and Adolescents

Not applicable. We are only enrolling subjects 18 years of age and older.

## 1.3 Adult Subjects Not Competent to Give Consent

We plan to enroll only those patients who are competent to provide consent for themselves. **A competency screening tool will be administered to anyone 75 years or older to ensure they are competent enough to consent and enroll in the study. We have chosen the Ottawa 3DY and the AD8 Dementia Screening Tool to assess for competency during our enrollment phase of our program. The Ottawa 3DY is a four-question tool designed to screen for cognitive impairment in the elderly. The AD8 Dementia Screening Tool is sensitive to detecting early cognitive changes associated with many common dementing illnesses. If a patient answers one or more questions incorrect on the Ottawa 3DY then the AD8 Dementia Screening Tool can be administered to an available caregiver to determine whether the patient is eligible for participation in the program. These tools were both shown to be effective in screening for cognitive impairment, are brief to administer and can be administered by non-clinicians. The enrolling PA or Social Worker (depending on who is speaking with the patient/caregiver when it is determined they are ineligible) will refer any patient who is ineligible for participation for any reason back to their doctor as well as provide the Alzheimer's Association 24/7 Helpline that provides reliable information and support to all those who need assistance (800-272-3900).**

## 1.3 Waiver of Consent

**Waiver of written documentation of informed consent: the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context**

## 1.4 Written Statement of Research

All patients recruited through remote procedures will be mailed a Recruitment Letter and a copy of the Combined Consent/HIPPA authorization for this study. For in person enrollments at UPHS, the study coordinator will have copies of the written statement of the research on hand to provide to all participants.

### **Potential Study Risks**

As this study does not involve any medical decision making and only tests the use of social behavioral approaches to encouraging patients to use evidence-based treatments that their providers have prescribed following a heart attack, we consider this study minimal risk. The primary risk would be from a breach of confidentiality involving medical records reviews and monitoring of statin adherence with GlowCaps, which will be maintained on the Way to Health platform. This risk has been mitigated by extensive privacy protection protocols, a highly secure data storage system, and a plan to remove identifiers from the data wherever possible. In addition, all personnel will be held to high standards of upholding confidentiality and safeguarding patient privacy.

### **Potential Study Benefits**

The immediate benefits of this study for participants may include an improvement in adherence to medications that have been proven to be effective in improving patient outcomes. It is possible that the benefits for many participants will be minimal. However, as mentioned, we believe the risks are also minimal. Overall the risk to benefit ratio is favorable given the long term potential of on health and health related behaviors Database Security/Protection against Risk. Participants in this study may not receive any direct benefits. Some may benefit directly by improving their adherence to the medications and thus lower their risk for future heart attacks, strokes and death, improve their quality of life, and reduce future medical care costs. The control group is unlikely to directly benefit, as this group will continue to simply receive usual care.

Knowledge gained from the study will assist in development of interventions in other high-risk patient populations in which non-adherence rates are high. The potential public health impact of a successful intervention to improve adherence to statin medications is enormous and could reduce the number of deaths from heart attacks and strokes by tens of thousands in the United States each year.

The risks of loss of confidentiality are minimal in this study. Thus, the benefits of this research to the participants studied, and to society at large, far surpass the risks.

### **Alternatives to Participation (optional)**

Patients are free not to participate in this study and will thereby receive no reduction in the usual care received from their health care providers or insurers for this condition.

**Data and Safety Monitoring**

While we consider this study of minimal risk to participants, we have set up an external DSMB. This DSMB is scheduled to meet every 6 months to review study progress and ensure patient safety is maintained.

The members making up this board are a highly experienced group that includes Donald Lloyd Jones, MD, Chairman of Preventive Medicine at Northwestern and one of the leading cardiology clinical researchers nationally; Eugene Oddone MD, Chief of the Durham VA Health Services Research Center of Excellence and a leading health services researcher; and Constantine Gatsonis, Henry Ledyard Goddard University Professor of Biostatistics and Chair of the Department of Biostatistics at Brown University.

**Risk/ Benefit Assessment**

Poor medication adherence following AMI events is a major public health problem with few scalable, cost-effective solutions. This study is designed to test an intervention that incorporates many components that have previously demonstrated improvement in past studies. We believe the combination of these approaches in this study will provide the research and public health communities with important information that can lead to broad generalizability in treating people at risk for coronary events and death nationally, as these types of interventions could be set up by insurers and healthcare systems to be broadly utilized.

**Summary of Protocol Changes  
Modifications LOG**

**Protocol: HeartStrong:** Automated Hovering for Myocardial Infarction Patients  
**University of Pennsylvania**  
**Principal Investigator:** Kevin Volpp

Date of Submission	Description of Modification	Rationale for Modification	Approval date
12/14/2012	Initial submission		2/4/2013
2/22/2013	1. Revised versions of the Consent/HIPAA document 2. Revised version of Welcome Letter 3. Revised text for messaging to participants and feedback partners 4. Revised text for 6 month and end of study messaging 5. We have also <b>updated the Key Inclusion Criteria</b> , "Patients must be between 18 and 80 years old"		3/14/2013
3/8/2013	1. Adding Chantell Ketchem to study team, research coordinator		3/14/2013
3/29/2013	1. Removing Baseline and PSSUQ surveys from the protocol 2. Adding PHQ-2 to enrollment process, <b>study protocol update</b>	1. Participants in this study are not required to access the Way to Health website, so any questionnaires completed need to be done via telephone with study coordinators. The decision to remove these surveys was intended to reduce the burden on participants. 2. The PHQ2 survey consists of 2 questions to assess the participant's mood over the past two week period. The PHQ2 is not intended to establish a diagnosis for depressed, but may be a first step in screening for signs of depression. Previous studies have produced evidence that depression negatively effects medication adherence and we intend to study the effect of PHQ2 scores on the rate of adherence for participants in this study. We plan to ask the 2 question survey to participants both in control and intervention arms during the enrollment phone call. Participants scoring 3 or greater will be recommended to follow-up with their primary care doctor about the results of the survey.	4/1/2013
5/1/2013	1. Adding Genevieve Cattanea to study team, Social Worker		5/3/2013
5/13/2013	1. We have revised the recruitment letter for this study. 2. We plan to incorporate 3 different mailing methods to determine which is the most effective method.	2. All recruitment mailings will contain the same study material (Recruitment letter, Informed Consent/ HIPPA document). The only difference will be in the mode used for mailing the materials to patients. We plan to randomly assign patients to 1 of the following 3 mailing methods. Method 1: hand addressed envelope sent via standard USPS mail. Method 2: same as	5/22/2013

		method 1, but will also include a \$5 bill for the patient to keep regardless of whether or not they choose to enroll in the study. Method 3: send recruitment materials via UPS, 2 day express mailing.	
5/29/2013	1. Adding Jaclyn Sadicario to study team, research coordinator		6/6/2013
6/14/2013	1. Adding \$25 compensation payment for patients randomized to the control, <b>study protocol update</b> 2. Adding Lin Yang to study team, data analyst	1. Add compensation for patients randomized to the control group as compensation for time spent during the enrollment process. We are offering this only to those patients randomized to the control group and not those participants randomized to the intervention group since this group will receive GlowCaps and has the opportunity for sweepstakes winnings	6/18/2013
6/28/2013	1. Adding electronic signature of the Principal Investigator, Kevin Volpp to recruitment letter 2. Adding patient phone number to letter, instructing patient to call us if phone number on record if wrong 3. Update to IBC Recruitment letter, per IBC request 4. Update to consent to clarify the role of the Program Advisors		7/1/2013
7/17/2013	1. Adding Brandon Ciaudelli to study team, research coordinator		7/22/2013
8/15/2013	1. Adding Participant testimonial card to recruitment mailing 2. Adding Participant contact letter to be sent to participants who have not connected their device, <b>study protocol update</b> 3. Penn Medicine and Aetna co-branded letterhead, following permission from Aetna.	1. We would like to include an index card with participant statements about their experience in the HeartStrong program in the recruitment mailings to give potential participants the opportunity to hear about the experiences of current participants with hopes it will provide some insight to the services the program offers. 2. We are submitting a letter to mail to participants that have enrolled and have been randomized to the intervention, have been mailed the GlowCaps, but have been unresponsive to the standard follow-up phone calls from study staff to set-up the GlowCap devices. The contact letter will be used as final outreach attempt from our team to set-up the participant's GlowCap.	8/15/2013
8/27/2013	1. Removing Effient from drugs followed 2. Revising set up instructions removing Effient from the list.	1. Packaging for Effient indicates the medication should remain in the original bottle. After follow-up with pharmacists and cardiologists for guidance, we concluded that the optimal course was to not actively encourage the use of GlowCaps to store Effient. Given this, we have decided to remove Effient from the list of eligible medications for this study.	8/29/2013
9/19/2013	1. We are adding Alicia Gilbert to study team, Social Worker 2. We are adding Genevieve Cattanea to the HS ERA submission. Cattanea was added to the study team in a modification approved on 03-May-2013, but was not available from the dropdown list to add to the HS ERA application. 3. We are removing John Coats from study team		9/20/2013

10/11/2013	1. We are adding Kelsey Dochelli to study team, research coordinator		10/22/2013
10/24/2013	1. Adding Kristen Caldarella to study team, research coordinator 2. Adding Healthfirst Letter for recruitment, including changes requested by Healthfirst 3. Adding Toll free number 4. Submitted the Horizon logos for NJ and PA to add to recruitment letter		10/29/2013
11/1/2013	1. \$25 compensation enrollment payments for both intervention and control. Consent form and recruitment letter updated to include payment. <b>Study protocol update</b> 2. \$25 compensation payment for GlowCap set up for participants in the intervention. <b>Study protocol update</b> 3. <b>Eligibility criteria updated</b> , participants are only eligible to enroll in the study for up to 60 days after hospital discharge for heart attack. 4. Last day of eligibility included in enrollment letter 5. Test between standard check mailing and \$25 gift card 6. Updating consent, recruitment letter, welcome letter, with the above changes in the hs-era application	1. Instead of just compensating the participants randomized to the control for their effort during the enrollment process, we also want to compensate participants randomized to the intervention. The proportion of patients who have been hospitalized who enroll in the study has been relatively low, hampering generalizability and we feel that we need to increase this proportion significantly. 2. This is intended to pay participants for the effort of completing the device setup call and setting up their device for use. 4. Patients are eligible to enroll in the study for us to 60 days after their discharge from the hospital. In order to make patients aware of how much time they have to enroll in the study, we want to include the last date of eligibility for each patient in the recruitment letter to make patients aware of when their eligibility expires if they are interested in enrolling. 5. Proposed test will involve 350 participant mailings divided into the following groups. Group 1: 175 mailings with payment for enrollment in the study via typical method of processing a \$25 check, through the Way to Health platform, mailed to the participant's home. Group 2: 175 mailings with a \$25 Visa gift card included in the recruitment mailing. The letter would explain the gift cards will be activated once the participant completes the enrollment process.	11/17/2013
11/20/2013	1. We are adding Caroline Carney to study team, research coordinator		11/25/2013
12/11/2013	1. We are adding Raymond Lim to study team, data analyst 2. Clarifying contact timeline for non-adherence, <b>study protocol update</b> 3. 2 letters for re-contacting participants stopping using device, <b>study protocol update</b>	2. On the 5 <sup>th</sup> day of no GlowCaps openings, the engagement advisory will attempt to contact participant by phone. On the 6 <sup>th</sup> day of no device openings an automated message will be sent to participant saying that their engagement advisory will be reaching out to their feedback partner (if named) if we do not hear back from participant by tomorrow. On the 7 <sup>th</sup> day with no device openings, the feedback partner will be called to be informed that the participant is no longer using their GlowCap devices. On the 8 <sup>th</sup> day of no GlowCap openings, the study team will mail a letter to the participant reminding them our next step is to contact their physician (if named during enrollment) to	12/19/2013

		<p>let the physician know that the participant is not using their GlowCap devices. On the 14<sup>th</sup> day without GlowCap openings and no contact from the participant, the engagement advisor will attempt to reach the participant's primary care provider's office.</p> <p>3. These letters are intended to provide follow-up communications after a participant contact the study team to say they want to stop using the GlowCaps. At the time of the call, the Engagement Advisor will let the participant know the amount of time they still have remaining from the 12 month participation period so they know they have the opportunity to change their mind and begin to use the GlowCaps again in this time period. All participants in the intervention arm have 12 months which they are eligible to participate in the study, if they choose to discontinue use for a period of time, they will be allowed to being using the device again up to their original projected end date in the study. Version 1 of letter: Participants willing to be re-contacted. Version 2: Participant does not want to be re-contacted.</p>	
1/17/2014	1. Adding Noora Marcus to study team, research coordinator		1/23/2014
2/11/2014	1. Adding new insurance partner, Humana, to the study partners. Submission includes a copy of the new recruitment letter to be used for recruiting patients from this insurer		2/12/2014
2/26/14	1. Adding End of Program study protocol. Transition documents include: End of study letter, End of study survey, and End of study text messages to Participant and Partner. Protocol updates added to HS ERA sections Procedures and Design, <b>study protocol update</b>	1. We are modifying the research protocol to include a procedure for transitioning participants in the intervention group of the program. The goal of this process is to make sure participants are aware participation is ending and that the GlowCap will no longer function as they have during the study. We also want to let participants know that the Program Advisor will no longer be monitoring their adherence (GlowCap openings) or reaching out to them as they have during the intervention period. We are also including a brief End of Study Survey to collect participant feedback about the program to use for improving the current study, as well as future studies. End of study protocol includes: 2 months before last day in program, End of Program Letter and End f Program Survey mailed to participant and an automated message sent to feedback partner notifying of study end date. 1 month before last day in program, and automated text to participant and a follow-up phone call made to participant to review end of study protocol and a reminder to return end of program survey. Last day in the program, an end of program automated message sent to participant.	3/7/2014
3/12/2014	1. Add Wenli Wang to study team, data analyst 2. Updated IBC recruitment letter, per IBC request	3. We have added a question to the enrollment process for patients being recruited from Humana insurance. We are	4/7/2014

	<p>3. Adding Screening Question for Humana patients, <b>key exclusion criteria update.</b></p> <p>4 Updated our consent, including typographical errors and adding our new 1-800 number for the study.</p>	<p>adding this question only for Humana because another researcher at the University of Pennsylvania is recruiting a similar population of Humana patients into a medication management study using GlowCap devices. We wanted to include this screening question to ensure that Humana patients are not enrolled in both studies. We have updates Key Exclusion Criteria section to say, "we are excluding patients who are enrolled in any other medication management studies that incorporate the GlowCap electronic pill bottle."</p>	
4/21/2014	<p>1. Revised version of the HeartStrong-website and a recruitment brochure</p>	<p>1. The purpose of the website will be to refer patients to if they want to view study information online. The brochure will be included in recruitment mailings.</p>	4/25/2014
5/12/2014	<p>1. We are adding Tirza Calderon to study team, research coordinator</p>		5/20/2014
6/02/2014	<p>1. Adding PHQ-2 to transition call, and updating protocol for PHQ2 referral to Social Work.</p> <p>2. Modifications to the Aetna recruitment letter, per Aetna's request.</p> <p>3. Adding 2-page resources list created by the Social Workers to send to patients randomized to the control arm.</p> <p>4. Modifications to wording in the informed consent</p>	<p>1. Adding PHQ-2 Questions end of study phone call: Currently we ask all participants to answer the PHQ-2 questionnaire during the enrollment phone call. We would like to include this questionnaire in our end of program phone call with participants as well for the following reasons. We feel asking these questions at this time is an extra measure we can include to ensure we are safely and responsibly discharging participants from the HeartStrong Program as it will provide our team with an opportunity to assess whether a participant needs additional resources before they exit the program. In addition, asking these questions again at this time will provide additional data for comparison to the baseline PHQ-2 survey administered during enrollment into the HeartStrong Program. We hope this comparison may shed some light on the effect our program may have had on the way a patient scores on the PHQ2 at the end of the program. The PHQ-2 questions will only be asked of those participants who were randomized into the intervention arm of the study. We will not reach out to control participants for this purpose.</p> <p>In addition to this, we have also updated the response for participants who score a 5 or 6 on their PHQ2. If participants score a 5 or 6 on this questionnaire, they will be given the opportunity to be contacted by one of our 2 Research Coordinators who are also Social Workers. The Social Workers can link these participants to resources and supports to meet their expressed needs and will reach out to these participants within 24 hours. This process will be followed for PHQ-2 surveys administered during baseline enrollment and transition off of the study.</p> <p>3. Addition of 2-page resource list: Our study Social Workers have developed a collection of resources and guidance with additional information and tips pertinent to recent heart attack</p>	6/17/2014

		patients. We would like to share this document with participants who are randomized into the Control arm of the study if they indicate they have a need or interest in receiving this kind of information. This document will be sent via email or USPS mail, depending on participant preference. This impetus for creating this document was to improve patient experience by offering to provide important post-heart attack resources to those who indicate an interest to know more about this information.	
6/20/2014	1. Add Helen Admasu to study team, research assistant		6/23/2014
7/1/2014	1. Dr. Shivan Mehta has been moved from Study Contacts to Key Study Personnel 2. We have added Amanda Hodlofski and Tori Ulrich to the study team, project managers 3. We have added Devon Taylor to the study team, research coordinator		7/8/2014
7/17/2014	1. We are moving Tori Ulrich from Key Study Personnel to Study Contacts (so can submit IRB modifications) 2. We are removing Chris Meussner and Brandon Ciaudelli from study roster 3. We are adding Christina Jameson, research assistant 4. We are adding Michael Kopinsky, web developer 5. <b>Updates to study protocol</b> (see rationale for details). Updates include changes to: key inclusion criteria, subject confidentiality, accrual and subject recruitment, procedures, study duration, and the addition of MedSignals devices	5. We have made changes to the following: <b>A) Key inclusion criteria</b> – add criteria that patients must receive their health benefits through one of our insurance partners. <b>B) Subject confidentiality</b> – Changed the language around data that will be sent to Vitality to only include name and dosage schedule. We do not collect email addresses or phone number. <b>C) Accrual and Subject Recruitment</b> – removed Keystone Mercy as an insurer. We had intended to initially recruit from this insurer, but we no longer plan to work with them. <b>D) Accrual and Subject Recruitment</b> – Target population expanded to include the entire United States, not just NJ, PA and N. <b>E) Procedures</b> – Updated the process in pace to send alerts when non-adherence occurs. <b>F) Study Duration</b> – We are only implementing version 1.0, so we deleted dates for version 2.0. We have updated the dates of expected recruitment to last through December 2014. <b>G) Accrual and Subject Recruitment</b> – We have decided to no recruit in person. All UPHS patients will be recruited remotely, just as other patients. <b>F) Subject Recruitment</b> – We revised our recruitment plans to include USPS priority mail with tracking. <b>G) Procedures</b> – Addition of MedSignals device. For a small handful of participants who cannot establish a signal with the GlowCaps, we will provide them with a MedSignals device that collects adherence data in the same way. Updates have been made to our security document.	8/8/2014
8/14/14	1.Submitted 7/17/14 DSMB Minutes 2.Added Email as recruitment method (attached sample email) 2. Informed consent changes, per the IRB recommendations	2. The email will be sent to patients whose email we have on file and will be sent a week after the enrollment letter is sent. 3. In consultation with Megan Kasimatis Singleton and Penn's Chief Privacy Officer, Lauren Steinfeld, we have revised our consent to improve the language and to help clarify our	8/26/2014

		consent/ HIPPA process for our participants going forward.	
8/27/14	1. We are adding Kelsey Gangemi to Study Team, research coordinator 2. Addition of promotional materials in mailings (pens, magnetpads, "checklist for better health", notecards)	2. We plan to include a few promotional materials into the mailings, to help increase the rate at which patients open our recruitment letters. The new recruitment materials will be included with existing recruitment materials.	9/8/2014
9/10/2014	1. We are adding Rachael Hutchinson to Study Team, research assistant		9/16/14
9/26/2014	1. Update the informed consent: clarify why we ask for Physician contact information. 2. Use of anonymous feedback for marketing of WTH platform 3. Blurb to add to the website regarding the team's upcoming participation in the AHA's 5k	1. We collect physician information for all patients before they are randomized to either control or intervention. In the event we are unable to reach a patient enrolled in the intervention, we reach out to the physician for follow-up. 2. We would like to anonymously use some of the positive feedback we have received from participants in the marketing materials for the Way to Health platform.	10/3/14
11/11/14, resubmitted on 11/19/14. Resubmitted again on 11/25/14	1. Submitting all 6 recruitment letters to remove the last date to enroll as we approach our enrollment target. Also adding line to enrollment letter that study is approaching target enrollment. 2. Request to enroll above target of 1500, <b>changes to Accrual</b>	1. The reason we are doing this is because we are approaching our enrollment target. The letter currently indicates that participants have 60 days after a cardiac event to enroll in the study. The issue is that we expect to meet our target by late December, and for some patients, 60 days after their cardiac event would be mid-January or later. In an effort to not misinform participants, we would like to remove the last date to enroll. Study staff will still track last date to enroll to ensure we do not enroll someone who is ineligible. In addition, in our effort to be transparent as possible to potential participants, we also added a line to the recruitment letter that the study is approaching its enrollment target and we encourage participants to reach out to us if they are especially interested in our program. 2. We will continue to with our current recruitment methods of calling everyone that we send a letter to, but once we hit our target, we will no longer call participants because we want to keep our enrollment as close to goal (1500) as possible. We would like, however, to accept participants who call in to the study in order to give them the opportunity to enroll. As such, we are asking permission to enroll additional participants over our goal 1500. We have updated our recruitment goal to 1520 participants.	12/1/14
12/2/14; resubmitted on 12/4/14	1. Adding competency screening tools, Ottawa 3DY and AD8 Dementia Screening, to enrollment process (protocol changes). <b>Updates to study protocol</b> 2. Revised consent to include new HIPAA/privacy language	1. We have chosen the Ottawa 3DY and the AD8 Dementia Screening Tool to assess for competency during our enrollment phase of our program. The Ottawa 3DY is a four questions tool designed to screen for cognitive impairment in the elderly. The AD8 Dementia Screening Tool is sensitive to detecting early cognitive changes associated with many common dementing illnesses. If a patient answers one or more questions incorrect	12/8/14

		on the Ottawa 3DY then the AD8 Dementia Screening Tool can be administered to an available caregiver to determine whether the patient is eligible for participation in the program. These tools were both shown to be effective in screening for cognitive impairment, are brief to administer and can be administered by non-clinicians	
1/22/15	<p>1. Introduction of "Hotspotting" procedures. <b>Updates to study protocol</b></p> <p>2. We have removed Rachel Hutchinson, Kelsey Gangemi, and Caroline Carney from study team.</p>	<p>1. In an effort to reach participants who have enrolled in the program, but who have not set up their GlowCaps, we have developed a set of procedures, which we call "Hotspotting", to try and re-engage these participants. After a participant has consented to be in the study and has been randomized, the program advisors attempt to set the participant up with their GlowCap devices. Some participants never get setup on the devices, so with this effort, the PAs will attempt to get them set up. Within 6 weeks of enrollment, the PAs will try to call the participant, and if unsuccessful, will send them a letter as well as an automated message through the Way to Health platform. If there is no response, then about 4 months after enrollment, the PAs will attempt to call the patient, and if we cannot reach the patient by phone, the PA will send another letter. If there is still no response, then about 8 months after enrollment, the PAs will attempt to re-engage the patient again and call the patient, and if we cannot reach the patient by phone, the PA will send another letter. Our hope is that these efforts encourage and allow renewed participation from those individuals who have already enrolled in the program and have been assigned to the intervention group. If at any point the coordinators are able to contact the patient and identify any social work issues that are preventing re-engagement with the intervention, the coordinator will refer the participant to one of the social workers for further follow-up.</p>	2/11/15
6/15/15	<p>1. HCIA participant survey, conducted by Acumen/ Westat</p> <p>2. We have removed Chantell Ketchem, Ling Yang, Yuanyuan Tao, Helen Amadsu, Amanda Hodlofski from the study team.</p> <p>3. We have moved Noora Marcus from Key Study Personnel to Study Contacts, (so can submit IRB modifications, project manager)</p>	<p>1. As part of their evaluation process, Acumen and Westat (CMS affiliates) would like to conduct a participant survey with intervention patients. The surveys will be mailed to participants and include a letter which describes the purpose of the survey. The survey will be sent to patients after they have completed the 12 month intervention. Additionally, the surveys will only be sent to participants who gave consent using the updated consent from indicating their data could be shared with CMS and its affiliates.</p>	6/25/15
2/23/16	<p>1. We are adding Coleman Humphrey to study team, data analyst</p>		2/24/16

## Original Analysis Plan

### 1.1 Overall objectives

The specific aims of this study are to:

1. Test the effectiveness of a state-of-the-art web-based portal with home-based wireless medication adherence devices and behavioral economic feedback mechanisms in preventing vascular events or re-hospitalization in the 12 months following hospital admission for AMI
2. Deploy a new model of evidence based evolutionary learning that uses rapid cycle innovation in 3 successive planning cycles over the 36 months of this proposal

### 1.2 Primary outcome variable(s)

Primary outcomes will be vascular events (AMI, stroke, acute coronary syndrome admission, or death)

### 1.3 Secondary outcome variable(s)

Secondary outcomes will be hospitalization, repeat or new cardiovascular procedures, medication possession/gap ratios (for those patients for whom we can link to CVS Caremark pharmacy benefits data) and total cost of care.

## Background

### 1.1 Statistical Considerations

#### 1.2 Power and sample size (from 4.1.b.i. of the full grant):

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%,<sup>60</sup> and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1500 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 500 control and 1000 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurer partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but

enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

## 1.2 Data analysis

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding<sup>96,97</sup> (references listed in full grant submission) or predictive ability. Models will be assessed using standard diagnostic techniques.<sup>98</sup> (references listed in full grant submission)

We expect to have nearly complete follow-up data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## **Analysis Plan**

### **1.1 Power and sample size**

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%,<sup>60</sup> (reference from full grant proposal) and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1500 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 500 control and 1000 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

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blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health and be available 24/7. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

## **1.2. Data analysis**

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We expect to have nearly complete follow-up data since our primary outcomes will be analyzed using claims data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## Final Analysis Plan

**\*\*New changes from initial analysis plan notated in bold, parts removed from initial analysis plan notated in strikethrough**

### 1.1 Overall objectives

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Power and sample size. (from 4.1.b.i. of the full grant):

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%, 60 and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue ~~4500~~ **1520** patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield ~~500~~ **506** control and ~~4000~~ **1014** intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurer partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the

possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

## 1.2 Data analysis

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding 96,97 (references listed in full grant submission) or predictive ability. Models will be assessed using standard diagnostic techniques.98 (references listed in full grant submission)

We expect to have nearly complete follow-up data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## **Analysis Plan**

### **1. 1 Power and sample size**

Our primary outcome is time to first fatal or nonfatal acute vascular event or revascularization, including AMI, unstable angina, stroke, or death. The primary comparison will be the time to event compared between the overall intervention arm and the usual care arm; that is, the primary hypothesis is whether a series of interventions, adapted to the behavior and outcomes of each particular patient, will reduce vascular events or revascularization rates compared to usual care. Hypotheses of secondary interest include distinct comparisons of Versions 1.0 and 2.0 against usual care and each other.

We expect the 1-year event rate in the usual care group to be approximately 23%, 60 (reference from full grant proposal) and require 80% power to detect a hazard ratio of about 0.7; this corresponds to a 6% decrease in the event rate in the intervention group. Thus we will accrue 1520 patients over the 24-month period in which Versions 1.0 and 2.0 are implemented; the 2:1 randomization ratio will yield 506 control and 1014 intervention subjects, approximately 500 each receiving Version 1.0 and 2.0. When comparing the individual versions to the usual care group, 500 subjects per arm provide 80% power to detect a hazard ratio of about 0.5, which corresponds to a reduction in the 1-year event rate of 11 percentage points. In direct comparisons of Version 1.0 and 2.0, we allow a more generous Type I error of 0.25, since this comparison will proceed only if both versions are more effective than usual care, and in that scenario strict control of Type I error is markedly less important. With 500 patients receiving each version, we have 80% power to detect a hazard ratio of 0.62; assuming a baseline event rate of 17% in Version 1.0, this corresponds to a reduction of about 6% in Version 2.0.

Randomization will be stratified by patient source (UPHS or insurance partner) using permuted blocks with variable block sizes, to minimize imbalances in study arm assignment, and remove the possibility of time-cohort effects. Online, web-based randomization will be implemented via Way to Health and be available 24/7. The trial design combines the best elements of standardized clinical trials and rapid-cycle innovation theory, preserving the direct comparability afforded by randomization but enabling comparisons both of the overall intervention and its primary iterative components to enable the most efficient decision-making method based on valid evidentiary standards. This is a substantial innovation.

## **1.2 Data analysis**

The primary analysis will consist of unadjusted intent-to-treat hypothesis tests using the logrank test to compare time to vascular events between intervention and usual care groups; Cox proportional hazards models will be estimated to adjust for the stratification variables and other covariates of interest (e.g., accrual mechanism, patient sex, income, race, diagnosis at initial admission), retaining these given evidence of confounding<sup>96,97</sup> (refs from original submission) or predictive ability. Models will be assessed using standard diagnostic techniques.<sup>98</sup> (ref from original submission).

We expect to have nearly complete follow-up data since our primary outcomes will be analyzed using claims data. We will be able to capture any events that result in hospitalization even for participants lost to follow up. We will compare dropout rates by arm, attempt to find the reasons for missing data, and compare baseline characteristics in participants with complete vs. incomplete follow-up. In secondary analyses we will investigate the sensitivity to modeling assumptions using imputation models and inverse-probability-weighted estimating equations and models that adjust for informative missing data.

## **Summary of Changes to Statistical Analysis Plan**

No formal changes were made to the analysis plan.

Target enrollment was increased from 1500 to 1520, in order to enroll all interested potential participants from the final recruitment mailing. As a result, the intervention arm changed from 1000 participants to 1014, and the control arm change from 500 participants to 506. At the close of enrollment, we enrolled 1509 participants, with 1003 in the intervention and 506 in the control.