Supplement

Asch DA, Troxel AB, Stewart WF, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.14850.

This supplement provides additional information about the work. It contains the following items:

Original Study Protocol

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1. Abstract

Cardiovascular disease (CVD) is the leading cause of death in the United States. Despite strong evidence that reducing low-density lipoproteins (LDL) with statins successfully lowers CVD risk, physicians under-prescribe statins, physicians fail to intensify treatment when indicated, and more than 50% of patients stop taking statins within one year of first prescription though such therapy typically should be lifelong. In this study, we will test the effectiveness of different behavioral economic interventions in increasing statin use and reducing LDL cholesterol among patients with poor cholesterol control who are at very high risk for CVD.

The application of conceptual approaches from behavioral economics offers considerable promise in advancing health and health care. Pay for performance initiatives represent one such potential application but one in which incorporating the underlying psychology of decision makers has not generally been done, and experimental tests have not been conducted. We will test these approaches among primary care physicians and their patients at very high risk of CVD at Geisinger Health System and University of Pennsylvania outpatient clinics.

Using a 6-arm, cluster-randomized controlled trial, we aim to answer these questions: [1] How does the provision of provider incentives compare to the provision of patient incentives, to a combination of patient and provider incentives, or to no incentives at all? [2] Is success with provider incentives improved with enhanced information about patient adherence? [3] How does the provision of financial incentives compare to an alternative clinical approach in which lipid management defaults to a nurse practitioner rather than physician? [4] Are results sustained after incentives and other interventions are withdrawn? [5] How do these approaches compare in implementation, acceptability, cost, and cost-effectiveness?

2. Significance

2.1. Cardiovascular Disease is the Single Leading Cause of Death in the United States

1.2 million Americans each year have a new or recurrent myocardial infarction (AMI) and 38% of them die from it in a given year. Clinical practice guidelines recommend HMG-CoA reductase inhibitors (statins) to lower cholesterol, and clinical trials have shown that statins lower the risk of AMI by about 30%. Despite their proven benefits and benign side effect profile, the population effectiveness of statins is limited for two reasons. First, physicians may under-prescribe statins or fail to intensify treatment when indicated. Second, patient adherence to statins is moderate at best: approximately half of patients prescribed statins discontinue usage within a year. Poor adherence leads to worse outcomes, higher hospitalization and mortality rates, and increased health care costs among CVD patients. However, many seemingly successful efforts to improve medication adherence have been too complex to be implemented or required extensive resources, limiting applicability and sustainability. In addition, providers rarely have data on patient adherence or are limited to examination of prescription fill rates.

2.2. Annual Direct and Indirect US Expenditures Attributable to CVD are about $500 Billion

Statins can reduce CVD events requiring hospitalization by nearly 20%, which could save over $15 billion annually from CVD and stroke hospitalizations alone. For secondary prevention, the cost-effectiveness ratios of statins range from being cost-saving to approximately $30,000 per quality-adjusted life-year (QALY) gained. For primary prevention, cost per QALY ratios are well below accepted thresholds; for example, in the United Kingdom from £10,000 to £31,000 per QALY for 10-year CVD risk ranging from 30% to 5%.

Both provider and patient factors contribute to high rates of under-treatment. About two-thirds of US patients at high risk for CVD are un- or under-treated due in part to the complexity of provider guidelines. A review of 23 studies suggests that improvement in adherence reduces overall treatment costs, reduces disease-related costs, and improves cost-effectiveness of cardiovascular medications; in many cases, small improvements in adherence lead to large improvements in cost-effectiveness ratios.

2.3. Volume-based Payment Systems Work Against the Management of Chronic Illness

Activities to promote prescription and adherence of medications for chronic disease are poorly reimbursed if at all, while acute procedural interventions typically have the highest profit margins. There is widespread agreement that incentive approaches that reward improved patient health instead of increased volume need to be developed and rigorously tested. Pay-for-performance (P4P) systems were developed with a focus on patient outcomes, but from a behavioral economic standpoint, the typical physician P4P program has several design features that likely limit success: [1] payments are typically awarded as a lump sum bonus at year end (ignores present-biased preferences); [2] bonus payments are typically added to a physician's paycheck (ignores mental accounting principles, since smaller payments bundled with larger payments are less salient); and [3] payments are typically based on meeting single threshold-based measures such as 90% of appropriate patients getting a mammogram (ignores evidence that people exert more effort as they get closer to goals and a high threshold is unlikely to motivate people who think a goal is largely unreachable).

2.4. Behavioral Economists Have Proposed an "Asymmetric Paternalism" Approach to Public Policy

Approaches using asymmetric paternalism aim to make it easier for people to make good choices, without restricting those choices, e.g., arranging food on a buffet such that healthy foods are more likely to be chosen. Asymmetric paternalism is paternalistic in the sense of attempting to help individuals achieve their own goals, as compared to conventional regulation designed to prevent harm to others. Asymmetric paternalism is asymmetric in the sense of helping individuals prone to making irrational decisions while not limiting freedom of choice and not harming those making informed, deliberate, decisions. Setting default options to the most desirable, beneficial, or popular choices is an example of

choice architecture. Using financial incentives to encourage certain behaviors is another example of asymmetric paternalism.

2.5. Biases That Ordinarily Lead to Self-Harming Behavior Can be Used to Promote Healthy Behaviors

Individuals put disproportionate value on present relative to future costs and benefits. This "present-biased preference" typically works against healthy behaviors. However, incentives can be structured (e.g., providing tangible small but frequent positive feedback or rewards) so that present-bias works in favor of adopting healthy behaviors. For patients, the most effective approaches have been those requiring monitoring several times a week, suggesting the importance of frequent feedback. For providers, frequent feedback should be defined differently. Patients need to take statins daily, but providers typically consider an individual patient's LDL after lab tests that may be months apart.

Indeed, an important part of our work has been to move beyond thinking about financial incentives as all-or-none, but instead to design the structure and timing of incentives to correspond to established principles of psychology and how different decision makers (e.g., physicians versus patients) act. For example, we have tested the use of daily lotteries for patients to improve medication adherence and weight loss. Americans spend $48 billion annually on state lottery tickets. However, the average pay-out rate across state lotteries is just 52%, ranging from 26-71%. Several features combine to make lotteries attractive despite their poor return. Frequent small payoffs give lottery players intermittent positive reinforcement. Feedback is often very rapid: most games have daily draws and instant scratch-off tickets. The small chance of a large payoff is especially attractive because people tend to overweigh small probabilities in making decisions. For these reasons, structuring financial incentives as a lottery has several benefits for a daily incentive. We are less enthusiastic about using daily lotteries for physicians: their decisions for each patient are not daily, and the perceptions of lotteries may be inconsistent with professional norms in clinical care. However, other decision errors such as present-biased preferences, loss aversion and mental accounting can be usefully applied.

3. Background

3.1. Feasibility

We have successfully completed numerous randomized trials of financial incentives in a wide variety of settings as well as a number of quality improvement projects at both UPENN and Geisinger, the proposed study sites. The experience acquired and infrastructure developed from these studies will ensure successful completion of the proposed work. There are approximately 355 primary care providers at UPENN and Geisinger. Moreover, analysis of the UPENN and Geisinger electronic records indicate a significant number of patients with a Framingham Risk Score (FRS) of greater than $\geq$ 20% with LDL $\geq$ 120, or FRS = 10-20% with LDL $\geq$ 140, or a coronary artery disease equivalent (diabetes, peripheral

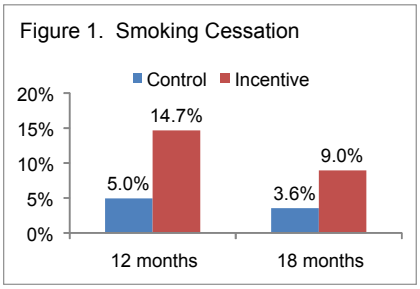
artery disease, ischemic CVD, arteriosclerotic CVD, stroke/TIA, CABG, coronary stenting, or coronary bypass anastomosis) with LDL $\geq$ 120. Such patients should have LDL of 100, leaving substantial opportunity for improvement. Based on previous recruitment experience at UPENN, Geisinger we expect to readily achieve the targeted enrollment of 200 physicians and 1400 patients for this low-risk study with minimal requirements and generous incentives for participation. Current approaches have evidently not succeeded in managing CVD risk among these patients highlighting the need for effective and scalable interventions to improve management. With support from an RC2 grant (Volpp and Asch Multiple PIs), we have developed the capacity to facilitate behavioral economic studies with an easily customizable web-based platform supported by a secure multi-terabyte data repository. This Way to Health platform can take inputs from either home-based biometric measurement devices (e.g., Vitality GlowCaps) or EpicCare medical record lab values; convert these into visually appealing and informative content displays; automatically calculate patient or provider incentives based on the study design; push messages back out to patients or providers via text message, email, or interactive voice recordings (patient or provider preference) at any time interval; and automatically transfer incentive payments electronically. The Way to Health platform has many other capabilities, including flexible and automated participant randomization, electronic consent functions, and participant tracking and will be fully operational by August 2010. The teams from Geisinger and Penn have extensive experience working with EpicCare records, automatically generating reports to push out to web-based portals and facilitating access from within EpicCare to web-based portals.

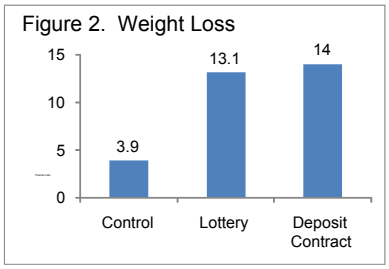
3.1.1. Preliminary Studies

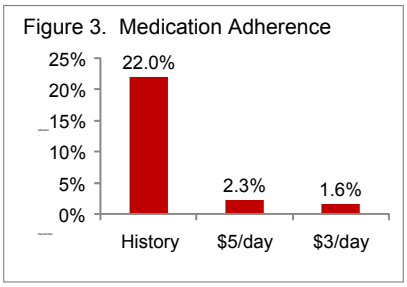
3.1.1.1. Evaluation and design of new P4P initiatives for physicians.

Dr. Asch has examined the clinical impact of physician performance measurement. He is currently co-leading an evaluation of the Department of Veterans Affairs roll out of the Southeastern Pennsylvania Medical Home. Dr. Rosenthal has conducted numerous studies of the adoption and evolution of pay for performance in the U.S. health care system, and has developed recommendations for the design of P4P programs based on both economic theory and evidence. She has also led evaluations of several major P4P programs including Bridges to Excellence and PacifiCares Quality Incentive Program, part of the largest multi-payer P4P program in the U.S. Currently, Dr. Rosenthal is evaluating a broad range of physician payment incentive models including primary care Medical Home initiatives and an episode-based payment system. Dr. Volpp is co-leading an evaluation of the Southeastern Pennsylvania Medical Home as well as serving as PI of an RWJ-funded study of differential hospital service line profitability on patient mortality and readmission rates. Our team has introduced many behavioral economics concepts into health care through discussion of issues related to asymmetric paternalism in health care settings, choice architecture and the use of defaults, and use of common decision errors in designing interventions to help people as opposed to taking advantage of them.

3.1.1.2. Incentives for health behaviors







Our team has studied lotteries and other incentives to improve health behaviors in the context of smoking, obesity, and medication adherence. These include: [1] A CDC-funded study of 878 participants at 85 General Electric work sites testing the effectiveness of financial incentives worth $750 in increasing smoking cessation rates. Smoking cessation rates after 12 months were nearly triple in the incentive group (14.7% vs. 5.0%, p0.0001) and this ratio was sustained at 18 months after incentives were discontinued (Figure 1). GE implemented a program based on this in January, 2010 for all 152,000 employees nationally. Published in NEJM, this effort won the British Medical Journal 2010 Award for Getting Research into Practice. [2] Two studies testing the impact of copayment reduction on blood pressure and medication adherence in 820 veterans with poorly controlled blood pressure. These studies showed that, counter to conventional wisdom, copayment reductions have much smaller effects on outcomes and adherence than had been indicated by observational studies of copayment increases, likely because reducing copayments targets the behavior of non-adherent patients, a much more challenging group. [3] A study funded by USDA and the Hewlett Foundation to encourage weight loss using lottery-based incentives and deposit contracts, in which patients voluntarily put their own money at risk and win it back conditional on success. This study, published in JAMA, used a lottery system similar to the patient incentive proposed here: a daily lottery with expected value near $3 per day (about 1 in 5 chance of winning $10, 1 in 100 chance of winning $100) with receipt of payments conditional on periodically verified improvement in outcomes (weight loss). In this study, incentive group participants lost significantly more weight than control group participants (control = 3.9 pounds; lottery = 13.1 lbs, p = .01; deposit contract = 14.0 lbs, p = .003; Figure 2). Only 7% of participants were lost to follow-up by the end of the study. Among incentive group subjects not lost to follow-up, participants called in daily weights 98% of the time, indicating both the feasibility and effectiveness of a daily lottery in providing variable reinforcement to change behavior. [4] Several studies funded by NHLBI and the Aetna Foundation testing the use of daily lotteries to improve medication adherence. In all studies, participants were eligible for the daily lotteries if they correctly took their warfarin. In two separate studies testing $5 and $3 expected value lotteries over 979 and 813 patient-days, respectively, non-adherence was 2.3% and 1.6% compared to historic proportions of 22%.89 (Figure 3) These studies indicate that expected values of $3 and $5 have comparable impact, as the effectiveness of lotteries may be due not only to expected winnings but also to regret, reinforcement, and entertainment. A follow-up RCT of incentives for warfarin adherence in 100 participants (under review) indicated that lottery-based incentives improved INR within target range for patients with below-range INR at baseline, but offered little benefit to those already well controlled. These results highlight the utility of targeting

interventions, where possible, to participants with evidence of suboptimal adherence to efficacious medications at baseline.

3.1.2. Clinical Informatics

Over the past five years, the Geisinger Center for Health Research has conducted extensive research developing and testing how web-based tools can be used interactively with the electronic health record to improve care efficiency and quality in the Geisinger Clinic. The inventory includes real-time use of patient reported data for diagnosis and outcomes tracking; patient decision aids; visual display tools to facilitate physician decision making, and web-display tools that deliver point of care expert advice. At Penn, Dr. Weiner developed the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) System in 1997, to promote research in the clinical enterprise. PICARD compiles UPENNs electronic records (Epic and Sunrise), billing, and laboratory results reporting across its hospitals and ambulatory sites. PICARD includes all patient demographics, location of the encounter, participating physicians, as well as diagnoses assigned during the encounter and charges and reimbursements for all procedures performed.

3.1.3. Cost-effectiveness of health promotion interventions

Dr. Glick has written extensively on methods for economic assessments in clinical trials, including issues of study design, economic data collection, unit cost estimates for within-trial medical service use, and analysis of costs and cost-effectiveness. Dr. Gaziano has done extensive evaluation of long-term cost-effectiveness of CVD interventions including LDL lowering, blood pressure guidelines, absolute risk assessment, and multi-drug therapy for primary and secondary prevention. Dr. Weinstein is a co-developer of the Coronary Heart Disease Policy Model, which has been used to evaluate the cost-effectiveness of cardiovascular prevention and treatment including cholesterol lowering.

3.1.4. Way to Health Platform

With support from an RC2 grant (Volpp and Asch Multiple PIs), we have developed the capacity to facilitate behavioral economic studies with an easily customizable web-based platform supported by a secure multi-terabyte data repository. This “Way to Health” platform (waytohealth.org – see figure in Resources section) can take inputs from either home-based biometric measurement devices (e.g., Vitality GlowCaps) or EpicCare medical record lab values; convert these into visually appealing and informative content displays; automatically calculate patient or provider incentives based on the study design; push messages back out to patients or providers via text message, email, or interactive voice recordings (patient or provider preference) at any time interval; and automatically transfer incentive payments electronically. The Way to Health platform has many other capabilities, including flexible and automated participant randomization, electronic consent functions, and participant tracking and will be

fully operational by August 2010. The teams from Geisinger and Penn have extensive experience working with EpicCare records, automatically generating reports to push out to web-based portals and facilitating access from within EpicCare to web-based portals.

3.1.5. Adherence measured using Vitality GlowCaps

Our group has conducted several randomized trials using adherence monitoring technology. That experience led us to select Vitality GlowCaps for this study. GlowCaps are used in place of regular pill bottle caps and electronically monitor bottle opening with a small remote device that plugs into a wall outlet. The technology allows provision of adherence feedback to many patients and/or providers. Through our Way to Health platform, we can connect this feedback with our lottery-based incentives, making the system feasible for large-scale adherence interventions.

Figure 4: Vitality GlowCap and Plug-in Transmitter

Several methods have been used to measure adherence; no "gold standard" exists. There are multiple limitations to methods such as patient self-report and pill counts. GlowCaps provides an unbiased assessment of pill bottle opening and a valid approach to verifying self-administered pill taking, reflecting not only daily use but also patterns of drug use and timing. This method assumes that each time the cap is opened, a dose is taken, and that doses are not taken when the cap is not opened. GlowCaps are just like regular pill bottles so there is little need for patients to decant pills into other containers—a process that can lead to false negative measures of adherence. Similarly, although it is possible for patients to open a pill bottle but not take their medication, evidence suggests that once an individual opens a pill bottle, pills are nearly always taken and numerous studies have established the validity of electronic pill container measures.

Each day the GlowCap will electronically transmit whether a participant opened his/her prescription bottle to take his/her cholesterol-lowering medication via a built-in modem to the central server (there is no internet charge to participants) and a simple wireless device plugged into an outlet. Participants will be considered adherent only if we receive electronic notification signaling that the pill bottle was opened once the previous day. GlowCaps and the wireless transmitters are easily portable and can be used while traveling. Each patient will receive instructions to call the study nurse for any changes in dose frequency (an unlikely event in the context of cholesterol-lowering medications, most of which are recommended as once-a-day medications), in which case the GlowCap will be reprogrammed.

3.2. Summary of Preliminary Studies and Study Feasibility

Our pilot data and experiences reveal: [1] Our study sites offer sufficient eligible participants. [2] Many high-risk CVD patients at these sites have poorly controlled LDL cholesterol. [3] Intervention studies by our group using financial incentives have shown substantial increases in healthy behaviors. [4] We have

built an infrastructure capable of supporting this project using a high degree of automation, lowering research costs and increasing feasibility of clinical adoption of results. [5] Our team has experience in designing, conducting, and analyzing trials of financial and behavioral interventions. [6] Our team has expertise in evaluating cost-effectiveness in the context of clinical trials and CVD. [7] We have successfully conducted trials and recruited patients in a wide variety of study sites.

4. Innovation

This study would be the first to experimentally test whether incenting providers based on the outcomes their patients achieve is effective. It would be the first to test whether, dollar-for-dollar, provider incentives are more effective than patient incentives or provider/patient hybrid incentives.

The context is CVD, the top killer of Americans. The study's motivation is the simultaneous availability of well-tolerated and effective medications to reduce CVD risk and evidence that they are under-prescribed by physicians and under-adhered to by patients. Incentives offer great promise in this context as standard approaches have not sufficiently improved adherence rates among high-risk non-adherent patients and reasons include inadequate positive reinforcement and insufficient attention to 'important' vs 'urgent' issues for providers due to the incentives embedded in visit-based fee for service provider payment.

The provider incentives will be the first P4P intervention that sets goals designed to motivate all providers to participate by rewarding continuous improvement rather than a single target threshold, that considers present-biased preferences by providing rewards to providers on a quarterly basis, and that considers mental accounting issues in the disbursement of those payments.

5. Overall Objectives

This proposal is motivated by several observations: [1] Cardiovascular disease (CVD) is the leading cause of death in the United States. [2] There is strong evidence from multiple clinical trials that reducing low-density lipoproteins (LDL) with statins successfully lowers CVD risk. [3] Despite this evidence, physicians under-prescribe statins and fail to intensify treatment when indicated. More than 50% of patients stop taking statins within one year of first prescription though such therapy typically should be life-long. We propose to test the effectiveness of different behavioral economic techniques in increasing statin use and reducing LDL cholesterol among patients with suboptimal cholesterol control who are at very high risk for CVD.

Financial incentives and the modification of choice architecture (e.g., setting default options to the most desirable, beneficial, or popular choices) are two approaches to change physician and patient behavior. Considerable conceptual grounding from behavioral economics supports both approaches, though their empiric validation has largely come from contexts like savings behavior rather than health care settings. We and others have developed and tested incentive-based interventions that significantly improve

patient health behaviors, but these approaches have not been well tested in parallel with efforts to change provider behavior. Recent pay for performance (P4P) efforts have used payments to motivate providers to improve quality, but the focus has often been on process measures of plausible but uncertain value. Moreover, economic P4P incentives have not accounted for the underlying psychology of physician decision-makers. Perhaps as a result, there is little evidence that existing P4P interventions improve patient health outcomes. We propose to address an important gap in behavioral economics at the intersection of the burden of poorly controlled chronic diseases, the recognition that payment reform should redirect incentives to improvements in patient outcomes rather than increases in the volume of services, and the unrealized promise of P4P approaches to improve patient outcomes.

Using a 6-arm, cluster-randomized controlled trial (RCT) among primary care physicians and their patients at Geisinger Health System and the University of Pennsylvania outpatient clinics, we propose to test and compare the effectiveness and cost effectiveness of alternative approaches to reducing LDL cholesterol. We will test the absolute and relative effect of incentives for providers, patients, and providers and patients together. In four of six arms we will provide clinicians with feedback on patient adherence, using Vitality GlowCaps, and test the value of providing patient adherence data to providers in achieving LDL reduction. We will enroll patients who have a 10- year CVD risk of 20% or more and an LDL of at least 160, indicating under-utilization of statins. These patients are particularly important to target in achieving effective risk management of CVD outcomes and offer promising returns from behavioral economic strategies. Physicians caring for those patients will be randomly assigned to one of 6 arms: [1] Physician incentives (no GlowCaps information); [2] Physician incentives (with GlowCaps adherence information); [3] Patient incentives (with GlowCaps information); [4] Physician and patient combined incentives (with GlowCaps information); [5] Choice architecture approach with GlowCaps and lab data provided to dedicated nurse practitioner (NP CA); [6] Usual care (no GlowCaps information or patient or provider incentives).

6. Aims

6.1. Primary Aims

Aim 1: To evaluate the effectiveness of physician incentives (with and without GlowCaps), patient incentives, provider/patient incentives, and nurse practitioner choice architecture systems on improvement in LDL cholesterol relative to usual care during a 12-month intervention among patients at high risk of CVD. H1: Each of these approaches will be more effective than usual care in reducing LDL cholesterol.

Aim 2: To evaluate the relative effectiveness of those intervention arms superior to control in reducing LDL cholesterol. H2: Incentives for patients (Arms 3 or 4) will be more effective than incentives for providers (Arms 1 or 2); NP CA (Arm 5) will be more effective than provider-based incentives (Arms 1 or 2); provider outcome incentives including GlowCaps (Arm 2) will be more effective than without GlowCaps (Arm 1).

6.2. Secondary Aims

Aim 3: To evaluate the impact of each effective intervention in sustaining adherence and reduced LDL after the 12-month intervention period.

Aim 4: To assess the cost effectiveness of each of the interventions relative to usual care.

Aim 5: To conduct a rigorous qualitative process evaluation to examine why some interventions were more effective than others and to address other factors relevant to broader implementation.

7. Primary Outcome Variable

7.1. LDL cholesterol (primary outcome)

Change in LDL from baseline to 12 months. The evidence base linking improvements in LDL cholesterol to reductions in CVD is extensive, supporting about a 20% reduction in CVD per 40 mg/dL reduction. LDL cholesterol is easily monitored through a simple blood test. The primary outcome will be change in LDL between baseline (prior to randomization) and 12 months.

8. Secondary Outcome Variable(s)

8.1. LDL Cholesterol (secondary outcome)

Change in LDL from baseline to 15 months.

8.2. Hemoglobin A1c (secondary outcome)

We will also measure Hemoglobin A1c, an assessment of intermediate term glycemic control, among patients with diabetes. This measure is related to CVD risk but is not a target of the intervention. We measure it to examine positive or negative spillover effects from targeting LDL cholesterol: a focus on LDL may crowd out attention to other conditions or, alternatively, might stimulate it.

8.3. Process Evaluation (secondary outcome)

8.3.1. Potential confounders and mediators

Although this randomized trial is designed to balance all factors that could alter LDL levels (other than the interventions), we will measure potential residual confounders at baseline and adjust for them in later analyses. Many of these variables may also serve as either moderators (factors that predict which people are helped by the intervention) or mediators (variables related to mechanisms whereby the

intervention works) in the intervention-outcome pathway. For physicians, this will include hire date and demographic characteristics as well as information on training and certification. For patients, we will have information on demographics, socioeconomic status, comorbidities, and baseline LDL.

8.3.2. Method of data collection

Baseline data will be collected by structured, in-person interviews performed by either the study intake coordinator at each clinical site or via the web using standardized data collection forms to be developed with assistance from Dr. Shea and modeled after data collection instruments used in our previous studies. Baseline data will include detailed demographics (e.g., age, sex, race/ethnicity, income, education, marital status, employment, health insurance). Other variables to be collected include: (1) Risk perceptions measured using a visual analog scale; (2) Numeracy using pre-validated measures of numeracy; and (3) Health status measured using the SF-12 to assess health-related quality of life and the Health Utility Index (HUI) to assess health preferences. At the 12-month visit, participants will be surveyed about all variables that may change, such as health status. A select number of participants may also be contacted to complete post-intervention interviews that will include questions regarding perceived benefits and drawbacks, complications with the study, and areas of improvement.

8.3.3. Measurement of costs and cost effectiveness

We will conduct a "within-trial" analysis comparing incremental costs and incremental change in LDL during the intervention period from a payer/provider system perspective. Secondary analyses will evaluate this same ratio from a limited societal perspective, including incentive payments (which are transfers and typically omitted from the societal perspective) and valuing direct medical costs using federal fee schedules as proxies for social opportunity costs.

Measured costs will include: incentive payments, administrative costs of providing the interventions, and medical costs. Incentive payments to providers and patients will be computed as the sum of their conditional incentives, excluding participation incentives. Administrative costs of providing the interventions will be estimated based on [1] project personnel quarterly responses to time-diaries detailing their time spent on administrative tasks in the past week, including time administering all participant-related aspects of the intervention and usual care (excluding time related to general project administration), [2] the GlowCaps costs (about $16.25 per patient per month), and [3] monthly computer support fees. Wages will be used to convert measured administrative time to costs. We will amortize the computer support fees over the 1400 participants in the study. In sensitivity analysis, we will test the effect of varying the estimates of the fixed costs per person.

All medical care costs incurred by trial participants will be collected using the resource costing method. Health care utilization, including physician visits, ER visits, lab tests, hospitalizations, and medication use will be derived from the UPENN and Geisinger EPIC data. Cost data reported by EPIC will be used to

assign a cost to these services. Non-UPENN or Geisinger health care utilization will be derived from participant self-report as part of regular interviews with participants. These services will then be mapped into the data from EPIC to derive cost estimates. For the limited social perspective all services will be costed out by use of Federal fee schedules and databases of hospital inpatient resource use.

The focus of the "within trial" CEA is on changes in LDL cholesterol from improved adherence. Yet, because an important, long-term goal is to reduce mortality and long-term morbidities, we will update and expand a previously published model of long-term cardiac risk that has been used for such projections. All incentive strategies will be compared with usual care. We will use the model to translate observed short-term cost and effectiveness outcomes into projected long-term estimates of avoided disease, avoided direct medical costs, and gains in quality-adjusted life-years (QALYs) based on LDL reductions.

The procedures for computing costs and conducting the "societal perspective" cost-effectiveness analysis will follow the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. We will identify all available and relevant sources of cost data, including Medicare Fee Schedules, databases of hospital inpatient resource use, and estimates from the published literature. Drug costs will be estimated by adjustment of average wholesale prices. Costs of managing side-effects will also be included. Patient travel and waiting time will be based on data from the National Medical Expenditure Panel Survey, and patient and caregiver time costs will be valued based on average wage rates corresponding to the target population. We will use age- and sex-specific utility weights for healthy people derived from EuroQol EQ-5D utility scores collected in the 2000 wave of the Medical Expenditure Panel Survey, and the National Health Interview Survey. All costs and benefits will be discounted 3% per annum.

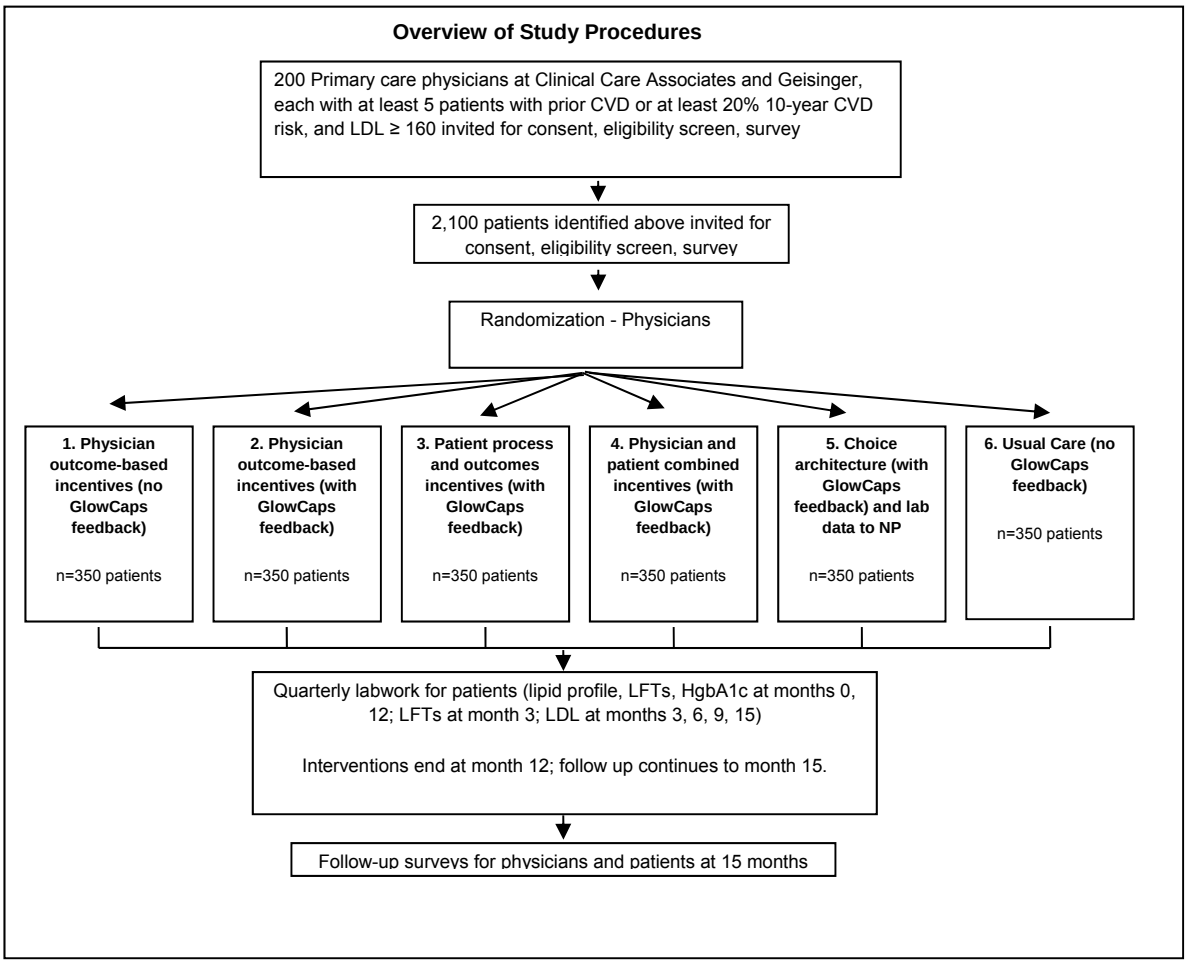
9. Study Design

9.1. Phase

Phase III

9.2. Design

This is a 6-arm cluster-RCT to test the relative effectiveness and cost-effectiveness of several innovative approaches to improving LDL management (largely through statin use) in patients at high risk for CVD. Incentives will be awarded quarterly to patients and bi-annually to physicians, based on an a quarterly improvement of at least 10 mg/dl in LDL relative to the patient's baseline LDL or achieving or sustaining LDL of 100, depending on baseline LDL and FRS. Adherence in all groups will be measured using Vitality GlowCaps as a recording device and in most arms (all arms except usual care) this information on daily patient adherence will be available to providers in monthly reports and available online at any time. Physicians and their panel of patients will be randomized evenly into one of 6 arms described in the figure, drawing on a conceptual framework from both traditional and behavioral economics. This design



allows a variety of comparisons across arms, answering conceptually and procedurally important questions in the application of behavioral economic approaches to advance health: 1. How does the provision of provider incentives compare to the provision of patient incentives, to a combination of patient and provider incentives, or to no incentives at all? 2. Are results sustained after incentives and other interventions are withdrawn? 3. How do these approaches compare in implementation, acceptability, cost, and cost-effectiveness?

[1] In all arms except for usual care, we will provide more frequent feedback to providers than has typically been the case in P4P programs, in recognition of present-biased preferences. In the patient

incentive and split incentive arms, patients will get adherence feedback electronically with daily lottery awards to match the timing of their task. [2] Since the goal is to improve patient outcomes, the physician incentives (physician incentive and split incentive arms) will be based on improvement in those outcomes. Physicians can use the tools at their disposal: counseling of patients, initiation and intensification of medications, referral to specialized lipid programs. [3] We will use loss aversion as a motivator; patients will retain their accumulated adherence-based daily lottery winnings only if their LDL meets their quarterly goal. We do not use strict loss aversion for physicians, but since physicians who are successful in achieving goals in the first 6 months likely will not want to lose the money they expect to receive in the subsequent 6 months, their motivation will be augmented by that expectation. [4] For both providers and patients, each quarter we will focus on significant improvement of LDL as opposed to attainment of a single threshold. This motivates all participants, as people generally exert more effort as they get closer to goals. It also recognizes that a single threshold (e.g., LDL<100) is unlikely to motivate physicians or patients who think that goal is largely unreachable (e.g. a patient with baseline LDL of 220, who might have the most to gain from improvements). [5] We will use mental accounting principles and unbundle these awards from larger sums of money such as salaries, as rewards are much more salient when separated from, and not cognitively diluted by, larger amounts. [6] Because regret aversion affects decision making, non-adherent patients will receive daily feedback about what they would have won had they been adherent.

Randomization will occur at the physician level, but the primary unit of analysis will be the patient. Patients and providers will receive an active intervention for 12 months followed by 3 months of observation without incentives or other intervention to examine sustainability post-intervention. The primary outcome will be change in LDL cholesterol from baseline to 12 months. Each quarter, participants will be eligible for incentives if the patient's LDL has improved by at least an additional 10 mg/dl compared to the patient's baseline LDL or previous quarter's goal. Patients whose LDL reaches AHA goals (< 100 mg/dl) will also meet criteria each quarter that they remain at that level. Incentives for physicians will be distributed twice-yearly and based simply on patients meeting the LDL goals described above. Incentives for patients will be structured as an adherence-based lottery with an expected value of $2.80. Patients will observe the accumulation of any winnings (with perfect adherence, these winnings will average $256 every quarter—$128 in the split incentive arm in which incentives are shared between patients and physicians). Patients will be told they will receive these lottery winnings only if their LDL, chemically assessed each quarter, has met the outcome goals - an approach combining frequent feedback and daily engagement to stimulate adherence and using loss aversion to further augment motivation.

9.3. Study Duration

Participants will be in the study for 15 months. The project duration is 3 years, beginning September 30, 2010.

9.4. Facilities

The study will take place at UPENN and Geisinger. UPENN primary care is distributed across its Clinical Practices group (the Clinical Practices of the University of Pennsylvania, CPUP) and its Clinical Care Associates (CCA)—the former representing about 35 full time primary care clinicians and 50,000 patients in a largely urban and racially diverse practice, the latter serving approximately 160,000 patients in the Philadelphia metropolitan area spanning Pennsylvania and New Jersey with over 100 additional primary care physicians distributed across 30 sites. Geisinger Clinic serves 400,000 primary care patients and more than 500,000 specialty care patients in central and northeastern Pennsylvania. The clinic has 220 primary care providers who practice in 37 clinic sites. The population in the region is 40% rural. We have chosen these sites for 3 reasons: [1] Target population: The populations served by UPENN and Geisinger include patients of mixed socioeconomic status, with a high rate of CVD, many with inadequate management of LDL. [2] Logistics: We have conducted numerous intervention studies in both the UPENN clinics and Geisinger, and have experience and comfort conducting studies in these settings. [3] Same electronic medical record system: Both UPENN and Geisinger use EpicCare, simplifying the interface with our Way to Health web-based platform, as similar approaches can be used in both systems.

9.5. Key Inclusion Criteria

9.5.1. Key inclusion Criteria for Physicians

All primary care providers who have at least 5 eligible patients will be eligible.

9.5.2. Key inclusion Criteria for Patients

To meet general study eligibility criteria and be included on the study roster, patients must:

- → Be between the ages of 18 and 80;
- → Have a consenting PCP in a participating site;
- → FRS of $\geq$ 20% with LDL $\geq$ 160.

9.6. Key Exclusion Criteria

9.6.1. Key Exclusion Criteria for Physicians

No exclusion criteria.

9.6.2. Key Exclusion Criteria for Patients

The following patients will be excluded from participation in the study:

- → Patients with a history of side effects to statins. Patients with a history of side effects to statins will be forwarded to the study's medical monitor (a physician aligned with the study) and may still participate in the study if, after the medical monitor reviews the patient's medical record, he/she determines that the patient may safely participate in the study;
- → Patients who will not or cannot give consent;
- → Patients with terminal illness who are no longer suitable candidates for aggressive lipid management as determined by the patient's primary care physician;
- → Patients with ALT values detected at greater than 80 U/L;
- → Patients with active or progressive liver disease.

10. Subject Recruitment

10.1. Target Population

The populations served by UPENN and Geisinger include patients of mixed socioeconomic status, with a high rate of CVD, many with inadequate management of LDL. We have conducted numerous intervention studies in both the UPENN clinics and Geisinger and have experience and comfort conducting studies in these settings. These sites use the same electronic medical record system: Both UPENN and Geisinger use EpicCare, simplifying the interface with our Way to Health web-based platform, as similar approaches can be used in both systems.

10.2. Subjects at Penn

1050

10.3. Subjects at Geisinger

1050

10.4. Accrual

LDL cholesterol is strongly associated with CVD outcomes, so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dL change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and

Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The study has been powered for two phases of hypothesis testing. In the first phase, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms. We will accrue 2100 participants evenly randomized across the 6 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (10% per year) at both sites. 150 physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.01 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference153 approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests will vary from a maximum of 10 (if all five active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement). Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between 80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

10.5. Physician Subject Recruitment

All eligible primary care physicians at UPENN and Geisinger will be invited to join the study and we will schedule a half-hour visit to obtain informed consent, review study procedures, provide a web portal orientation, and do a short baseline survey. Eligible primary care physicians at UPENN and Geisinger will be mailed an opt-out letter. Those who do not opt out will be automatically enrolled in the study. A baseline visit will be scheduled by study staff. Within each practice, we will identify patients meeting eligibility criteria by monitoring laboratory data. The study will provide the physicians involved in the

study with a copy of their patient list (which includes last date of service) at least 48 hours in advance of the meeting on order to give them the opportunity to review the list in more detail. This patient list will include a cover sheet with instructions for reviewing their patient list. Staff will meet with the physician to review study procedures, provide a web portal orientation, and do a short baseline survey. Study procedures will be summarized using a study information handout. After randomizations, those physicians taking part in the physician incentive and split incentive arms will be asked to complete a survey regarding the use of incentives. Finally, physicians will be asked to review their patient lists. Study staff will review patient lists with the physicians, guiding physicians through the instructions on the patient list cover sheet. Physicians will be reimbursed by RVU for this baseline visit (meaning that their practice will compensate them as if this was a regular patient visit). Additionally, physicians with the Clinical Care Associates (CCA) of the University of Pennsylvania will be invited to attend an information session on the study. Physicians that attend this one-hour information session will be paid $100, which is the norm for CCA physicians. We will use an opt-out mechanism for physician consent, since there is no appreciable risk to physicians in participating (incomes can only go up); our discussions with the UPENN IRB indicate that this is likely to be acceptable. Given the potential for income supplementation with minimal incremental effort, we anticipate high physician interest in the study.

10.6. Patient Subject Recruitment

Each patient will be asked to opt in to the study and will be required to fill out an informed consent/HIPAA authorization to enroll. Patients will be able to consent for this study both electronically, via the Way to Health platform, and by paper.

Regarding recruitment, we have already initiated a strategy of mail-based recruitment of patients for whom approval was received from their primary care provider. The letter invited patients to enroll in this research study by utilizing the online Way to Health platform.

10.6.1. Identification of Potential Patient Subjects

Within each practice, we will identify patients meeting eligibility criteria by monitoring laboratory data, via a query of the EPIC electronic medical record database.

10.6.2. Geisinger Survey Research Unit

This study plans to utilize the Geisinger Survey Research Unit's call center to facilitate the completion of study-related questionnaires and some aspects of patient screening. The Geisinger Survey Research Unit has capabilities that are not available at the University of Pennsylvania, specifically a trained staff of 18 professionals who have evening and weekend hours and can be used for help with recruitment and questionnaires by institutions that partner with Geisinger Health System in research. The staff uses 12

computerized workstations running WIN-CATI (Computer-Assisted Telephone Interviewing). The CATI system guides interviewers through telephone scripts, and accommodates complex skip patterns within questionnaires. Interviewers staff the call center throughout the week, and data from questionnaires can be exported in a number of electronic formats.

Potential subjects will be given ten days after sending letters of introduction to the study to enroll in the study via the Way to Health platform. If during that time the patient does not enroll via the Way to Health platform, and the patient does not opt out by contacting the UPenn study team, the patient's contact information will be forwarded to the Geisinger Survey Research Unit call center for follow-up. Specifically, the patient's name, phone number, and a unique study identification number, different from the patient's medical record number, will be forwarded to the call center. The call center will try calling the patient at the contact phone number listed in the patient's EPIC electronic medical record.

The information exchange between the University of Pennsylvania, Geisinger Health System, and the Way to Health platform is facilitated by the fact that each of these entities will have access to their own schema on a mySQL database running on a University of Pennsylvania-owned and managed server. Using this database, we will track responses to the recruitment materials and maintain a continuously updated table of responders and associated non-responders. The database software allows setting access privileges such that specific users with access to the Geisinger Health System component of the database can also be allowed to access certain tables within the University of Pennsylvania component of the database. We plan to enable Geisinger Health System users to access the specific table within the University of Pennsylvania schema that contains the names and phone numbers of the non-responders so that the Geisinger Survey Research Unit can know who needs to be contacted by their service. Study staff at Geisinger Health System will download these data and transmit it to the Survey Research Unit in the same secure manner with which they manage their own protected health information. mySQL can maintain logs of when and who accessed this single table. Geisinger Health System staff will not have access to other University of Pennsylvania-based study data, nor access to other UPHS information systems.

This information will be made available to the Geisinger Survey Research Unit call center via a mySQL database system, which includes numerous information security mechanisms, previously described. Upon making contact with the patient, the patient will be given a brief overview of the study and demographic information will be collected from the patient. Basic screening questions will be asked of the patient, akin to enrollment via the Way to Health platform, and then the patient will be asked to complete a study-related survey by phone.

At the 6-month and 12-month marks, patients who are screened via the call center and choose to enroll in the study will be called again by the call center to complete 6-month and 12-month surveys by phone, again, akin to patients who enroll via the Way to Health platform. The survey completed at the 12-month time point in the patient's involvement in the study will be substantially similar to the survey completed at baseline. The 6-month survey is a subset of the 6 and 12-month surveys.

Geisinger Survey Research Unit employees have expertise and resources that allow them to recruit patients more easily, more efficiently, and in a more standardized manner than at The University of Pennsylvania. Using standard processes at the Geisinger Survey Research Unit call center, patients can be called upward of ten times in a given week by the research team. Such recruitment efforts cannot be paralleled easily using available resources at the University of Pennsylvania, and recruitment of the approximately 700 University of Pennsylvania patients by research staff at the University of Pennsylvania would probably not be financially feasible and could probably not be completed in a timely manner.

The Geisinger Survey Research Unit employs numerous measures to ensure that data collection is of the highest quality, while making every effort to preserve patient rights and privacy at all rimes. Survey Unit interviewers complete a comprehensive training curriculum presented in conjunction with the Geisinger Institutional Review Board (IRB). These courses include a block of training that teaches interviewers of the obligation of researchers to respect participant rights, and regarding HIPAA privacy regulations and Protected Health Information (PHI) best practices. In addition, projects are monitored by management staff and performance statistics are evaluated daily. The Geisinger Center for Health Research study team, led by the project manager, will train the Geisinger Survey Research Unit interviewer staff to provide an overview of the study, screening questions, and surveys, in order to prepare the Geisinger Survey Research Unit interviewers to field questions about the study by potential participants. At least two training sessions will be held, one during the day shift and one during the evening shift, so that all interviewers have the ability to attend the training session. All interviewers (and indeed, all Geisinger employees), sign a confidentiality statement. Geisinger uses encryption technologies extensively, and user authentication systems (i.e. password and personal identification number) protect all electronic records containing PHI. The Survey Unit, where the call center is located, is locked at all times.

The Geisinger Survey Research Unit provides survey support for a wide variety of research studies. Based on the main campus of the Geisinger Health System in Danville, Pennsylvania, the Geisinger Survey Research Unit offers a call center for administration of telephone surveys, as well as facilities and staff for the completion of focus groups and mailed surveys. While the Geisinger Survey Research Unit primarily works with Geisinger researchers, the Survey Research Unit has previously worked with researchers at the Fox Chase Cancer Center and at Thomas Jefferson University Hospital. At this time, the call center only accommodates outgoing phone calls and does not support incoming phone calls.

10.7. Subject Compensation

10.7.1. Compensation for Physicians

Physicians will be paid by RVU credit for the initial visit and for the 12 month follow up visit as compensation for their time. Those assigned to an incentives arm (physician incentive and split incentive groups) can win additional incentives based on an adherence-based lottery (total of $1,024 per year per patient or $256 per quarter per patient for those in the physician incentive Group and $512 per year per patient or $128 per quarter per patient for those in the split incentive Group who share their incentive

with their enrolled patient) based solely on whether a given patient achieves an LDL reduction of at least 10 mg/dl each quarter relative to the patient's baseline LDL or the last quarter's target. Thirty providers will be asked to participate in a post-study interview and respond to questions about how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Providers will be paid by RVU credit for their time.

10.7.2. Compensation for Patients

Patients will be paid $75 after completion of the first visit ($50 for the blood draw, and $25 for the questionnaire) and then $40 for lab checks at 3, 6, and 9 months, and then $80 for lab checks at 12 and 15 months as compensation for their time and to improve participation rates, as noted in Table 1. Generous participation incentives have succeeded in minimizing differential drop out in our previous studies. Additional incentives for patients assigned to the patient incentive Group or split incentive Group will be structured as an adherence-based lottery with an expected value of $2.80. Patients will observe the accumulation of any winnings (with perfect adherence, these winnings will average $256 every quarter and $128 in the split incentive arm in which incentives are shared between patients and physicians). Patients will be told they will receive these lottery winnings only if their LDL, chemically assessed each quarter, has met the outcome goals - an approach combining frequent feedback and daily engagement to stimulate adherence and using loss aversion to further augment motivation. Patients will only be eligible for the daily lottery if they are taking a cholesterol-lowering medication at the time of the lottery drawing. Assessment that a patient is taking a cholesterol-lowering medication will be based upon a patient's answer to the question "Do you take any prescribed medications to lower your cholesterol?" at baseline and 6 months, and whether a cholesterol-lowering medication is noted in the patient's Epic electronic medical record at the time of the lottery drawing. Data pulls of patients' medical records will occur at least daily and in an automated fashion using the PICARD system, previously described in this protocol. Patients will be exempt from the baseline blood draw if they have received the necessary labs within the 8 weeks prior to the receipt of the patient's consent form, and if these labs took place within the setting of the University of Pennsylvania Healthcare System. Patient post-study interviews: We will conduct three waves of interviews: [1] eligible participants who declined to enroll; [2] 60 (10 per arm) participants who enrolled but did not complete the intervention; [3] 180 (30 per arm) participants who were least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm.166 Those who drop out will be offered $15 incentives; the least and most successful participants will be offered $25. Examples of topics that will guide full script development include motivations for enrolling, perceived benefits and barriers to participation, and the impact of incentives. Patient post-study focus groups: We will conduct three focus groups of 8-10 participants at each of the two sites, moderated by Dr. Shea: one among participants for whom the intervention effects were negligible, one for whom the intervention effects were moderate to large, and one mixed, general group. Groups will last 60 minutes and will be recorded. Participants will be offered $40 incentives. We will examine perceived impact of the financial incentives, barriers faced in changing behaviors, and changes to the intervention that might help more people. We will also discuss

unanticipated effects, such as how participation may have changed the physician-patient relationship or elements of health behaviors outside of the health care context.

Table 1. Patient Payment Schedule

Description of Compensation	Amount of Compensation
Baseline Blood Draw	$50
Blood Draw at Months 3,6,and 9	$40 each
Blood Draw at Month 12	$80
Blood Draw at Month 15	$80
Questionnaires	$25
Interview	$25(subjects who complete the study) or $15 (subjects who drop out of the study)
Focus Group	$40

11. Study Procedures

11.1. Consent

11.1.1. Patient Consenting Process

Eligible patients will be invited to join the study, and those interested will either consent through the online Way to Health platform, which will explain the study procedures, risks, benefits and voluntary nature of participation, or sign a paper consent form. Potential participants will be offered the opportunity to ask study staff questions about participation in the study. They will be provided the opportunity to review the consent form at their leisure and talk to friends, family and others before making a decision about participating.

Patients will be given ten days after sending letters of introduction to the study to enroll in the study via the Way to Health platform. If during that time the patient does not enroll via the Way to Health platform and does not actively call our research team to opt out of the study, the patient's contact information will be forwarded to the Geisinger Survey Research Unit call center. In order for the Geisinger Survey Research Unit call center to contact and enroll patients to the study, the call center will need to access the patient's name, address, phone number, and a unique study identification number, different from the patient's medical record number, only for those patients who do not enroll via the Way to Health platform. The patient's name and phone number are necessary to allow the call center staff to contact the patient; the patient's study identification number is necessary because the data

generated from the call center's telephone encounters with these patients will need to be married to the patient's profile in the study database. If the patient agrees to participate and satisfies the screening requirements, the subject will be sent a study packet with an informed consent document and a HIPAA authorization form to sign and return to the study team. The main part of the study will operate under a signed informed consent and HIPAA authorization.

11.1.2. Physician Waiver of Documentation of Consent

We are requesting a waiver of written informed consent for physicians. Eligible primary care physicians at will be mailed an opt-out letter. Those who do not opt out will be automatically enrolled in the study. A baseline visit will be scheduled by study staff. Staff will meet with the physician to review study procedures, provide a web portal orientation, and do a short baseline survey. Study procedures will be summarized using a study information handout. After randomizations, those physicians taking part in the physician incentive and split incentive arms will be asked to complete a survey regarding the use of incentives. Physicians will be paid by RVU credit for this baseline visit. We will use an opt-out mechanism for physician consent, since there is no appreciable risk to physicians in participating (incomes can only go up); our discussions with the UPENN IRB indicate that this is likely to be acceptable. Given the potential for income supplementation with minimal incremental effort, we anticipate high physician interest in the study. Physicians are among the participants in this study. Several conceptual and logistic factors indicate that an opt out approach would have several advantages to an opt in approach. First, the study has no meaningful risks to patients associated with physician participation. Indeed, health systems around the nation and the world have implemented related financial incentive schemes to improve patient care. However, they have done so without evidence of effectiveness. This project aims to compare interventions whose fundamental approach is already in use in settings where no consent is required. Second, the goal of the study is to improve cholesterol management among patients with poor control. Such patients may be more likely to be clustered in providers who are less engaged and who would be relatively unlikely to volunteer to be part of a research study. Third, similar to point [1], there is no incremental risk to physicians involved in participation in this study. The only uncertain event is how much additional money physicians will receive as a result of the care they provide. Brief questionnaires are given to physicians at various times within the study, but those are administered with tacit and implied consent given their nature and are compensated with participant incentives. Fourth, there is ample precedent at Penn for opt-out consent of physicians in research studies that carry either no or minimal risk to physicians, and for which there are considerable scientific benefits of broad participation (see, for example, the IRB protocols that approved the email-based opt-out consent for RCTs using Sunrise order entry at HUP to see if physicians prescribing of heparin and other drugs could be achieved by manipulating their electronic order templates). Fifth, although it is important to distinguish opt-out consent from informed consent, opt-out consent is just another term for simple consent, and there are well-developed normative arguments for why simple consent is actually preferred to true informed consent under certain circumstances (see: Whitney, McGuire, McCullough. A Typology of Shared Decision-Making, Informed Consent, and Simple Consent. Ann Intern Med 2003; 140:54-59). The key features guiding which circumstances are appropriate for choosing simple vs.

informed consent are generally (i) the level of risk (which low or none favoring simple) and (ii) the a priori probability that all people to whom the choice is presented will have true preferences in the default direction (with greater a priori probability favoring simple consent). The gains to this study of using an opt out approach are in fact informed by the very principles of behavioral economics that underlie the study as a whole: [a] All studies are enhanced by the generalizability achieved with more universal participation; [b] It is logical that given the zero to limited risk of this study to physicians and the potential for gain that all or most physicians would want to participate; and [c] non participation would probably in most cases reflect a physician simply failing to complete a consent form rather than not wanting to participate, meaning that physicians might just not get around to completing a consent form when in most cases we suspect they would want to. This is a well-known phenomenon of human behavior that this study targets in its clinical endpoint of LDL Cholesterol management. However, those physicians who truly do not want to participate can of course opt out and we will make it easy for them to do so. Overall, the opt out mechanism preserves participant choice, makes the study easier to administer, and probably best reflects the appropriate default for a study with this particular risk profile and in which the benefits to participants (both patients and physicians) are potentially significant. Both physicians and their enrolled patients will be given a debriefing letter following their completion of all study procedures. The letter will describe the four study arms and states the reason for non-disclosure of this information prior to their finishing the study. These are enclosed with this application.

11.1.2.1. Waiver or Alteration of Informed 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

11.1.2.2. Minimal Risk

In this study physicians will be offered extra money if they are successful in managing lipids. There is no possibility of them getting less or otherwise experiencing risks or downsides from participation.

11.1.2.3. Impact on Subject Rights and Welfare

We will give physicians an opt out if they don't want to participate and we do not think the waiver will have any conceivable adverse effects on the rights or welfare of the physician participants.

11.1.2.4. Waiver Essential to Research

We will have very limited time with the physicians for the enrollment process and will need to streamline this as much as possible for the enrollment to be successful. Elements of the enrollment visit will include an introduction to the study, randomization to a study arm, and the completion of study-related paperwork and questionnaires.

11.1.2.5. Additional Information to Subjects

We will provide all physicians with full debriefing about the study aim and objectives and results at the conclusion of the study.

11.1.3. Written Statement of Research

This study operates under a written statement of research.

11.2. Procedures

11.2.1. Baseline pre-treatment assessment for patients

Potentially eligible patients will be sent letters inviting them to participate. Patients interested in enrolling who agree to provide consent (See §E.2.a.) will complete an intake form and consent using, at their preference, either our web portal, or by paper. Patients enrolling by paper may be mailed the consent form, in which case patients will be asked to sign and mail back the consent form to the study staff. Scheduling of baseline LDL and ensuring LDL is within study parameters is the final step in confirming eligibility

11.2.2. Randomization

Randomization of physicians to one of the 6 study arms will be performed through the Way to Health platform. Randomization will be stratified by primary site (Geisinger or Penn). After confirmation of patient eligibility, research staff will notify each patient participant of assignment (based on the assignment their physician has received) using their preferred means of communication (text message, email, phone) and ask for confirmation of receipt. Both patients and physicians will be given detailed instructions for the arm of the study to which they have been assigned and patients in all arms will be given the GlowCaps and instructions on use. Patients will be instructed to call study staff for all questions or problems with GlowCaps use. We will enroll up to 25 patients per physician.

11.2.3. Scheduling

Physician participants will have 2 in-person visits, at baseline and 12 months. Patient participants will have six laboratory checks, at months 0, 3, 6, 9, 12, and 15 (Table 2). At the baseline and 12-month visit, we will test each participant's full lipid profile and hemoglobin A1c (diabetic patients only) to measure impact on all lipids from baseline to the primary outcome point as well as potential positive or negative spillover effects on glycemic control. Additionally, liver function tests (LFTs) will be completed at months 0, 3, and 12, to monitor patients for signs of liver damage. LDLs at baseline and at months 3, 6, 9 and 15 will be by direct, non-fasting LDL. Surveys will be completed at baseline and 12 months. Participants will return GlowCaps at the 15 month exit interview.

Table 2: Laboratory Test Schedule

	Month					
	0	3	6	9	12	15
LDL Direct	X	X	X	X	X	X
Lipid Profile	X				X	
LFT	X	X			X	
HbA1c*	X				X	

* Only if the patient has diabetes

The Way to Health participant tracking system will automatically remind the study coordinators that each enrolled subject has a scheduled follow-up visit at the end of months 3, 6, 9, 12, and 15. We will obtain extensive contact information from each participant and update it at each follow-up visit. We will call participants who miss follow-up visits weekly for 4 weeks and send 2 letters during these 4 weeks. If any participants appear lost to follow-up, we will call their primary physician to ascertain their status.

11.2.4. Structure of Intervention Arms

For each of the incentive arms, eligibility for an incentive will be based on at least 10 mg/dl improvement in LDL within each quarter relative to the last quarter's target. This moving target is intended to foster continued engagement, as it is readily achievable and relevant to each patient or physician regardless of baseline LDL. For example, if a patient starts with an LDL of 200, eligibility for rewards (to physician or patient or both) will depend on LDL being at or below 190 at 3 months, 180 at 6 months, 170 at 9 months, and 160 at 12 months. Large early moves (e.g., if a patient's LDL drops from 200 to 170 in the first quarter) will continue to generate rewards if sustained: in this case, if the LDL remains at or below 170, the physician or patient will be eligible for incentives at the end of quarter 2 (when the target would be 180) and the end of quarter 3 (when the target would be 170). Incentives will not be provided at the end of quarter 4 unless the LDL was reduced a further 10 mg/dl to 160 or below. Patients/providers will automatically be eligible for incentives each quarter a patient achieves an LDL.< 100 (or another AHA target appropriate for the patient).

11.2.4.1. Physician Interventions

We will provide feedback on each patient's daily adherence using GlowCaps (all arms except usual care) as well as quarterly LDL (all arms except usual care) via the Way to Health online portal. The Way to Health portal will provide graphical feedback on patients' adherence and LDL from baseline to present and relative to goals and which can be used interactively with the EpicCare electronic health record to activate response options (have nurse call patient, intensify medications, refer to lipid clinic). Monthly patient reports will be mailed to providers until EPIC functionalities are developed to allow the delivery of these monthly reports via EPIC message. Physician incentives (total of $1,024 per year) will be determined solely by whether a given patient achieves the LDL reduction goals described above. This will be paid out as a reward separate from paychecks to increase salience.

11.2.4.2. Patient Incentives

At study entry, we will assign each participant a two-digit number. Each day GlowCaps will automatically upload adherence data for the previous day via the internet to a database housed at UPENN. The Way to Health system generates two-digit random daily lottery numbers and compares them electronically to the participant's two-digit identification number to determine eligibility for awards. If the two digit number matches, which will happen about 1 in 100 times, the participant will be eligible to win $100 if s/he was adherent the day before. If the two digit number does not match, but either the first digit or second digit matches in the right place, the subject is eligible to win $10, which will happen about 1 in 5 times (more precisely, 18 in 100 times). The expected value of this lottery is $2.80/day such that total winnings per year for a fully adherent participant have an expected value of $1,022 (but could be more or less for an individual participant depending upon chance). As in our previous studies, we have designed the lottery-based incentives so that, each day, adherent participants receive rapid feedback about whether they won, and non-adherent participants receive rapid feedback about whether they would have won had they been adherent. This program incorporates key aspects of optimal design, including objective and reliable confirmation of behavior change at frequent intervals, large potential payments to reinforce the target behavior, frequent reinforcement using smaller payments, and the use of anticipated regret, a powerful motivator. We set the expected value of the lottery at about $3/day based on our success in significantly affecting weight loss and medication adherence with these parameters. In addition, there is evidence that a patient with established CVD has health expenditures ranging from $18,000-$30,000 per year, suggesting that incentives of $1,022, if effective, could be cost effective due to the potential savings.

Information on whether the participant won will be electronically transmitted each day by text message, phone, or email (patient choice) and will also be available on the patient's page on the Way to Health portal. Participants in the lottery group will be informed that they will receive their accumulated winnings at the end of the quarter only if their LDL meets the above goals; this is a way of using loss aversion to drive ongoing motivation to remain fully adherent through the entire quarter.

11.3. Timeline and Project Management

Task Description	YEAR 1						YEAR 2						YEAR 3					
	S	N	J	M	M	J	S	N	J	M	M	J	S	N	J	M	M	J
CRF Design																		
Staff hiring and training																		
Subject recruitment																		
Baseline visits																		
Interventions																		
Follow-up visits																		
Data Analysis																		
Manuscripts/dissemination																		

In-person meetings among the UPENN, Geisinger, CMU and Harvard team members are planned upon project initiation and annually thereafter. Ongoing project management will be facilitated by weekly or bi-weekly conference calls and the use of Basecamp online project management software. Team members will correspond as frequently as needed via email and telephone. To minimize the impact of geographic distance between the participation sites, the team will use available technologies appropriate to the particular meeting, including videoconferencing or webinar. The team will be organized similarly to how we have conducted multi-center studies previously, with project leaders at both the staff and faculty level and clear lines of responsibility for achievement of milestones.

11.4. Dissemination

Our dissemination activities will be led by LDI's research dissemination program to extend beyond publication in scholarly journals and presentations at professional meetings to reach specific audiences of approximately 4,000 leading figures in health care delivery with information they can use. We will utilize the expertise of the Study Advisory Board, which was designed with this in mind.

12. Analysis Plan

12.1. Statistical Considerations

LDL cholesterol is strongly associated with CVD outcomes—so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dl change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The study has been powered for two phases of hypothesis testing. In the first, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a

difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms.

We will accrue 2100 participants evenly randomized across the 6 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (<10% per year) at both sites. Physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.01 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests in the second phase will vary from a maximum of 10 (if all five active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement). Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between 80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

12.2. Potential Limitations

We will minimize data loss by reimbursing all participants for study visits and mailing/emailing reminders plus follow-up phone calls for participants for their follow-up visits. We will address selection bias using sensitivity analyses about the characteristics of the larger, target population, making extreme assumptions about the variables that drive selection in different directions and determining their effect upon inference. Contamination is possible but should not be problematic because our outcomes are individual, lipid management is not typically addressed in acute care visits by cross-covering providers, and we pay incentives only to incentive arm participants. The Hawthorne effect can improve outcomes in observed groups if participants are more likely to achieve goals than if they had not been observed, but this should be mitigated by a usual care control group that is similarly observed. We have guarded against Type I error by employing a conservative Bonferroni procedure for the five primary hypotheses as well as the Tukey honest significant difference approach to test the comparative effectiveness of the active interventions. A study period longer than 3 years would have allowed for better evaluation of

sustainability post-active phase of intervention; however, we have included a 3 month post-intervention observation period that will give us considerable information on adherence given the daily GlowCaps information.

12.3. Data Analysis Plan

Prior to analysis, we will produce data summaries including graphical methods to assess data quality, examine central tendencies and distributional assumptions and randomization success. The primary analysis will consist of unadjusted intent-to-treat hypothesis tests for the significance of coefficients associated with treatment assignment in linear models of change in LDL; these models will adjust for the clustering of patients within physicians. We will also estimate regression models adjusted for the stratification variables and other covariates of interest (such as patient sex, income, race, baseline LDL, and study site), retaining these given evidence of confounding or predictive ability. We will employ a confounder selection method based on "change in estimate" criterion. We will assess interaction terms between the a priori potential effect modifiers such as study site, income level, race, and baseline LDL. All hypothesis tests will be two-sided and use adjusted Type I error rates as described above to maintain control of false positive test results. Models will be assessed using standard diagnostic techniques. We will assess the normality of the outcome and use transformations to improve the approximation if necessary or robust regression techniques, if suitable transformations cannot be found. Handling of missing data is an important issue in all RCTs. Follow-up data will be missing if participants miss visits and do not have labs taken. We anticipate low levels of loss to follow-up, but will conservatively assume that these patients fail to achieve any reduction in LDL and are non-adherent. We will compare dropout rates by arm for both patients and physicians, will attempt to find the reasons for missing data and will 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. The analyses for secondary outcomes in Aims 1 and 2 will parallel those for the primary outcome.

12.4. Cost-Effectiveness Analysis

To assess the cost-effectiveness of the interventions, we will use analytic methods for economic evaluations in clinical trials. Our approach will be similar to Specific Aims 1 and 2 using cost as the outcome. We will use generalized linear models to adjust for the stratification variables and other factors. Cost-effectiveness ratios will be calculated as the difference in costs divided by the difference in LDL calculated under Specific Aims 1 and 2 for the within-trial analysis, with parametric 95% CIs for the cost per percentage point increase in adherence and acceptability curves. Standard errors and the correlation of the difference in cost and effect will be obtained using a bootstrap procedure. A further cost-effectiveness analysis from the societal perspective will be conducted to assess the impact of the LDL cholesterol reductions on CVD events measured as cost per QALY gained. To address uncertainty in the micro simulation model, we will also conduct a probabilistic sensitivity analysis (PSA) by defining

probability distributions for the variables in the model used to calculate costs and effectiveness. We will use the results of the PSA to calculate confidence (or credible) intervals and acceptability curves. This research study will request Pennsylvania Health Care Cost Containment Council (PHC4) administrative discharge data for all the patients in the study, and this will be used to measure hospitalizations and resource utilization as part of the study's cost effectiveness analysis. In requesting this data, the study will transfer PHI (in this case, patients' social security numbers, dates of birth, genders and ID numbers, unique from the patients' study ID numbers) to and from PHC4 in a secure manner, and information regarding this transfer of PHI will be included in the patient informed consent/HIPAA documents.

12.5. Process Evaluation

To improve the design of future interventions, we will engage in a qualitative process evaluation throughout the study to learn why some study participants succeed in changing behavior and others do not, and what elements of the approach were acceptable to participants.

12.6. Patient Interviews

We will conduct two waves of interviews:

[1] 180 (30 per arm) participants who were the least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm. The least and most successful participants will be offered $25 for completing the phone interview. Examples of topics that will guide full script development include: motivations for enrolling, perceived benefits and barriers to participation, and the impact of financial incentives.

Procedures

Potential participants will be mailed an invitation letter sent by the study team (attached as a separate document). Patients will be provided opt-out instructions detailed in the invitation letter, prior to being contacted by study personnel. Study personnel will contact patient subjects by phone and ask whether they would like to participate in a post-study phone interview. Personnel will follow a detailed phone script (attached as a separate document), explaining the elements of the interview. Verbal consent will be obtained prior to conducting the phone interview. The original signed consent form contains information regarding the post-study interview, therefore patients are aware in advance they may be contacted for a post-study interview. The phone interviews are expected to last approximately 30 minutes..

Analysis

All phone interviews will be digitally recorded and sent to a transcription service (ADA Transcription) to be transcribed. ADA Transcription is a transcription agency located in Mount Holly, NJ. (http://www.adatranscription.com/). Identifying patient information will be de-identified prior to sending to ADA Transcription. The purpose of the analysis will be to extract themes and narratives relevant to the research questions. Audio recordings of the interviews will be uploaded to ADA Transcription's website. ADA Transcription uses a file transfer program called Citrix Sharefile. All communications between Citrix ShareFile and the user are encrypted using either Secure SocketLayer (SSL) or Transport Layer Security (TLS) encryption protocols and up to AES 256-bit encryption, a level of encryption that is similar to what banks use (which is higher than most medical facilities). The data will be encrypted during uploads and downloads, and ShareFile also encrypts stored files when they are at rest on our servers for an additional layer of security. ADA password protects all audio files and can track users' access to the data. All audio is only stored for set periods of time and then purged completely from the system. Transcripts are returned in password-protected Word files via email. The data will be sent back to the study sites via Penn+Box, as described in the section above.

Subject Confidentiality

All computerized study databases will be housed on a secure server. The server is also protected by a firewall to limit unauthorized access to study information. Study personnel will use a confidential subject identification number to identify all subject study data in research databases. Once the interviews are completed, no personally identifiable information will be associated with participant's responses or their data. In addition to these measures, all information that is collected as part of this study will not be shared with other groups or investigators who are part of the research team, except as required by the Institutional Review Board for the protection of human subjects. Further, data that are prepared for statistical analyses will be de-identified and will be stored in study databases using a confidential identification number.

Subject Privacy

Each participant will be assigned a unique ID number. The link between name and ID number will be kept in a separate database that is accessible only to the key study personnel. Names of participants will not be included on the transcripts that derive from the interviews. After each digital recording has been transcribed, it will be destroyed. We will take extensive precautions to protect the privacy of subjects. A key containing information will be kept in locked file cabinets until study interviews are completed and the data have been checked for completeness and accuracy.

Consent Process Overview

Prior to participation, all participants will be asked to provide verbal consent. These documents will be read aloud by the individual conducting the interview. It will be made clear to all subjects that all information will be kept confidential and that their participation is entirely voluntary and they are allowed to leave or withdraw consent at any time.

Potential Study Risks

There are minimal risks involved in participating in the phone interviews. There is a slight risk of potential breaches of confidentiality for subjects participating in the phone interviews. Every effort will be made to maintain subject privacy and confidentiality.

Potential Study Benefits

From the perspective of those interviewed, there are few individual benefits from participating in the interviews than being given an opportunity to voice their personal experiences and opinions about participating in the Way to Heart Health Study. Interview participants might also benefit from feeling that their efforts will affect positive change in patient health outcomes.

12.7. Provider interviews

During year 3, Dr. Shea and staff will conduct 30 in-depth interviews with physician participants, using a written script, similar to the patient post-study interview script. We will examine how participation in this intervention influenced interactions with patients and solicit narratives describing patient experiences that provide a deeper understanding of the impact of trial arms on provider patient interactions. We will ask how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Participants will be offered RVU credit incentives.

12.8. Exit Surveys

At trial end, all provider and patient participants will complete exit surveys administered on the telephone or through the Way to Health platform (dependant on initial choice in enrollment mechanism). These surveys will systematically assess acceptability of the study and its various components, as well as possible effects in other domains including conditions other than cardiovascular risk, and effects other than health care. We will conduct surveys on attitudes towards using incentives, and trust in physicians, at baseline and at completion of the study. As noted above, patients will receive $25 after completing the baseline visit (of which the survey forms a part).

At conclusion all physicians will be asked the same set of general questions, and those in the incentive arms a modified version of the specific questions, to ascertain if participation in the study has led to a change in attitudes. As noted above, physicians will be paid by RVU credit for completion of the baseline visit.

12.9. Qualitative Data Analysis and Management of Focus Groups

All patient interviews and focus groups will be audio-taped, transcribed, and content analyzed, with analyses based on the grounded theory approach. We will use NVivo 8.0 to manage the data. Two independent reviewers will code the transcripts; Drs. Shea and Metlay will resolve discrepancies.

13. Investigators

The team includes investigators experienced in clinical medicine, health behavior interventions, clinical trials, behavioral economics, cost-effectiveness analysis, and psychometrics and program evaluation.

13.1. Multiple PIs

Dr. Kevin Volpp directs the LDI CHI and the NIA-funded PENN-CMU Roybal P30 Center on Behavioral Economics and Health and is Associate Professor of Medicine at the UPENN School of Medicine (SOM) and Associate Professor of Health Care Management at the Wharton School. He has led numerous studies of patient financial incentives. Dr. David Asch is the Robert D Eilers Professor of Health Care Management and Economics at the Wharton School and the UPENN SOM and the Executive Director of LDI. He is a well-known authority on the clinical and economic decisions of patients and providers.

13.2. Statistical Analysis

Dr. Andrea Troxel (Co-I, Statistician) is Professor of Biostatistics at UPENN and Director of Biostatistics for LDI CHIBE. She has 15 years of experience in the design, conduct, and analysis of clinical studies, including randomized trials that involve repeated measurements.

13.3. Cost Effectiveness Analysis

Dr. Henry Glick (Co-I) is a leading cost effectiveness expert who has led economic analyses for many randomized controlled trials. Dr. Tom Gaziano (Co-I) is an Assistant Professor of Medicine at Harvard Medical School and Co-Director of the CVD Working Group at the Center for Health Decision Science at the Harvard School of Public Health (HSPH) and an expert in the cost-effectiveness of CVD interventions. Dr. Milton Weinstein (Co-I) is the Henry J. Kaiser Professor of Health Policy and Management at HSPH and is a leading expert in modeling the long term cost-effectiveness of interventions. Drs. Gaziano and Weinstein have done extensive work modeling the impact of better LDL control on longer-term CVD outcomes.

13.4. UPenn Site

Dr. Mark Weiner (Co-I) is Associate Professor of Medicine and Director of Clinical Research Informatics at UPENN. Dr. Ron Barg, Director of CCA, (Co-I) has extensive experience implementing trials in their network

13.5. Geisinger Site

Dr. Walter Stewart, Director, Geisinger Center for Health Research (Site PI Geisinger) has extensive experience in health services research and working with the Geisinger Clinic on large scale studies. Drs. Stewart and JB Jones (Co-I) have extensive experience testing web-based tools that interact with EHRs to deliver highly tailored guidance at the point of encounter, integrate patient preferences into exam room dialogue, and obtain and present patient reported data at appropriate times during encounters to foster tailored care decisions. Dr. Peter Berger, Director of the Geisinger Center for Clinical Studies (Co-I) is a Cardiologist internationally recognized for his expertise in clinical trials design and implementation. Dr. Tom Graf, (Co-I) is the Chairman of the Community Practice Network as will serve as a key liaison to the Geisinger Clinic.

13.6 Behavioral Economics

Dr. Meredith Rosenthal (Co-I) is Associate Professor of health economics and policy at the Harvard University School of Public Health (HSPH) and a leading authority on P4P incentives. Dr. George Loewenstein (Co-I) is the Herbert A. Simon Professor of Economics and Psychology at Carnegie Mellon University and a founder of the fields of behavioral economics and neuroeconomics. Dr. Jennifer Lafata (Consultant), a Professor at Virginia Commonwealth University who has extensive experience in quality improvement initiatives for providers.

13.7 Process Evaluation

Dr. Judy Shea (Co-I) is the Associate Dean of Medical Education at UPENN SOM and an experienced leader in psychometrics and process evaluation. Dr. Joshua Metlay (Co-I) is Professor of Medicine and Epidemiology at UPENN SOM and an expert in process implementation.

13.8 Advisory Board

Dr. Harlan Krumholz, Hines Professor of Medicine, Yale; Francois De Brantes, CEO Bridges to Excellence, a major initiative to transform incentives in physician payment; Dr. Ron Paulus, the Chief Medical and Chief Innovation Officer at Geisinger; Ralph Muller, the CEO of the UPENN Health System and a former member of MedPAC; and Dr. Barbara Kahn, an expert in consumer behavior who is Dean of the School of Business Administration at the University of Miami.

14. Human Research Protection

14.1. Research Staff

All study investigators and study staff who work with this data will have undergone all of the required human subjects training. They will work with the data in password protected files and once interviews or focus groups are completed the responses will be separated from the identifying information.

14.2. Participating Institutions

The proposed research project will take place at the Leonard Davis Institute Center for Health Incentives (LDI CHI) at the University of Pennsylvania (UPENN), the Geisinger Health System, and research faculty offices involved in study design and analysis at Harvard University and Carnegie Mellon University; these sites provide substantial research experience, infrastructure support, and expertise in areas important to this project. Note that faculty at Harvard University and Carnegie Mellon University will have access to only de-identified data.

14.3. Data Confidentiality

The following methods will be employed to protect patient PHI for this research study:

☒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.
☐A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☐Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

14.3.1. Subject Confidentiality

To assure that patient and physician confidentiality is preserved, individual identifiers (such as name and medical record number/physician billing identifier) will only be used to link databases. All resulting datasets and computer files with identifiers will be password protected. Once linkage has been achieved, these linkage-identifiers will be dropped from the dataset and each individual will be given a unique study identification number (ID). We will maintain one master list that will link study identification numbers to patient and physician identifiers. This list will be maintained by the principal investigators in a locked file drawer and on a highly secure server (with levels of security sufficient to maintain records from Medicare patients per CMS standards) to ensure file security and available to other research staff on a need to know basis only. The study ID will be used on all analytical files. Only deidentified analytical files will be shared with co-investigators at Carnegie Mellon University and Harvard University. The same procedure used for the analysis of automated data sources to ensure protection of participant information will be used for the survey data, in that patient participant identifiers will be used only for linkage purposes or to contact participants. The study identification number, and not other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. No results will be reported in a personally identifiable manner.

14.3.2. Subject Privacy

The UPENN Biomedical Informatics Consortium (BMIC) will be the hub for the hardware and database infrastructure that will support the project and where the project 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. GlowCaps devices will be linked to each participant through a unique device number. Data transmitted wirelessly to the Vitality server will not contain any identifiers. The information that will be transmitted includes 2 items -- the device number and date/time the cap was opened. Data is sent to the Vitality server via a secure HTTPS/SSL channel. the server. The server resides behind a dedicated firewall and is only available to limited Vitality staff on a need-to-know basis via a secure, password-protected login. The server sits behind a fully-enclosed locked steel mesh cage

housing. Data will be available to the investigators via an interface between the Vitality server and Way to Health web portal. Transmission of the data to the Way to Health portal will be via a secure HTTPS/SSL channel. 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.

14.3.3. 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.
- → Pennsylvania Health Care Cost Containment Council (PHC4), a group that provides information about the utilization of health services and the cost of health care for all hospitalizations in the state of Pennsylvania. Patients' social security numbers, dates of birth, and genders will be sent to them so that we can obtain a dataset that only contains study participants healthcare utilization information.
- → P'unk Ave., LLC, a software development company designing the Way to Health website. P'unk Ave. will not store any of the patients' PHI, but they will have access to de-identified patient information, for the purposes of website administration and development.
- → Wells Fargo, the company which processes study-related payments. Patients' addresses and account balances will be stored on their secure computers.
- → Twilio, Inc., the company which processes some study-related messages. Twilio will store patients' phone numbers on their secure computers.
- → Qualtrics, Inc., the company which processes most study-related surveys. Qualtrics will house de-identified answers to these surveys on their secure servers.
- → Quest Diagnostics, Inc., a company which will process some study-related laboratory checks. Patients' names, addresses and the results from these laboratory checks will be stored on their secure computers.

- → The National Institute on Aging, the study sponsors. Representatives from the National Institute on Aging would have access to all study-related PHI in case of an audit.
- → 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

14.3.4. Data Protection

The following PHI identifiers may be collected and stored as part of this research:

☒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
☐Certificate/license numbers
☐Vehicle identifiers and serial numbers, including license plate numbers
☐Device identifiers/serial numbers
☐Web addresses (URLs)
☐Internet IP addresses
☐Biometric identifiers, incl. finger and voice prints
☐Full face photographic images and any comparable images
☐Any other unique identifying number, characteristic, or code
☐None

14.4. Populations Vulnerable to Undue Influence or Coercion

There are no highly vulnerable populations such as prisoners that will be enrolled in this study. The physician participants will be employees of Penn and Geisinger. We will be careful to make sure we don't induce any undue influence to enroll in the study by having trained study staff who are not colleagues or supervisors of the potential participants carry out the recruitment efforts and study procedures.

The following populations may be vulnerable to undue influence or coercion. Vulnerable populations recruited to the study are marked below:

☐Children (refer to SOP 501 for definition of children)
☐Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus)
☐Fetuses and/or Neonates
☐Prisoners
☐Other
☒None of the above populations are included in the research study

14.5. Data and Safety Monitoring

14.5.1. Data and Safety Monitoring Plan

The entire data and safety monitoring plan, including the members of the Data and Safety Monitoring Board (DSMB), will be submitted to the study sites' IRBs and subsequently to the funding IC for approval prior to the accrual of human subjects. Individual-level data for participants will be kept confidential and will only be stored on highly secure servers available for patient-level data. Only authorized project personnel will have access to the data and the data will be stored on servers only and not stand-alone PCs or laptops. All data will be reported at units of aggregation which make impossible the identification of individual patients and physicians and project managers. However, because we are contacting patients after their initial enrollment, there is an obvious need to have data with identifiers and contact information from the master enrollment files for each study. Study personnel who work with this data will have undergone all of the required human subjects training. They will work with the data in password protected files and once interviews or focus groups are completed the responses will be separated from the identifying information.

The DSMB has been constituted and is listed below, under Data and Safety Monitoring Board.

This Data and Safety Monitoring Plan, including the composition of the DSMB, will require approval of the IRBs and the funding IC and will be modified as needed based on the review of these groups. The data and safety monitoring plan will have 3 parts. First, the BMIC will develop and implement methods of verifying entered data and of quality control. Second, the PIs will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the IRBs and funding agency promptly, as appropriate. They will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB (described below) at least biannually (and more frequently if there are serious adverse events). Unanticipated adverse events that occur at either participating site -- Penn or Geisinger -- will be reported immediately to the Multiple PIs. Interim analyses are not planned. Third, there will be a DSMB responsible for monitoring the trial. Modifications to the protocol initiated by either participating site --Penn or Geisinger -- that affect the study procedures or increase the risk to participants will be submitted to both participating sites' IRBs. The Project Director, in collaboration with the two site Project Managers, will initiate the process of communicating protocol modifications between the sites and will ensure current site IRB approvals are obtained.

14.5.2. Data and Safety Monitoring Board

The DSMB will be composed of experts in cardiology, clinical trials, epidemiology, general internal medicine, and biostatistics, along with project PIs, Drs. Asch and Volpp, and statistician, Dr. Troxel, as non-voting members. The PIs will be responsible for maintaining communication between the DSMB and the individual project staff. We consider the proposed trial to be relatively low risk. Therefore, we have arranged for a monitoring committee that is assigned to review the study and staff training protocols, monitor the trial for safety and adverse events, and conduct bi-annual meetings. These members will not be involved directly with the trial. The members that we propose to serve on this committee and their activities are: 1. Donald Lloyd-Jones, MD, ScM is Chair of the Department of Preventive Medicine at Northwestern University's Feinberg School of Medicine; Director of the Program in Risk Estimation, Communication and Prevention; and an Associate Professor in Preventive Medicine and Medicine. Dr. Jones is a trained cardiologist and epidemiologist who participates in multiple NIH panels rewriting the cardiovascular disease clinical practice prevention guidelines. Dr. Jones will serve as Chair of this project's DSMB. 2. Constantine Gatsonis, PhD is Professor of Medical Science (Biostatistics), Acting Head of the Biostatistics Section, and Director of the Center for Statistical Sciences at Brown University. Dr. Gatsonis conducts research in the design and analysis of clinical trials, as well as in methods in medical technology assessment, health services research and outcomes research. 3. Eugene Oddone, MD, MHSc is Professor of Medicine, Director of the Center for Health Services Research in Primary Care at the Durham Veterans Affairs Medical Center and Chief of General Internal Medicine at Duke University. He has previously served on multiple DSMBs. The DSMB will perform several duties. First, they will review and approve the research protocol and plans for data and safety monitoring prior to the study. Second, they will evaluate the progress of the trial. This will include assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and study outcomes. This assessment will be performed at meetings every 6 months during the clinical trial and more frequently if needed. Third, they will make recommendations to ensure that all of the issues above are appropriately addressed. Drs. Asch and Volpp as the study PIs will be responsible for responding to all recommendations of the DSMB and submitting DSMB reports to the UPENN IRB.

14.6. Risk/Benefit

14.6.1. Potential Study Risks

14.6.1.1. Risks Involved in the Main Study

There is minimal risk to subjects participating in this trial. For physicians, prescribing behavior will be monitored and financial incentives awarded if their study enrolled patients achieve improvement in cholesterol control. As prescribing behavior at this level is not usually monitored for physicians there is a risk of disclosure and breach of confidentiality. For all subjects, there is a risk of breach of confidentiality

and privacy for completion of study surveys. Participants will be prescribed a cholesterol-lowering medication and treated with that medication only in accordance with standard clinical care. The interventions in this study attempt to improve adherence with prescribing what is standard of care on the part of physicians and taking medication among patients. In designing the intervention, we considered whether incentives might result in over-prescribing or overdosing to get higher incentives. These risks are mitigated by tying the incentives to reaching target LDL and maintaining it. Physicians or patients will receive no incentives for incremental decreases in LDL below target goal, and the amount of the incentive payment will not change based on incremental decreases in LDL below target goal in a given quarter. For patients, medication adherence behavior will be monitored and financial incentives awarded to those on some arms of the study if they achieve a 10 mg/ dl reduction in LDL cholesterol over baseline or the previous quarters goal. Of note is that the use of the GlowCaps may facilitate a patient's adherence to physician recommended medication regimen(s).

Completion of the pre- and post-intervention assessment and survey by the patient as well as the pre- and post-intervention phlebotomy poses minimal risk. Risk involved is limited to that of discomfort, disclosure and breach of confidentiality.

14.6.1.2. Risks Involved in Process Evaluation and Cost-Effectiveness Analysis

The immediate benefits of this study for participants are minimal; however, as mentioned, so are the risks. Overall the risk benefit ratio is favorable given the long-term potential of this study to significantly contribute to our knowledge of financial incentive programs, and their impact on health and health-related behaviors

14.6.2. Potential Study Benefits

There are no anticipated benefits to physicians other than the financial incentives that they receive for study participation. There may be no benefits to patients other than the financial incentives that they receive for study participation. However, some patients may achieve better cholesterol control, which would lower their risk of a heart attack, as a result of participation in this study.

14.6.3. Alternatives to Participation

To not participate in the study.

14.6.4. Risk/Benefit Assessment

There is important knowledge to be gained from this project. The impact of financial incentives in general is only beginning to be understood and much remains to be learned about how best to design financial incentives as well as the applications for which they are best suited. While financial incentives have been tested in other health care applications there has yet to be an application that simultaneously targets patients and physicians. While improving care quality has been a national priority for decades, methods to achieve large and robust improvements in quality of care have remained elusive, and significant quality deficits remain in U.S. health care. Although educational programs and life-style counseling are fundamental to effective cholesterol management, adherence to and titration of pharmaceutical therapy represents a major strategy by which cholesterol control can be achieved among patients at high risk of CVD. We have designed an innovative, theoretically-grounded financial incentive program that is potentially scalable and cost-effective through the leveraging of existing and emerging informatics infrastructure to address both medication adherence and titration. Study participation presents minimal risks to both providers and their patients.

Final Study Protocol

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15. Abstract

Cardiovascular disease (CVD) is the leading cause of death in the United States. Despite strong evidence that reducing low-density lipoproteins (LDL) with statins successfully lowers CVD risk, physicians under-prescribe statins, physicians fail to intensify treatment when indicated, and more than 50% of patients stop taking statins within one year of first prescription though such therapy typically should be life-long. In this study, we will test the effectiveness of different behavioral economic interventions in increasing statin use and reducing LDL cholesterol among patients with poor cholesterol control who are at very high risk for CVD. The application of conceptual approaches from behavioral economics offers considerable promise in advancing health and health care. Pay for performance initiatives represent one such potential application but one in which incorporating the underlying psychology of decision makers has not generally been done, and experimental tests have not been conducted. We will test these approaches among primary care physicians and their patients at very high risk of CVD at Geisinger Health System, University of Pennsylvania outpatient clinics and Harvard Vanguard Medical Associates (HVMA). Using a 4-arm, cluster-randomized controlled trial, we aim to answer these questions: [1] How does the provision of provider incentives compare to the provision of patient incentives, to a combination of patient and provider incentives, or to no incentives at all? [2] Is success with provider incentives improved with enhanced information about patient adherence? [3] Are results sustained after incentives and other interventions are withdrawn? [4] How do these approaches compare in implementation, acceptability, cost, and cost-effectiveness?

16. Significance

16.1. Cardiovascular Disease is the Single Leading Cause of Death in the United States

1.2 million Americans each year have a new or recurrent myocardial infarction (AMI) and 38% of them die from it in a given year. Clinical practice guidelines recommend HMG-CoA reductase inhibitors (statins) to lower cholesterol, and clinical trials have shown that statins lower the risk of AMI by about 30%.Despite their proven benefits and benign side effect profile, the population effectiveness of statins is limited for two reasons. First, physicians may under-prescribe statins or fail to intensify treatment when indicated. Second, patient adherence to statins is moderate at best: approximately half of patients prescribed statins discontinue usage within a year. Poor adherence leads to worse outcomes, higher hospitalization and mortality rates, and increased health care costs among CVD patients. However, many seemingly successful efforts to improve medication adherence have been too complex to be implemented

or required extensive resources, limiting applicability and sustainability. In addition, providers rarely have data on patient adherence or are limited to examination of prescription fill rates.

16.2. Annual Direct and Indirect US Expenditures Attributable to CVD are about $500 Billion

Statins can reduce CVD events requiring hospitalization by nearly 20% which could save over $15 billion annually from CVD and stroke hospitalizations alone. For secondary prevention, the cost-effectiveness ratios of statins range from being cost-saving to approximately $30,000 per quality-adjusted life-year (QALY) gained. For primary prevention, cost per QALY ratios are well below accepted thresholds; for example, in the United Kingdom from £10,000 to £31,000 per QALY for 10-year CVD risk ranging from 30% to 5%.

Both provider and patient factors contribute to high rates of under-treatment. About two-thirds of US patients at high risk for CVD are un- or under-treated due in part to the complexity of provider guidelines. A review of 23 studies suggests that improvement in adherence reduces overall treatment costs, reduces disease-related costs, and improves cost-effectiveness of cardiovascular medications; in many cases, small improvements in adherence lead to large improvements in cost-effectiveness ratios.

16.3. Volume-based Payment Systems Work Against the Management of Chronic Illness

Activities to promote prescription and adherence of medications for chronic disease are poorly reimbursed if at all, while acute procedural interventions typically have the highest profit margins. There is widespread agreement that incentive approaches that reward improved patient health instead of increased volume need to be developed and rigorously tested. Pay-for-performance (P4P) systems were developed with a focus on patient outcomes, but from a behavioral economic standpoint, the typical physician P4P program has several design features that likely limit success: [1] payments are typically awarded as a lump sum bonus at year end (ignores present-biased preferences); [2] bonus payments are typically added to a physician's paycheck (ignores mental accounting principles, since smaller payments bundled with larger payments are less salient); and [3] payments are typically based on meeting single threshold-based measures such as 90% of appropriate patients getting a mammogram (ignores evidence that people exert more effort as they get closer to goals and a high threshold is unlikely to motivate people who think a goal is largely unreachable).

16.4. Behavioral Economists Have Proposed an "Asymmetric Paternalism" Approach to Public Policy

Approaches using asymmetric paternalism aim to make it easier for people to make good choices, without restricting those choices, e.g., arranging food on a buffet such that healthy foods are more likely to be chosen. Asymmetric paternalism is paternalistic in the sense of attempting to help individuals achieve their own goals, as compared to conventional regulation designed to prevent harm to others. Asymmetric paternalism is asymmetric in the sense of helping individuals prone to making irrational decisions while not limiting freedom of choice and not harming those making informed, deliberate, decisions. Setting default options to the most desirable, beneficial, or popular choices is an example of choice architecture. Using financial incentives to encourage certain behaviors is another example of asymmetric paternalism.

16.5. Biases That Ordinarily Lead to Self-Harming Behavior Can be Used to Promote Healthy Behaviors

Individuals put disproportionate value on present relative to future costs and benefits. This "present-biased preference" typically works against healthy behaviors, However, incentives can be structured (e.g., providing tangible small but frequent positive feedback or rewards) so that present-bias works in favor of adopting healthy behaviors. For patients, the most effective approaches have been those requiring monitoring several times a week, suggesting the importance of frequent feedback. For providers, frequent feedback should be defined differently. Patients need to take statins daily, but providers typically consider an individual patient's LDL after lab tests that may be months apart.

Indeed, an important part of our work has been to move beyond thinking about financial incentives as all-or-none, but instead to design the structure and timing of incentives to correspond to established principles of psychology and how different decision makers (e.g., physicians versus patients) act. For example, we have tested the use of daily lotteries for patients to improve medication adherence and weight loss. Americans spend $48 billion annually on state lottery tickets. However, the average pay-out rate across state lotteries is just 52%, ranging from 26-71%. Several features combine to make lotteries attractive despite their poor return. Frequent small payoffs give lottery players intermittent positive reinforcement. Feedback is often very rapid: most games have daily draws and instant scratch-off tickets. The small chance of a large payoff is especially attractive because people tend to overweigh small

probabilities in making decisions. For these reasons, structuring financial incentives as a lottery has several benefits for a daily incentive. We are less enthusiastic about using daily lotteries for physicians: their decisions for each patient are not daily, and the perceptions of lotteries may be inconsistent with professional norms in clinical care. However, other decision errors such as present-biased preferences, loss aversion and mental accounting can be usefully applied.

17. Background

17.1. Feasibility

We have successfully completed numerous randomized trials of financial incentives in a wide variety of settings as well as a number of quality improvement projects at both UPENN and Geisinger, the proposed study sites. The experience acquired and infrastructure developed from these studies will ensure successful completion of the proposed work. There are approximately 355 primary care providers at UPENN and Geisinger. Moreover, analysis of the UPENN, and Geisinger electronic records indicate a significant number of patients with a Framingham Risk Score (FRS) of greater than $\geq$ 20% with LDL $\geq$ 120, or FRS = 10-20% with LDL $\geq$ 140, or a coronary artery disease equivalent (diabetes, peripheral artery disease, ischemic CVD, arteriosclerotic CVD, stroke/TIA, CABG, coronary stenting, or coronary bypass anastomosis) with LDL $\geq$ 120. Such patients should have LDL of 100, leaving substantial opportunity for improvement. Based on previous recruitment experience at UPENN, Geisinger we expect to readily achieve the targeted enrollment of 200 physicians and 1400 patients for this low-risk study with minimal requirements and generous incentives for participation. Current approaches have evidently not succeeded in managing CVD risk among these patients highlighting the need for effective and scalable interventions to improve management. With support from an RC2 grant (Volpp and Asch Multiple PIs), we have developed the capacity to facilitate behavioral economic studies with an easily customizable web-based platform supported by a secure multi-terabyte data repository. This Way to Health platform can take inputs from either home-based biometric measurement devices (e.g., Vitality GlowCaps) or EpicCare medical record lab values; convert these into visually appealing and informative content displays; automatically calculate patient or provider incentives based on the study design; push messages back out to patients or providers via text message, email, or interactive voice recordings (patient or provider preference) at any time interval; and automatically transfer incentive payments electronically. The Way to Health platform has many other capabilities, including flexible and automated participant randomization, electronic consent functions, and participant tracking and will be fully operational by August 2010. The teams from Geisinger and Penn have extensive experience working with EpicCare records, automatically generating reports to push out to web-based portals and facilitating access from within EpicCare to web-based portals.

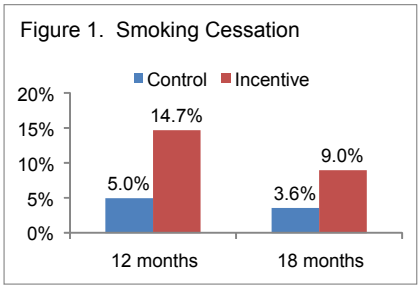
17.1.1. Preliminary Studies

17.1.1.1. Evaluation and design of new P4P initiatives for physicians.

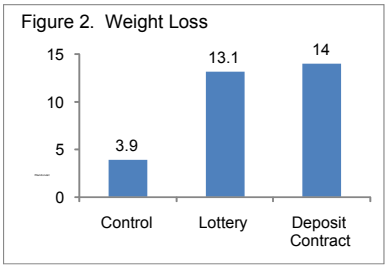
Dr. Asch has examined the clinical impact of physician performance measurement. He is currently co-leading an evaluation of the Department of Veterans Affairs roll out of the Southeastern Pennsylvania Medical Home. Dr. Rosenthal has conducted numerous studies of the adoption and evolution of pay for performance in the U.S. health care system, and has developed recommendations for the design of P4P programs based on both economic theory and evidence. She has also led evaluations of several major P4P programs including Bridges to Excellence and PacifiCares Quality Incentive Program, part of the largest multi-payer P4P program in the U.S. Currently, Dr. Rosenthal is evaluating a broad range of physician payment incentive models including primary care Medical Home initiatives and an episode-based payment system. Dr. Volpp is co-leading an evaluation of the Southeastern Pennsylvania Medical Home as well as serving as PI of an RWJ-funded study of differential hospital service line profitability on patient mortality and readmission rates. Our team has introduced many behavioral economics concepts into health care through discussion of issues related to asymmetric paternalism in health care settings, choice architecture and the use of defaults, and use of common decision errors in designing interventions to help people as opposed to taking advantage of them.

17.1.1.2. Incentives for health behaviors

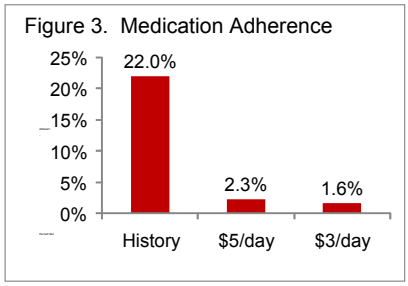
Our team has studied lotteries and other incentives to improve health behaviors in the context of smoking, obesity, and medication adherence. These include: [1] A CDC-funded study of 878 participants at 85 General Electric work sites testing the effectiveness of financial incentives worth $750 in increasing smoking cessation rates. Smoking cessation rates after 12 months were nearly triple in the incentive group (14.7% vs. 5.0%, p0.0001) and this ratio was sustained at 18 months after incentives were discontinued (Figure 1). GE implemented a program based on this in January, 2010 for all 152,000 employees nationally. Published in NEJM, this effort won the British Medical Journal 2010 Award for Getting Research into Practice. [2] Two studies testing the impact of copayment reduction on blood pressure and medication adherence in 820 veterans with poorly controlled blood pressure. These studies



showed that, counter to conventional wisdom, copayment reductions have much smaller effects on outcomes and adherence than had been indicated by observational studies of copayment increases, likely because reducing copayments targets the behavior of non-adherent patients, a much more challenging group. [3] A study funded by USDA and the Hewlett Foundation to encourage weight loss using lottery-based incentives and deposit contracts, in which patients voluntarily put their own money at risk and win it back conditional on success. This study, published in JAMA, used a lottery system similar to the patient incentive proposed here: a daily lottery with expected value near $3 per day (about 1 in 5 chance of winning $10, 1 in 100 chance of winning $100) with receipt of payments conditional on periodically verified improvement in outcomes (weight loss). In this study, incentive group participants lost significantly more weight than control group participants (control = 3.9 pounds; lottery = 13.1 lbs, p = .01; deposit contract = 14.0 lbs, p = .003; Figure 2). Only 7% of participants were lost to follow-up by the end of the study.



Among incentive group subjects not lost to follow-up, participants called in daily weights 98% of the time, indicating both the feasibility and effectiveness of a daily lottery in providing variable reinforcement to change behavior. [4] Several studies funded by NHLBI and the Aetna Foundation testing the use of daily lotteries to improve medication adherence. In all studies, participants were eligible for the daily lotteries if they correctly took their warfarin. In two separate studies testing $5 and $3 expected value lotteries over 979 and 813 patient-days, respectively, non-adherence was 2.3% and 1.6% compared to historic proportions of 22%.89 (Figure 3) These studies indicate that expected values of $3 and $5 have comparable impact, as the effectiveness of lotteries may be due not only to expected winnings but also to regret, reinforcement, and entertainment. A follow-up RCT of incentives for warfarin adherence in 100 participants (under review) indicated that lottery-based incentives improved INR within target range for patients with below-range INR at baseline, but offered little benefit to those already well controlled. These results highlight the utility of targeting interventions, where possible, to participants with evidence of suboptimal adherence to efficacious medications at baseline.



17.1.2. Clinical Informatics

Over the past five years, the Geisinger Center for Health Research has conducted extensive research developing and testing how web-based tools can be used interactively with the

electronic health record to improve care efficiency and quality in the Geisinger Clinic. The inventory includes real-time use of patient reported data for diagnosis and outcomes tracking; patient decision aids; visual display tools to facilitate physician decision making, and web-display tools that deliver point of care expert advice. At Penn, Dr. Weiner developed the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) System in 1997, to promote research in the clinical enterprise. PICARD compiles UPENNs electronic records (Epic and Sunrise), billing, and laboratory results reporting across its hospitals and ambulatory sites. PICARD includes all patient demographics, location of the encounter, participating physicians, as well as diagnoses assigned during the encounter and charges and reimbursements for all procedures performed.

17.1.3. Cost-effectiveness of health promotion interventions

Dr. Glick has written extensively on methods for economic assessments in clinical trials, including issues of study design, economic data collection, unit cost estimates for within-trial medical service use, and analysis of costs and cost-effectiveness. Dr. Gaziano has done extensive evaluation of long-term cost-effectiveness of CVD interventions including LDL lowering, blood pressure guidelines, absolute risk assessment, and multi-drug therapy for primary and secondary prevention. Dr. Weinstein is a co-developer of the Coronary Heart Disease Policy Model, which has been used to evaluate the cost-effectiveness of cardiovascular prevention and treatment including cholesterol lowering.

17.1.4. Way to Health Platform

With support from an RC2 grant (Volpp and Asch Multiple PIs), we have developed the capacity to facilitate behavioral economic studies with an easily customizable web-based platform supported by a secure multi-terabyte data repository. This “Way to Health” platform (waytohealth.org – see figure in Resources section) can take inputs from either home-based biometric measurement devices (e.g., Vitality GlowCaps) or EpicCare medical record lab values; convert these into visually appealing and informative content displays; automatically calculate patient or provider incentives based on the study design; push messages back out to patients or providers via text message, email, or interactive voice recordings (patient or provider preference) at any time interval; and automatically transfer incentive payments electronically. The Way to Health platform has many other capabilities, including flexible and automated participant randomization, electronic consent functions, and participant tracking and will be fully operational by August 2010. The teams from Geisinger, Penn and HVMA have extensive

experience working with EpicCare records, automatically generating reports to push out to web-based portals and facilitating access from within EpicCare to web-based portals.

17.1.5. Adherence measured using Vitality GlowCaps

Our group has conducted several randomized trials using adherence monitoring technology. That experience led us to select Vitality GlowCaps for this study. GlowCaps are used in place of regular pill bottle caps and electronically monitor bottle opening with a small remote device that plugs into a wall outlet. The technology allows provision of adherence feedback to many patients and/or providers. Through our Way to Health platform, we can connect this feedback with our lottery-based incentives, making the system feasible for large-scale adherence interventions.

Figure 4: Vitality GlowCap and Plug-in Transmitter

Several methods have been used to measure adherence; no "gold standard" exists. There are multiple limitations to methods such as patient self-report and pill counts. GlowCaps provides an unbiased assessment of pill bottle opening and a valid approach to verifying self-administered pill taking, reflecting not only daily use but also patterns of drug use and timing. This method assumes that each time the cap is opened, a dose is taken, and that doses are not taken when the cap is not opened. GlowCaps are just like regular pill bottles so there is little need for patients to decant pills into other containers—a process that can lead to false negative measures of adherence. Similarly, although it is possible for patients to open a pill bottle but not take their medication, evidence suggests that once an individual opens a pill bottle, pills are nearly always taken and numerous studies have established the validity of electronic pill container measures.

Each day the GlowCap will electronically transmit whether a participant opened his/her prescription bottle to take his/her cholesterol-lowering medication via a built-in modem to the central server (there is no internet charge to participants) and a simple wireless device plugged into an outlet. Participants will be considered adherent only if we receive electronic notification signaling that the pill bottle was opened once the previous day. GlowCaps and the wireless transmitters are easily portable and can be used while traveling. Each patient will receive instructions to call the study nurse for any changes in dose frequency (an unlikely event in the context of cholesterol-lowering medications, most of which are recommended as once-a-day medications), in which case the GlowCap will be reprogrammed.

17.2. Summary of Preliminary Studies and Study Feasibility

Our pilot data and experiences reveal: [1] Our study sites offer sufficient eligible participants. [2] Many high-risk CVD patients at these sites have poorly controlled LDL cholesterol. [3] Intervention studies by our group using financial incentives have shown substantial increases in healthy behaviors. [4] We have built an infrastructure capable of supporting this project using a high degree of automation, lowering research costs and increasing feasibility of clinical adoption of results. [5] Our team has experience in designing, conducting, and analyzing trials of financial and behavioral interventions. [6] Our team has expertise in evaluating cost-effectiveness in the context of clinical trials and CVD. [7] We have successfully conducted trials and recruited patients in a wide variety of study sites.

18. Innovation

This study would be the first to experimentally test whether incenting providers based on the outcomes their patients achieve is effective. It would be the first to test whether, dollar-for-dollar, provider incentives are more effective than patient incentives or provider/patient hybrid incentives.

The context is CVD, the top killer of Americans. The study's motivation is the simultaneous availability of well-tolerated and effective medications to reduce CVD risk and evidence that they are under-prescribed by physicians and under-adhered to by patients. Incentives offer great promise in this context as standard approaches have not sufficiently improved adherence rates among high-risk non-adherent patients and reasons include inadequate positive reinforcement and insufficient attention to 'important' vs 'urgent' issues for providers due to the incentives embedded in visit-based fee for service provider payment.

The provider incentives will be the first P4P intervention that sets goals designed to motivate all providers to participate by rewarding continuous improvement rather than a single target threshold, that considers present-biased preferences by providing rewards to providers on a quarterly basis, and that considers mental accounting issues in the disbursement of those payments.

19. Overall Objectives

This proposal is motivated by several observations: [1] Cardiovascular disease (CVD) is the leading cause of death in the United States. [2] There is strong evidence from multiple clinical trials that reducing low-density lipoproteins (LDL) with statins successfully lowers CVD risk. [3]

Despite this evidence, physicians under-prescribe statins and fail to intensify treatment when indicated. More than 50% of patients stop taking statins within one year of first prescription though such therapy typically should be life-long. We propose to test the effectiveness of different behavioral economic techniques in increasing statin use and reducing LDL cholesterol among patients with suboptimal cholesterol control who are at very high risk for CVD.

Financial incentives and the modification of choice architecture (e.g., setting default options to the most desirable, beneficial, or popular choices) are two approaches to change physician and patient behavior. Considerable conceptual grounding from behavioral economics supports both approaches, though their empiric validation has largely come from contexts like savings behavior rather than health care settings. We and others have developed and tested incentive-based interventions that significantly improve patient health behaviors, but these approaches have not been well tested in parallel with efforts to change provider behavior. Recent pay for performance (P4P) efforts have used payments to motivate providers to improve quality, but the focus has often been on process measures of plausible but uncertain value. Moreover, economic P4P incentives have not accounted for the underlying psychology of physician decision-makers. Perhaps as a result, there is little evidence that existing P4P interventions improve patient health outcomes. We propose to address an important gap in behavioral economics at the intersection of the burden of poorly controlled chronic diseases, the recognition that payment reform should redirect incentives to improvements in patient outcomes rather than increases in the volume of services, and the unrealized promise of P4P approaches to improve patient outcomes.

Using a 4-arm, cluster-randomized controlled trial (RCT) among primary care physicians and their patients at Geisinger Health System, University of Pennsylvania and HVMA outpatient clinics, we propose to test and compare the effectiveness and cost effectiveness of alternative approaches to reducing LDL cholesterol. We will test the absolute and relative effect of incentives for providers, patients, and providers and patients together. In three of four arms we will provide clinicians with feedback on patient adherence, using Vitality GlowCaps. We will enroll patients who have a 10-year CVD risk of $\geq$ 20% with LDL $\geq$ 120, or 10-year CVD risk = 10-20% with LDL $\geq$ 140, or a coronary artery disease equivalent (diabetes, peripheral artery disease, ischemic CVD, arteriosclerotic CVD, stroke/TIA, CABG, coronary stenting, or coronary bypass anastomosis) with LDL $\geq$ 120, indicating under-utilization of statins. These patients are particularly important to target in achieving effective risk management of CVD outcomes and offer promising returns from behavioral economic strategies. Physicians caring for those patients will be randomly assigned to one of 4 arms: Physician incentives (with GlowCaps adherence information); Patient incentives (with GlowCaps information); Physician and patient combined incentives (with GlowCaps information); and, Usual care (no GlowCaps information or patient or provider incentives).

20. Aims

20.1. Primary Aims

Aim 1: To evaluate the effectiveness of physician incentives, patient incentives, and provider/patient incentives on improvement in LDL cholesterol relative to usual care during a 12-month intervention among patients at high risk of CVD. H1: Each of these approaches will be more effective than usual care in reducing LDL cholesterol.

Aim 2: To evaluate the relative effectiveness of those intervention arms superior to control in reducing LDL cholesterol. H2: Incentives for patients (patient incentive and split incentive arms) will be more effective than incentives for providers (physician incentive arm).

20.2. Secondary Aims

Aim 3: To evaluate the impact of each effective intervention in sustaining adherence and reduced LDL after the 12-month intervention period.

Aim 4: To assess the cost effectiveness of each of the interventions relative to usual care.

Aim 5: To conduct a rigorous qualitative process evaluation to examine why some interventions were more effective than others and to address other factors relevant to broader implementation.

21. Primary Outcome Variable

21.1. LDL cholesterol (primary outcome)

Change in LDL from baseline to 12 months. The evidence base linking improvements in LDL cholesterol to reductions in CVD is extensive, supporting about a 20% reduction in CVD per 40 mg/dL reduction. LDL cholesterol is easily monitored through a simple blood test. The primary outcome will be change in LDL between baseline (prior to randomization) and 12 months.

22. Secondary Outcome Variable(s)

22.1. LDL Cholesterol (secondary outcome)

Change in LDL from baseline to 15 months.

22.2. Hemoglobin A1c (secondary outcome)

We will also measure Hemoglobin A1c, an assessment of intermediate term glycemic control, among patients with diabetes. This measure is related to CVD risk but is not a target of the intervention. We measure it to examine positive or negative spillover effects from targeting LDL cholesterol: a focus on LDL may crowd out attention to other conditions or, alternatively, might stimulate it.

22.3. Process Evaluation (secondary outcome)

22.3.1. Potential confounders and mediators

Although this randomized trial is designed to balance all factors that could alter LDL levels (other than the interventions), we will measure potential residual confounders at baseline and adjust for them in later analyses. Many of these variables may also serve as either moderators (factors that predict which people are helped by the intervention) or mediators (variables related to mechanisms whereby the intervention works) in the intervention-outcome pathway. For physicians, this will include hire date and demographic characteristics as well as information on training and certification. For patients, we will have information on demographics, socioeconomic status, comorbidities, and baseline LDL.

22.3.2. Method of data collection

Baseline data will be collected by structured, in-person interviews performed by either the study intake coordinator at each clinical site or via the web using standardized data collection forms to be developed with assistance from Dr. Shea and modeled after data collection instruments used in our previous studies. Baseline data will include detailed demographics (e.g., age, sex, race/ethnicity, income, education, marital status, employment, health insurance). Other variables to be collected include: (1) Risk perceptions measured using a visual analog scale; (2) Numeracy using pre-validated measures of numeracy; and (3) Health status measured using the SF-12 to assess health-related quality of life and the Health Utility Index (HUI) to assess health preferences. At the 12-month visit, participants will be surveyed about all variables that may change, such as health status. A select number of participants may also be

contacted to complete post-intervention interviews that will include questions regarding perceived benefits and drawbacks, complications with the study, and areas of improvement.

22.3.3. Measurement of costs and cost effectiveness

We will conduct a "within-trial" analysis comparing incremental costs and incremental change in LDL during the intervention period from a payer/provider system perspective. Secondary analyses will evaluate this same ratio from a limited societal perspective, including incentive payments (which are transfers and typically omitted from the societal perspective) and valuing direct medical costs using federal fee schedules as proxies for social opportunity costs.

Measured costs will include: incentive payments, administrative costs of providing the interventions, and medical costs. Incentive payments to providers and patients will be computed as the sum of their conditional incentives, excluding participation incentives. Administrative costs of providing the interventions will be estimated based on [1] project personnel quarterly responses to time-diaries detailing their time spent on administrative tasks in the past week, including time administering all participant-related aspects of the intervention and usual care (excluding time related to general project administration), [2] the GlowCaps costs (about $16.25 per patient per month), and [3] monthly computer support fees. Wages will be used to convert measured administrative time to costs. We will amortize the computer support fees over the 1400 participants in the study. In sensitivity analysis, we will test the effect of varying the estimates of the fixed costs per person.

All medical care costs incurred by trial participants will be collected using the resource costing method. Health care utilization, including physician visits, ER visits, lab tests, hospitalizations, and medication use will be derived from the UPENN, Geisinger and HVMA EPIC data. Cost data reported by EPIC will be used to assign a cost to these services. Non-UPENN, Geisinger or HVMA health care utilization will be derived from participant self-report as part of regular interviews with participants. These services will then be mapped into the data from EPIC to derive cost estimates. For the limited social perspective all services will be costed out by use of Federal fee schedules and databases of hospital inpatient resource use.

The focus of the "within trial" CEA is on changes in LDL cholesterol from improved adherence. Yet, because an important, long-term goal is to reduce mortality and long-term morbidities, we will update and expand a previously published model of long-term cardiac risk that has been used for such projections. All incentive strategies will be compared with usual care. We will use the model to translate observed short-term cost and effectiveness outcomes into projected

long-term estimates of avoided disease, avoided direct medical costs, and gains in quality-adjusted life-years (QALYs) based on LDL reductions.

The procedures for computing costs and conducting the "societal perspective" cost-effectiveness analysis will follow the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. We will identify all available and relevant sources of cost data, including Medicare Fee Schedules, databases of hospital inpatient resource use, and estimates from the published literature. Drug costs will be estimated by adjustment of average wholesale prices. Costs of managing side-effects will also be included. Patient travel and waiting time will be based on data from the National Medical Expenditure Panel Survey, and patient and caregiver time costs will be valued based on average wage rates corresponding to the target population. We will use age- and sex-specific utility weights for healthy people derived from EuroQol EQ-5D utility scores collected in the 2000 wave of the Medical Expenditure Panel Survey, and the National Health Interview Survey. All costs and benefits will be discounted 3% per annum.

23. Study Design

23.1. Phase

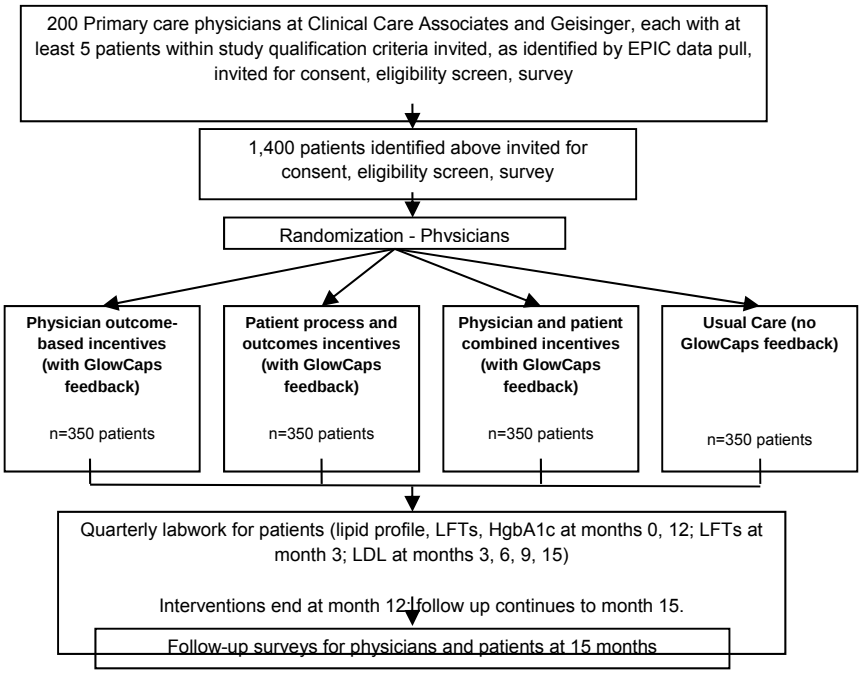
Phase III

23.2. Design

This is a 4-arm cluster-RCT to test the relative effectiveness and cost-effectiveness of several innovative approaches to improving LDL management (largely through statin use) in patients at high risk for CVD. Incentives will be awarded quarterly to patients and bi-annually to physicians, based on an a quarterly improvement of at least 10 mg/dl in LDL relative to the patient's baseline LDL or achieving or sustaining LDL of 100, depending on baseline LDL and FRS. Adherence in all groups will be measured using Vitality GlowCaps as a recording device and in most arms (all arms except usual care) this information on daily patient adherence will be available to providers in monthly reports and available online at any time. Physicians and their panel of patients will be randomized evenly into one of 4 arms described in Figure 5, drawing on a conceptual framework from both traditional and behavioral economics. This design allows a variety of comparisons across arms, answering conceptually and procedurally important questions in the application of behavioral economic approaches to advance health: 1. How does the provision of provider incentives compare to the provision of patient incentives, to a combination of patient and provider incentives, or to no incentives at all? 2. Are results

sustained after incentives and other interventions are withdrawn? 3. How do these approaches compare in implementation, acceptability, cost, and cost-effectiveness?

Figure 5. Overview of Study Procedures



[1] In all arms except for usual care, we will provide more frequent feedback to providers than has typically been the case in P4P programs, in recognition of present-biased preferences. In the patient incentive and split incentive arms, patients will get adherence feedback electronically with daily lottery awards to match the timing of their task. [2] Since the goal is to improve patient outcomes, the physician incentives (physician incentive and split incentive arms) will be based on improvement in those outcomes. Physicians can use the tools at their disposal: counseling of patients, initiation and intensification of medications, referral to specialized lipid programs. [3] We will use loss aversion as a motivator; patients will retain their accumulated adherence-based daily lottery winnings only if their LDL meets their quarterly goal. We do not use strict loss aversion for physicians, but since physicians who are successful in achieving goals in the first 6 months likely will not want to lose the money they expect to receive in the subsequent 6 months, their motivation will be augmented by that expectation. [4] For both providers and patients, each quarter we will focus on significant improvement of LDL as opposed to attainment of a single threshold. This motivates all participants, as people generally exert more effort as they get closer to goals. It also recognizes that a single threshold (e.g., LDL<100) is unlikely to motivate physicians or patients who think that goal is largely unreachable (e.g. a patient with baseline LDL of 220, who might have the most to gain from

improvements). [5] We will use mental accounting principles and unbundle these awards from larger sums of money such as salaries, as rewards are much more salient when separated from, and not cognitively diluted by, larger amounts. [6] Because regret aversion affects decision making, non-adherent patients will receive daily feedback about what they would have won had they been adherent.

Randomization will occur at the physician level, but the primary unit of analysis will be the patient. Patients and providers will receive an active intervention for 12 months followed by 3 months of observation without incentives or other intervention to examine sustainability post-intervention. The primary outcome will be change in LDL cholesterol from baseline to 12 months. Each quarter, participants will be eligible for incentives if the patient's LDL has improved by at least an additional 10 mg/dl compared to the patient's baseline LDL or previous quarter's goal. Patients whose LDL reaches AHA goals (< 100 mg/dl) will also meet criteria each quarter that they remain at that level. Incentives for physicians will be distributed twice-yearly and based simply on patients meeting the LDL goals described above. Incentives for patients will be structured as an adherence-based lottery with an expected value of $2.80. Patients will observe the accumulation of any winnings (with perfect adherence, these winnings will average $256 every quarter—$128 in the split incentive arm in which incentives are shared between patients and physicians). Patients will be told they will receive these lottery winnings only if their LDL, chemically assessed each quarter, has met the outcome goals - an approach combining frequent feedback and daily engagement to stimulate adherence and using loss aversion to further augment motivation.

23.3. Study Duration

Participants will be in the study for 15 months. The project duration is 3 years, beginning September 30, 2010.

23.4. Facilities

The study will take place at UPENN, Geisinger and HVMA. UPENN primary care is distributed across its Clinical Practices group (the Clinical Practices of the University of Pennsylvania, CPUP) and its Clinical Care Associates (CCA)—the former representing about 35 full time primary care clinicians and 50,000 patients in a largely urban and racially diverse practice, the latter serving approximately 160,000 patients in the Philadelphia metropolitan area spanning Pennsylvania and New Jersey with over 100 additional primary care physicians distributed across 30 sites. Geisinger Clinic serves 400,000 primary care patients and more than 500,000 specialty care

patients in central and northeastern Pennsylvania. The clinic has 220 primary care providers who practice in 37 clinic sites. The population in the region is 40% rural. Harvard Vanguard Medical Associates has identified 15 sites for participation in this study. These sites consist of about 200 primary care physicians serving approximately 350,000 patients across eastern Massachusetts. We have chosen these sites for 3 reasons: [1] Target population: The populations served by UPENN, Geisinger and HVMA include patients of mixed socioeconomic status, with a high rate of CVD, many with inadequate management of LDL. [2] Logistics: We have conducted numerous intervention studies in both the UPENN clinics, Geisinger and HVMA, and have experience and comfort conducting studies in these settings. [3] Same electronic medical record system: UPENN, Geisinger and HVMA use EpicCare, simplifying the interface with our Way to Health web-based platform, as similar approaches can be used in both systems.

23.5. Key Inclusion Criteria

23.5.1. Key inclusion Criteria for Physicians

All primary care providers who have at least 5 eligible patients will be eligible.

23.5.2. Key inclusion Criteria for Patients

To meet general study eligibility criteria and be included on the study roster, patients must:

- → Be between the ages of 18 and 80;
- → Have a consenting PCP at a participating site;
- → FRS of ≥ 20% with LDL ≥ 120, or FRS = 10-20% with LDL ≥ 140, or a coronary artery disease equivalent (diabetes, peripheral artery disease, ischemic CVD, arteriosclerotic CVD, stroke/TIA, CABG, coronary stenting, or coronary bypass anastomosis) with LDL ≥ 120.

23.6. Key Exclusion Criteria

23.6.1. Key Exclusion Criteria for Physicians

No exclusion criteria.

23.6.2. Key Exclusion Criteria for Patients

The following patients will be excluded from participation in the study:

- → Patients with a history of side effects to statins. Patients with a history of side effects to statins will be forwarded to the study's medical monitor (a physician aligned with the study) and may still participate in the study if, after the medical monitor reviews the patient's medical record, he/she determines that the patient may safely participate in the study;
- → Patients who will not or cannot give consent;
- → Patients with terminal illness who are no longer suitable candidates for aggressive lipid management as determined by the patient's primary care physician;
- → Patients with ALT values detected at greater than 80 U/L;
- → Patients with active or progressive liver disease.

24. Subject Recruitment

24.1. Target Population

The populations served by UPENN, Geisinger and HVMA include patients of mixed socioeconomic status, with a high rate of CVD, many with inadequate management of LDL. We have conducted numerous intervention studies in both the UPENN clinics, Geisinger and HVMA, and have experience and comfort conducting studies in these settings. These sites use the same electronic medical record system: Both UPENN, Geisinger and HVMA use EpicCare, simplifying the interface with our Way to Health web-based platform, as similar approaches can be used in both systems.

24.2. Subjects at Penn

700

24.3. Subjects at Sites Other than Penn

700

24.4. Accrual

LDL cholesterol is strongly associated with CVD outcomes, so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dL change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The study has been powered for two phases of hypothesis testing. In the first phase, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms. We will accrue 1400 participants evenly randomized across the 4 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (10% per year) at both sites. 150 physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.017 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference153 approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests will vary from a maximum of 3 (if all three active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement). Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between

80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

24.5. Physician Subject Recruitment

All eligible primary care physicians at UPENN, Geisinger and HVMA will be invited to join the study and we will schedule a half-hour visit to obtain informed consent, review study procedures, provide a web portal orientation, and do a short baseline survey. Eligible primary care physicians at UPENN, Geisinger and HVMA will be mailed an opt-out letter. Those who do not opt out will be automatically enrolled in the study. A baseline visit will be scheduled by study staff. Within each practice, we will identify patients meeting eligibility criteria by monitoring laboratory data. The study will provide the physicians involved in the study with a copy of their patient list (which includes last date of service) at least 48 hours in advance of the meeting on order to give them the opportunity to review the list in more detail. This patient list will include a cover sheet with instructions for reviewing their patient list. Staff will meet with the physician to review study procedures, provide a web portal orientation, and do a short baseline survey. Study procedures will be summarized using a study information handout. After randomizations, those physicians taking part in the physician incentive and split incentive arms will be asked to complete a survey regarding the use of incentives. Finally, physicians will be asked to review their patient lists. Study staff will review patient lists with the physicians, guiding physicians through the instructions on the patient list cover sheet. Physicians will be reimbursed by RVU for this baseline visit (meaning that their practice will compensate them as if this was a regular patient visit). Additionally, physicians with the Clinical Care Associates (CCA) of the University of Pennsylvania will be invited to attend an information session on the study. Physicians that attend this one-hour information session will be paid $100, which is the norm for CCA physicians. We will use an opt-out mechanism for physician consent, since there is no appreciable risk to physicians in participating (incomes can only go up); our discussions with the UPENN IRB indicate that this is likely to be acceptable. Given the potential for income supplementation with minimal incremental effort, we anticipate high physician interest in the study.

24.6. Patient Subject Recruitment

Each patient will be asked to opt in to the study and will be required to fill out an informed consent/HIPAA authorization to enroll. Patients will be able to consent for this study both electronically, via the Way to Health platform, and by paper.

Regarding recruitment, we have already initiated a strategy of mail-based recruitment of patients for whom approval was received from their primary care provider. The letter invited patients to enroll in this research study by utilizing the online Way to Health platform.

24.6.1. Identification of Potential Patient Subjects

Within each practice, we will identify patients meeting eligibility criteria by monitoring laboratory data, via a query of the EPIC electronic medical record database.

24.6.2. Geisinger Survey Research Unit

This study plans to utilize the Geisinger Survey Research Unit's call center to facilitate the completion of study-related questionnaires and some aspects of patient screening. The Geisinger Survey Research Unit has capabilities that are not available at the University of Pennsylvania or HVMA, specifically a trained staff of 18 professionals who have evening and weekend hours and can be used for help with recruitment and questionnaires by institutions that partner with Geisinger Health System in research. The staff uses 12 computerized workstations running WIN-CATI (Computer-Assisted Telephone Interviewing). The CATI system guides interviewers through telephone scripts, and accommodates complex skip patterns within questionnaires. Interviewers staff the call center throughout the week, and data from questionnaires can be exported in a number of electronic formats.

Potential subjects will be given ten days after sending letters of introduction to the study to enroll in the study via the Way to Health platform. If during that time the patient does not enroll via the Way to Health platform, and the patient does not opt out by contacting the UPenn study team, the patient's contact information will be forwarded to the Geisinger Survey Research Unit call center for follow-up. Specifically, the patient's name, phone number, and a unique study identification number, different from the patient's medical record number, will be forwarded to the call center. The call center will try calling the patient at the contact phone number listed in the patient's EPIC electronic medical record.

The information exchange between the University of Pennsylvania, Geisinger Health System and the Way to Health platform is facilitated by the fact that each of these entities will have access to their own schema on a mySQL database running on a University of Pennsylvania-owned and managed server. Using this database, we will track responses to the recruitment materials and maintain a continuously updated table of responders and associated non-responders. The database software allows setting access privileges such that specific users with

access to the Geisinger Health System component of the database can also be allowed to access certain tables within the University of Pennsylvania component of the database. We plan to enable Geisinger Health System users to access the specific table within the University of Pennsylvania schema that contains the names and phone numbers of the non-responders so that the Geisinger Survey Research Unit can know who needs to be contacted by their service. Study staff at Geisinger Health System will download these data and transmit it to the Survey Research Unit in the same secure manner with which they manage their own protected health information. mySQL can maintain logs of when and who accessed this single table. Geisinger Health System staff will not have access to other University of Pennsylvania-based study data, nor access to other UPHS information systems.

This information will be made available to the Geisinger Survey Research Unit call center via a mySQL database system, which includes numerous information security mechanisms, previously described. Upon making contact with the patient, the patient will be given a brief overview of the study and demographic information will be collected from the patient. Basic screening questions will be asked of the patient, akin to enrollment via the Way to Health platform, and then the patient will be asked to complete a study-related survey by phone.

At the 6-month and 12-month marks, patients who are screened via the call center and choose to enroll in the study will be called again by the call center to complete 6-month and 12-month surveys by phone, again, akin to patients who enroll via the Way to Health platform. The survey completed at the 12-month time point in the patient's involvement in the study will be substantially similar to the survey completed at baseline. The 6-month survey is a subset of the 6 and 12-month surveys.

Geisinger Survey Research Unit employees have expertise and resources that allow them to recruit patients more easily, more efficiently, and in a more standardized manner than at The University of Pennsylvania. Using standard processes at the Geisinger Survey Research Unit call center, patients can be called upward of ten times in a given week by the research team. Such recruitment efforts cannot be paralleled easily using available resources at the University of Pennsylvania, and recruitment of the approximately 700 University of Pennsylvania patients by research staff at the University of Pennsylvania would probably not be financially feasible and could probably not be completed in a timely manner.

The Geisinger Survey Research Unit employs numerous measures to ensure that data collection is of the highest quality, while making every effort to preserve patient rights and privacy at all rimes. Survey Unit interviewers complete a comprehensive training curriculum presented in conjunction with the Geisinger Institutional Review Board (IRB). These courses include a block of training that teaches interviewers of the obligation of researchers to respect participant rights, and regarding HIPAA privacy regulations and Protected Health Information (PHI) best

practices. In addition, projects are monitored by management staff and performance statistics are evaluated daily. The Geisinger Center for Health Research study team, led by the project manager, will train the Geisinger Survey Research Unit interviewer staff to provide an overview of the study, screening questions, and surveys, in order to prepare the Geisinger Survey Research Unit interviewers to field questions about the study by potential participants. At least two training sessions will be held, one during the day shift and one during the evening shift, so that all interviewers have the ability to attend the training session. All interviewers (and indeed, all Geisinger employees), sign a confidentiality statement. Geisinger uses encryption technologies extensively, and user authentication systems (i.e. password and personal identification number) protect all electronic records containing PHI. The Survey Unit, where the call center is located, is locked at all times.

The Geisinger Survey Research Unit provides survey support for a wide variety of research studies. Based on the main campus of the Geisinger Health System in Danville, Pennsylvania, the Geisinger Survey Research Unit offers a call center for administration of telephone surveys, as well as facilities and staff for the completion of focus groups and mailed surveys. While the Geisinger Survey Research Unit primarily works with Geisinger researchers, the Survey Research Unit has previously worked with researchers at the Fox Chase Cancer Center and at Thomas Jefferson University Hospital. At this time, the call center only accommodates outgoing phone calls and does not support incoming phone calls.

24.7. Subject Compensation

24.7.1. Compensation for Physicians

Physicians will be paid by RVU credit for the initial visit and for the 12 month follow up visit as compensation for their time. Those assigned to an incentives arm (physician incentive and split incentive Groups) can win additional incentives based on an adherence-based lottery (total of $1,024 per year per patient or $256 per quarter per patient for those in the physician incentive Group and $512 per year per patient or $128 per quarter per patient for those in the split incentive Group who share their incentive with their enrolled patient) based solely on whether a given patient achieves an LDL reduction of at least 10 mg/dl each quarter relative to the patient's baseline LDL or the last quarter's target. Thirty providers will be asked to participate in a post-study interview and respond to questions about how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Providers will be paid by RVU credit for their time.

24.7.2. Compensation for Patients

Patients will be paid $75 after completion of the first visit ($50 for the blood draw, and $25 for the questionnaire) and then $40 for lab checks at 3, 6, and 9 months, and then $80 for lab checks at 12 and 15 months as compensation for their time and to improve participation rates, as noted in Table 1. Generous participation incentives have succeeded in minimizing differential drop out in our previous studies. Additional incentives for patients assigned to the patient incentive Group or split incentive Group will be structured as an adherence-based lottery with an expected value of $2.80. Patients will observe the accumulation of any winnings (with perfect adherence, these winnings will average $256 every quarter and $128 in the split incentive arm in which incentives are shared between patients and physicians). Patients will be told they will receive these lottery winnings only if their LDL, chemically assessed each quarter, has met the outcome goals - an approach combining frequent feedback and daily engagement to stimulate adherence and using loss aversion to further augment motivation. Patients will only be eligible for the daily lottery if they are taking a cholesterol-lowering medication at the time of the lottery drawing. Assessment that a patient is taking a cholesterol-lowering medication will be based upon a patient's answer to the question "Do you take any prescribed medications to lower your cholesterol?" at baseline and 6 months, and whether a cholesterol-lowering medication is noted in the patient's Epic electronic medical record at the time of the lottery drawing. Data pulls of patients' medical records will occur at least daily and in an automated fashion using the PICARD system, previously described in this protocol. Patients will be exempt from the baseline blood draw if they have received the necessary labs within the 8 weeks prior to the receipt of the patient's consent form, and if these labs took place within the setting of the University of Pennsylvania Healthcare System. Patient post-study interviews: We will conduct three waves of interviews: [1] eligible participants who declined to enroll; [2] 40 (10 per arm) participants who enrolled but did not complete the intervention; [3] 120 (30 per arm) participants who were least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm.166 Those who drop out will be offered $15 incentives; the least and most successful participants will be offered $25. Examples of topics that will guide full script development include motivations for enrolling, perceived benefits and barriers to participation, and the impact of incentives. Patient post-study focus groups: We will conduct three focus groups of 8-10 participants at each of the two sites, moderated by Dr. Shea: one among participants for whom the intervention effects were negligible, one for whom the intervention effects were moderate to large, and one mixed, general group. Groups will last 60 minutes and will be recorded. Participants will be offered $40 incentives. We will examine perceived impact of the financial incentives, barriers faced in changing behaviors, and changes to the intervention that might help more people. We will also discuss unanticipated effects,

such as how participation may have changed the physician-patient relationship or elements of health behaviors outside of the health care context.

Table 1. Patient Payment Schedule

Description of Compensation	Amount of Compensation
Baseline Blood Draw	$50
Blood Draw at Months 3,6,and 9	$40 each
Blood Draw at Month 12	$80
Blood Draw at Month 15	$80
Questionnaires	$25
Interview	$25(subjects who complete the study) or $15 (subjects who drop out of the study)
Focus Group	$40

25. Study Procedures

25.1. Consent

25.1.1. Patient Consenting Process

Eligible patients will be invited to join the study, and those interested will either consent through the online Way to Health platform, which will explain the study procedures, risks, benefits and voluntary nature of participation, or sign a paper consent form. Potential participants will be offered the opportunity to ask study staff questions about participation in the study. They will be provided the opportunity to review the consent form at their leisure and talk to friends, family and others before making a decision about participating.

Patients will be given ten days after sending letters of introduction to the study to enroll in the study via the Way to Health platform. If during that time the patient does not enroll via the Way to Health platform and does not actively call our research team to opt out of the study, the patient's contact information will be forwarded to the Geisinger Survey Research Unit call center. In order for the Geisinger Survey Research Unit call center to contact and enroll patients to the study, the call center will need to access the patient's name, address, phone number, and a unique study identification number, different from the patient's medical record number, only for those patients who do not enroll via the Way to Health platform. The

patient's name and phone number are necessary to allow the call center staff to contact the patient; the patient's study identification number is necessary because the data generated from the call center's telephone encounters with these patients will need to be married to the patient's profile in the study database. If the patient agrees to participate and satisfies the screening requirements, the subject will be sent a study packet with an informed consent document and a HIPAA authorization form to sign and return to the study team. The main part of the study will operate under a signed informed consent and HIPAA authorization.

25.1.2. Physician Waiver of Documentation of Consent

We are requesting a waiver of written informed consent for physicians. Eligible primary care physicians at will be mailed an opt-out letter. Those who do not opt out will be automatically enrolled in the study. A baseline visit will be scheduled by study staff. Staff will meet with the physician to review study procedures, provide a web portal orientation, and do a short baseline survey. Study procedures will be summarized using a study information handout. After randomizations, those physicians taking part in the physician incentive and split incentive arms will be asked to complete a survey regarding the use of incentives. Physicians will be paid by RVU credit for this baseline visit. We will use an opt-out mechanism for physician consent, since there is no appreciable risk to physicians in participating (incomes can only go up); our discussions with the UPENN IRB indicate that this is likely to be acceptable. Given the potential for income supplementation with minimal incremental effort, we anticipate high physician interest in the study. Physicians are among the participants in this study. Several conceptual and logistic factors indicate that an opt out approach would have several advantages to an opt in approach. First, the study has no meaningful risks to patients associated with physician participation. Indeed, health systems around the nation and the world have implemented related financial incentive schemes to improve patient care. However, they have done so without evidence of effectiveness. This project aims to compare interventions whose fundamental approach is already in use in settings where no consent is required. Second, the goal of the study is to improve cholesterol management among patients with poor control. Such patients may be more likely to be clustered in providers who are less engaged and who would be relatively unlikely to volunteer to be part of a research study. Third, similar to point [1], there is no incremental risk to physicians involved in participation in this study. The only uncertain event is how much additional money physicians will receive as a result of the care they provide. Brief questionnaires are given to physicians at various times within the study, but those are administered with tacit and implied consent given their nature and are compensated with participant incentives. Fourth, there is ample precedent at Penn for opt-out consent of physicians in research studies that carry either no or minimal risk to physicians, and for which

there are considerable scientific benefits of broad participation (see, for example, the IRB protocols that approved the email-based opt-out consent for RCTs using Sunrise order entry at HUP to see if physicians prescribing of heparin and other drugs could be achieved by manipulating their electronic order templates). Fifth, although it is important to distinguish opt-out consent from informed consent, opt-out consent is just another term for simple consent, and there are well-developed normative arguments for why simple consent is actually preferred to true informed consent under certain circumstances (see: Whitney, McGuire, McCullough. A Typology of Shared Decision-Making, Informed Consent, and Simple Consent. Ann Intern Med 2003; 140:54-59). The key features guiding which circumstances are appropriate for choosing simple vs. informed consent are generally (i) the level of risk (which low or none favoring simple) and (ii) the a priori probability that all people to whom the choice is presented will have true preferences in the default direction (with greater a priori probability favoring simple consent). The gains to this study of using an opt out approach are in fact informed by the very principles of behavioral economics that underlie the study as a whole: [a] All studies are enhanced by the generalizability achieved with more universal participation; [b] It is logical that given the zero to limited risk of this study to physicians and the potential for gain that all or most physicians would want to participate; and [c] non participation would probably in most cases reflect a physician simply failing to complete a consent form rather than not wanting to participate, meaning that physicians might just not get around to completing a consent form when in most cases we suspect they would want to. This is a well-known phenomenon of human behavior that this study targets in its clinical endpoint of LDL Cholesterol management. However, those physicians who truly do not want to participate can of course opt out and we will make it easy for them to do so. Overall, the opt out mechanism preserves participant choice, makes the study easier to administer, and probably best reflects the appropriate default for a study with this particular risk profile and in which the benefits to participants (both patients and physicians) are potentially significant. Both physicians and their enrolled patients will be given a debriefing letter following their completion of all study procedures. The letter will describe the four study arms and states the reason for non-disclosure of this information prior to their finishing the study. These are enclosed with this application.

25.1.2.1. Waiver or Alteration of Informed 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

25.1.2.2. Minimal Risk

In this study physicians will be offered extra money if they are successful in managing lipids. There is no possibility of them getting less or otherwise experiencing risks or downsides from participation.

25.1.2.3. Impact on Subject Rights and Welfare

We will give physicians an opt out if they don't want to participate and we do not think the waiver will have any conceivable adverse effects on the rights or welfare of the physician participants.

25.1.2.4. Waiver Essential to Research

We will have very limited time with the physicians for the enrollment process and will need to streamline this as much as possible for the enrollment to be successful. Elements of the enrollment visit will include an introduction to the study, randomization to a study arm, and the completion of study-related paperwork and questionnaires.

25.1.2.5. Additional Information to Subjects

We will provide all physicians with full debriefing about the study aim and objectives and results at the conclusion of the study.

25.1.3. Written Statement of Research

This study operates under a written statement of research.

25.2. Procedures

25.2.1. Baseline pre-treatment assessment for patients

Potentially eligible patients will be sent letters inviting them to participate. Patients interested in enrolling who agree to provide consent (See §E.2.a.) will complete an intake form and consent using, at their preference, either our web portal, or by paper. Patients enrolling by

paper may be mailed the consent form, in which case patients will be asked to sign and mail back the consent form to the study staff. Scheduling of baseline LDL and ensuring LDL is within study parameters is the final step in confirming eligibility

25.2.2. Randomization

Randomization of physicians to one of the 4 study arms will be performed through the Way to Health platform. Randomization will be stratified by primary site (Geisinger, Penn or HVMA). After confirmation of patient eligibility, research staff will notify each patient participant of assignment (based on the assignment their physician has received) using their preferred means of communication (text message, email, phone) and ask for confirmation of receipt. Both patients and physicians will be given detailed instructions for the arm of the study to which they have been assigned and patients in all arms will be given the GlowCaps and instructions on use. Patients will be instructed to call study staff for all questions or problems with GlowCaps use. We will enroll up to 25 patients per physician.

Table 2: Laboratory Test Schedule

	Month					
	0	3	6	9	12	15
LDL Direct	X	X	X	X	X	X
Lipid Profile	X				X	
LFT	X	X			X	
HbA1c*	X				X	

* Only if the patient has diabetes

25.2.3. Scheduling

Physician participants will have 2 in-person visits, at baseline and 12 months. Patient participants will have six laboratory checks, at months 0, 3, 6, 9, 12, and 15 (Table 2). At the baseline and 12-month visit, we will test each participant's full lipid profile and hemoglobin A1c (diabetic patients only) to measure impact on all lipids from baseline to the primary outcome point as well as potential positive or negative spillover effects on glycemic control. Additionally, liver function tests (LFTs) will be completed at months 0, 3, and 12, to monitor patients for signs of liver damage. LDLs at baseline and at months 3, 6, 9 and 15 will be by direct, non-fasting LDL. Surveys will be completed at baseline and 12 months. Participants will return GlowCaps at the 15 month exit interview.

The Way to Health participant tracking system will automatically remind the study coordinators that each enrolled subject has a scheduled follow-up visit at the end of months 3, 6, 9, 12, and 15. We will obtain extensive contact information from each participant and update it at each follow-up visit. We will call participants who miss follow-up visits weekly for 4 weeks and send 2 letters during these 4 weeks. If any participants appear lost to follow-up, we will call their primary physician to ascertain their status.

25.2.4. Structure of Intervention Arms

For each of the incentive arms, eligibility for an incentive will be based on at least 10 mg/dl improvement in LDL within each quarter relative to the last quarter's target. This moving target is intended to foster continued engagement, as it is readily achievable and relevant to each patient or physician regardless of baseline LDL. For example, if a patient starts with an LDL of 200, eligibility for rewards (to physician or patient or both) will depend on LDL being at or below 190 at 3 months, 180 at 6 months, 170 at 9 months, and 160 at 12 months. Large early moves (e.g., if a patient's LDL drops from 200 to 170 in the first quarter) will continue to generate rewards if sustained: in this case, if the LDL remains at or below 170, the physician or patient will be eligible for incentives at the end of quarter 2 (when the target would be 180) and the end of quarter 3 (when the target would be 170). Incentives will not be provided at the end of quarter 4 unless the LDL was reduced a further 10 mg/dl to 160 or below. Patients/providers will automatically be eligible for incentives each quarter a patient achieves an LDL.< 100 (or another AHA target appropriate for the patient).

25.2.4.1. Physician Interventions

We will provide feedback on each patient's daily adherence using GlowCaps (all arms except usual care) as well as quarterly LDL (all arms except usual care) via the Way to Health online portal. The Way to Health portal will provide graphical feedback on patients' adherence and LDL from baseline to present and relative to goals and which can be used interactively with the EpicCare electronic health record to activate response options (have nurse call patient, intensify medications, refer to lipid clinic). Monthly patient reports will be mailed to providers until EPIC functionalities are developed to allow the delivery of these monthly reports via EPIC message. Physician incentives (total of $1,024 per year) will be determined solely by whether a given patient achieves the LDL reduction goals described above. This will be paid out as a reward separate from paychecks to increase salience.

25.2.4.2. Patient Incentives

At study entry, we will assign each participant a two-digit number. Each day GlowCaps will automatically upload adherence data for the previous day via the internet to a database housed at UPENN. The Way to Health system generates two-digit random daily lottery numbers and compares them electronically to the participant's two-digit identification number to determine

eligibility for awards. If the two digit number matches, which will happen about 1 in 100 times, the participant will be eligible to win $100 if s/he was adherent the day before. If the two digit number does not match, but either the first digit or second digit matches in the right place, the subject is eligible to win $10, which will happen about 1 in 5 times (more precisely, 18 in 100 times). The expected value of this lottery is $2.80/day such that total winnings per year for a fully adherent participant have an expected value of $1,022 (but could be more or less for an individual participant depending upon chance). As in our previous studies, we have designed the lottery-based incentives so that, each day, adherent participants receive rapid feedback about whether they won, and non-adherent participants receive rapid feedback about whether they would have won had they been adherent. This program incorporates key aspects of optimal design, including objective and reliable confirmation of behavior change at frequent intervals, large potential payments to reinforce the target behavior, frequent reinforcement using smaller payments, and the use of anticipated regret, a powerful motivator. We set the expected value of the lottery at about $3/day based on our success in significantly affecting weight loss and medication adherence with these parameters. In addition, there is evidence that a patient with established CVD has health expenditures ranging from $18,000-$30,000 per year, suggesting that incentives of $1,022, if effective, could be cost effective due to the potential savings.

Information on whether the participant won will be electronically transmitted each day by text message, phone, or email (patient choice) and will also be available on the patient's page on the Way to Health portal. Participants in the lottery group will be informed that they will receive their accumulated winnings at the end of the quarter only if their LDL meets the above goals; this is a way of using loss aversion to drive ongoing motivation to remain fully adherent through the entire quarter.

25.3. Timeline and Project Management

In-person meetings among the UPENN, Geisinger, CMU and Harvard team members are planned upon project initiation and annually thereafter. Ongoing project management will be facilitated by weekly or bi-weekly conference calls and the use of Basecamp online project management software. Team members will correspond as frequently as needed via email and telephone. To minimize the impact of geographic distance between the participation sites, the team will use available technologies appropriate to the particular meeting, including videoconferencing or webinar. The team will be organized similarly to how we have conducted multi-center studies previously, with project leaders at both the staff and faculty level and clear lines of responsibility for achievement of milestones.

Task Description	YEAR 1						YEAR 2						YEAR 3					
	S	N	J	M	M	J	S	N	J	M	M	J	S	N	J	M	M	J
CRF Design																		
Staff hiring and training																		
Subject recruitment																		
Baseline visits																		
Interventions																		
Follow-up visits																		
Data Analysis																		
Manuscripts/dissemination																		

25.4. Dissemination

Our dissemination activities will be led by LDI's research dissemination program to extend beyond publication in scholarly journals and presentations at professional meetings to reach specific audiences of approximately 4,000 leading figures in health care delivery with information they can use. We will utilize the expertise of the Study Advisory Board, which was designed with this in mind.

26. Analysis Plan

26.1. Statistical Considerations

LDL cholesterol is strongly associated with CVD outcomes—so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dl change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The

study has been powered for two phases of hypothesis testing. In the first, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms.

We will accrue 1400 participants evenly randomized across the 4 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (<10% per year) at both sites. Physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.017 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests in the second phase will vary from a maximum of 3 (if all three active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement). Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between 80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

26.2. Potential Limitations

We will minimize data loss by reimbursing all participants for study visits and mailing/emailing reminders plus follow-up phone calls for participants for their follow-up visits. We will address selection bias using sensitivity analyses about the characteristics of the larger, target population, making extreme assumptions about the variables that drive selection in different

directions and determining their effect upon inference. Contamination is possible but should not be problematic because our outcomes are individual, lipid management is not typically addressed in acute care visits by cross-covering providers, and we pay incentives only to incentive arm participants. The Hawthorne effect can improve outcomes in observed groups if participants are more likely to achieve goals than if they had not been observed, but this should be mitigated by a usual care control group that is similarly observed. We have guarded against Type I error by employing a conservative Bonferroni procedure for the three primary hypotheses as well as the Tukey honest significant difference approach to test the comparative effectiveness of the active interventions. A study period longer than 3 years would have allowed for better evaluation of sustainability post-active phase of intervention; however, we have included a 3 month post-intervention observation period that will give us considerable information on adherence given the daily GlowCaps information.

26.3. Data Analysis Plan

Prior to analysis, we will produce data summaries including graphical methods to assess data quality, examine central tendencies and distributional assumptions and randomization success. The primary analysis will consist of unadjusted intent-to-treat hypothesis tests for the significance of coefficients associated with treatment assignment in linear models of change in LDL; these models will adjust for the clustering of patients within physicians. We will also estimate regression models adjusted for the stratification variables and other covariates of interest (such as patient sex, income, race, baseline LDL, and study site), retaining these given evidence of confounding or predictive ability. We will employ a confounder selection method based on "change in estimate" criterion. We will assess interaction terms between the a priori potential effect modifiers such as study site, income level, race, and baseline LDL. All hypothesis tests will be two-sided and use adjusted Type I error rates as described above to maintain control of false positive test results. Models will be assessed using standard diagnostic techniques. We will assess the normality of the outcome and use transformations to improve the approximation if necessary or robust regression techniques, if suitable transformations cannot be found. Handling of missing data is an important issue in all RCTs. Follow-up data will be missing if participants miss visits and do not have labs taken. We anticipate low levels of loss to follow-up, but will conservatively assume that these patients fail to achieve any reduction in LDL and are non-adherent. We will compare dropout rates by arm for both patients and physicians, will attempt to find the reasons for missing data and will 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.

The analyses for secondary outcomes in Aims 1 and 2 will parallel those for the primary outcome.

26.4. Cost-Effectiveness Analysis

To assess the cost-effectiveness of the interventions, we will use analytic methods for economic evaluations in clinical trials. Our approach will be similar to Specific Aims 1 and 2 using cost as the outcome. We will use generalized linear models to adjust for the stratification variables and other factors. Cost-effectiveness ratios will be calculated as the difference in costs divided by the difference in LDL calculated under Specific Aims 1 and 2 for the within-trial analysis, with parametric 95% CIs for the cost per percentage point increase in adherence and acceptability curves. Standard errors and the correlation of the difference in cost and effect will be obtained using a bootstrap procedure. A further cost-effectiveness analysis from the societal perspective will be conducted to assess the impact of the LDL cholesterol reductions on CVD events measured as cost per QALY gained. To address uncertainty in the micro simulation model, we will also conduct a probabilistic sensitivity analysis (PSA) by defining probability distributions for the variables in the model used to calculate costs and effectiveness. We will use the results of the PSA to calculate confidence (or credible) intervals and acceptability curves. This research study will request Pennsylvania Health Care Cost Containment Council (PHC4) administrative discharge data for all the patients in the study, and this will be used to measure hospitalizations and resource utilization as part of the study's cost effectiveness analysis. In requesting this data, the study will transfer PHI (in this case, patients' social security numbers, dates of birth, genders and ID numbers, unique from the patients' study ID numbers) to and from PHC4 in a secure manner, and information regarding this transfer of PHI will be included in the patient informed consent/HIPAA documents.

26.5. Process Evaluation

To improve the design of future interventions, we will engage in a qualitative process evaluation throughout the study to learn why some study participants succeed in changing behavior and others do not, and what elements of the approach were acceptable to participants.

26.6. Patient Interviews

We will conduct two waves of interviews:

[1] 120 (30 per arm) participants who were the least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm. The least and most successful participants will be offered $25 for completing the phone interview. Examples of topics that will guide full script development include: motivations for enrolling, perceived benefits and barriers to participation, and the impact of financial incentives.

The research team will utilize the Mixed Methods Research Lab, a comprehensive qualitative analysis department at the University of Pennsylvania's Department of Family Medicine, for the conduct of patient interviews. The research lab is staffed with personnel who are experts in qualitative data collection, data management, and data analysis.

Procedures

All study sites will send patient contact information securely to MMRL in order to conduct the patient interviews. All study sites will be sending patient information to the MMRL via The University of Pennsylvania's SecureShare system, a HIPPA compliant transfer system that allows University members to share PHI.

Potential participants will be mailed an invitation letter sent by the study team (attached as a separate document). Patients will be provided opt-out instructions detailed in the invitation letter, prior to being contacted by the Mixed Method Research Lab. Personnel from the MMRL will contact patient subjects by phone and ask whether they would like to participate in a post-study phone interview. Personnel will follow a detailed phone script (attached as a separate document), explaining the elements of the interview. Verbal consent will be obtained prior to conducting the phone interview. The original signed consent form contains information regarding the post-study interview, therefore patients are aware in advance they may be contacted for a post-study interview. The phone interviews are expected to last approximately 30 minutes. All access to audio is password protected by the MMRL and is HIPAA compliant. All audio is only stored for set periods of time and then purged completely from the system.

Analysis

All phone interviews will be digitally recorded and sent to a transcription service (ADA Transcription) to be transcribed. ADA Transcription is a transcription agency located in Mount Holly, NJ. (http://www.adatranscription.com/). Identifying patient information will be de-identified prior to sending to ADA Transcription. The purpose of the analysis will be to extract themes and narratives relevant to the research questions. The data will be sent from the MMRL to ADA Transcription. Audio recordings of the interviews will be uploaded to ADA Transcription's website. ADA Transcription uses a file transfer program called Citrix Sharefile. All

communications between Citrix ShareFile and the user are encrypted using either Secure SocketLayer (SSL) or Transport Layer Security (TLS) encryption protocols and up to AES 256-bit encryption, a level of encryption that is similar to what banks use (which is higher than most medical facilities). The data will be encrypted during uploads and downloads, and ShareFile also encrypts stored files when they are at rest on our servers for an additional layer of security. ADA password protects all audio files and can track users' access to the data. All audio is only stored for set periods of time and then purged completely from the system. Transcripts are returned to the Mixed Methods Research Lab in password-protected Word files via email. The data will be sent back to the study sites via Penn+Box, as described in the section above.

Subject Confidentiality

All computerized study databases will be housed on a secure Windows NT server. The server is also protected by a firewall to limit unauthorized access to study information. The MMRL will use a confidential subject identification number to identify all subject study data in research databases. Once the interviews are completed, no personally identifiable information will be associated with participant's responses or their data. In addition to these measures, all information that is collected as part of this study will not be shared with other groups or investigators who are part of the research team, except as required by the Institutional Review Board for the protection of human subjects. Further, data that are prepared for statistical analyses will be de-identified and will be stored in study databases using a confidential identification number.

Subject Privacy

Each participant will be assigned a unique ID number. The link between name and ID number will be kept in a separate database that is accessible only to the key study personnel. Names of participants will not be included on the transcripts that derive from the interviews. After each digital recording has been transcribed, it will be destroyed. We will take extensive precautions to protect the privacy of subjects. A key containing information will be kept in locked file cabinets until study interviews are completed and the data have been checked for completeness and accuracy.

Consent Process Overview

Prior to participation, all participants will be asked to provide verbal consent. These documents will be read aloud by the individual conducting the interview. It will be made clear to all subjects that all information will be kept confidential and that their participation is entirely voluntary and they are allowed to leave or withdraw consent at any time.

Potential Study Risks

There are minimal risks involved in participating in the phone interviews. There is a slight risk of potential breaches of confidentiality for subjects participating in the phone interviews. Every effort will be made to maintain subject privacy and confidentiality.

Potential Study Benefits

From the perspective of those interviewed, there are few individual benefits from participating in the interviews than being given an opportunity to voice their personal experiences and opinions about participating in the Way to Heart Health Study. Interview participants might also benefit from feeling that their efforts will affect positive change in patient health outcomes.

26.7. Provider interviews

During year 3, Dr. Shea and staff will conduct 30 in-depth interviews with physician participants, using a written script, similar to the patient post-study interview script. We will examine how participation in this intervention influenced interactions with patients and solicit narratives describing patient experiences that provide a deeper understanding of the impact of trial arms on provider patient interactions. We will ask how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Participants will be offered RVU credit incentives.

26.8. Exit Surveys

At trial end, all provider and patient participants will complete exit surveys administered on the telephone or through the Way to Health platform (dependant on initial choice in enrollment mechanism). These surveys will systematically assess acceptability of the study and its various components, as well as possible effects in other domains including conditions other than cardiovascular risk, and effects other than health care. We will conduct surveys on attitudes towards using incentives, and trust in physicians, at baseline and at completion of the study. As noted above, patients will receive $25 after completing the baseline visit (of which the survey forms a part).

At conclusion all physicians will be asked the same set of general questions, and those in the incentive arms a modified version of the specific questions, to ascertain if participation in the study has led to a change in attitudes. As noted above, physicians will be paid by RVU credit for completion of the baseline visit.

26.9. Qualitative Data Analysis and Management of Focus Groups

All patient interviews and focus groups will be audio-taped, transcribed, and content analyzed, with analyses based on the grounded theory approach. We will use NVivo 8.0 to manage the data. Two independent reviewers will code the transcripts; Drs. Shea and Metlay will resolve discrepancies.

27. Investigators

The team includes investigators experienced in clinical medicine, health behavior interventions, clinical trials, behavioral economics, cost-effectiveness analysis, and psychometrics and program evaluation.

27.1. Multiple PIs

Dr. Kevin Volpp directs the LDI CHI and the NIA-funded PENN-CMU Roybal P30 Center on Behavioral Economics and Health and is Associate Professor of Medicine at the UPENN School of Medicine (SOM) and Associate Professor of Health Care Management at the Wharton School. He has led numerous studies of patient financial incentives. Dr. David Asch is the Robert D Eilers Professor of Health Care Management and Economics at the Wharton School and the UPENN SOM and the Executive Director of LDI. He is a well-known authority on the clinical and economic decisions of patients and providers.

27.2. Statistical Analysis

Dr. Andrea Troxel (Co-I, Statistician) is Professor of Biostatistics at UPENN and Director of Biostatistics for LDI CHIBE. She has 15 years of experience in the design, conduct, and analysis of clinical studies, including randomized trials that involve repeated measurements.

27.3. Cost Effectiveness Analysis

Dr. Henry Glick (Co-I) is a leading cost effectiveness expert who has led economic analyses for many randomized controlled trials. Dr. Tom Gaziano (Co-I) is an Assistant Professor of Medicine at Harvard Medical School and Co-Director of the CVD Working Group at the Center for Health

Decision Science at the Harvard School of Public Health (HSPH) and an expert in the cost-effectiveness of CVD interventions. Dr. Milton Weinstein (Co-I) is the Henry J. Kaiser Professor of Health Policy and Management at HSPH and is a leading expert in modeling the long term cost-effectiveness of interventions. Drs. Gaziano and Weinstein have done extensive work modeling the impact of better LDL control on longer-term CVD outcomes.

27.4. UPenn Site

Dr. Mark Weiner (Co-I) is Associate Professor of Medicine and Director of Clinical Research Informatics at UPENN. Dr. Ron Barg, Director of CCA, (Co-I) has extensive experience implementing trials in their network

27.5. Geisinger Site

Dr. Walter Stewart, Director, Geisinger Center for Health Research (Site PI Geisinger) has extensive experience in health services research and working with the Geisinger Clinic on large scale studies. Drs. Stewart and JB Jones (Co-I) have extensive experience testing web-based tools that interact with EHRs to deliver highly tailored guidance at the point of encounter, integrate patient preferences into exam room dialogue, and obtain and present patient reported data at appropriate times during encounters to foster tailored care decisions. Dr. Peter Berger, Director of the Geisinger Center for Clinical Studies (Co-I) is a Cardiologist internationally recognized for his expertise in clinical trials design and implementation. Dr. Tom Graf, (Co-I) is the Chairman of the Community Practice Network as will serve as a key liaison to the Geisinger Clinic.

13.7 Harvard Vanguard Medical Associates Site

Dr. Thomas Sequist, Director of Research, Harvard Vanguard Medical Associates (Site PI), is an assistant professor of medicine and health care policy at Harvard Medical School and Brigham and Women's Hospital. He practices internal medicine at the HVMA Kenmore site and is a recognized authority on ethnic and racial disparities in health outcomes. Dr. Sequist works closely with the leadership of HVMA on a wide spectrum of quality improvement projects involving health information technology, disease registries, organizational change and patient and provider education.

13.8 Behavioral Economics

Dr. Meredith Rosenthal (Co-I) is Associate Professor of health economics and policy at the Harvard University School of Public Health (HSPH) and a leading authority on P4P incentives. Dr. George Loewenstein (Co-I) is the Herbert A. Simon Professor of Economics and Psychology at Carnegie Mellon University and a founder of the fields of behavioral economics and neuroeconomics. Dr. Jennifer Lafata (Consultant), a Professor at Virginia Commonwealth University who has extensive experience in quality improvement initiatives for providers.

13.8 Process Evaluation

Dr. Judy Shea (Co-I) is the Associate Dean of Medical Education at UPENN SOM and an experienced leader in psychometrics and process evaluation. Dr. Joshua Metlay (Co-I) is Professor of Medicine and Epidemiology at UPENN SOM and an expert in process implementation.

13.9 Advisory Board

Dr. Harlan Krumholz, Hines Professor of Medicine, Yale; Francois De Brantes, CEO Bridges to Excellence, a major initiative to transform incentives in physician payment; Dr. Ron Paulus, the Chief Medical and Chief Innovation Officer at Geisinger; Ralph Muller, the CEO of the UPENN Health System and a former member of MedPAC; and Dr. Barbara Kahn, an expert in consumer behavior who is Dean of the School of Business Administration at the University of Miami.

28. Human Research Protection

28.1. Research Staff

All study investigators and study staff who work with this data will have undergone all of the required human subjects training. They will work with the data in password protected files and once interviews or focus groups are completed the responses will be separated from the identifying information.

28.2. Participating Institutions

The proposed research project will take place at the Leonard Davis Institute Center for Health Incentives (LDI CHI) at the University of Pennsylvania (UPENN), the Geisinger Health System, and research faculty offices involved in study design and analysis at Harvard University and Carnegie Mellon University; these sites provide substantial research experience, infrastructure support, and expertise in areas important to this project. Note that faculty at Harvard University and Carnegie Mellon University will have access to only de-identified data.

28.3. Data Confidentiality

The following methods will be employed to protect patient PHI for this research study:

☒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.
☐A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☐Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

28.3.1. Subject Confidentiality

To assure that patient and physician confidentiality is preserved, individual identifiers (such as name and medical record number/physician billing identifier) will only be used to link databases. All resulting datasets and computer files with identifiers will be password protected. Once linkage has been achieved, these linkage-identifiers will be dropped from the dataset and

each individual will be given a unique study identification number (ID). We will maintain one master list that will link study identification numbers to patient and physician identifiers. This list will be maintained by the principal investigators in a locked file drawer and on a highly secure server (with levels of security sufficient to maintain records from Medicare patients per CMS standards) to ensure file security and available to other research staff on a need to know basis only. The study ID will be used on all analytical files. Only deidentified analytical files will be shared with co-investigators at Carnegie Mellon University and Harvard University. The same procedure used for the analysis of automated data sources to ensure protection of participant information will be used for the survey data, in that patient participant identifiers will be used only for linkage purposes or to contact participants. The study identification number, and not other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. No results will be reported in a personally identifiable manner.

28.3.2. Subject Privacy

The UPENN Biomedical Informatics Consortium (BMIC) will be the hub for the hardware and database infrastructure that will support the project and where the project 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. GlowCaps devices will be linked to each participant through a unique device number. Data transmitted wirelessly to the Vitality server will not contain any identifiers. The information that will be transmitted includes 2 items -- the device number and date/time the cap was opened. Data is sent to the Vitality server via a secure HTTPS/SSL channel. the server. The server resides behind a dedicated firewall and is only available to limited Vitality staff on a need-to-know basis via a

secure, password-protected login. The server sits behind a fully-enclosed locked steel mesh cage housing. Data will be available to the investigators via an interface between the Vitality server and Way to Health web portal. Transmission of the data to the Way to Health portal will be via a secure HTTPS/SSL channel. 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.

28.3.3. 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.
- → Pennsylvania Health Care Cost Containment Council (PHC4), a group that provides information about the utilization of health services and the cost of health care for all hospitalizations in the state of Pennsylvania. Patients' social security numbers, dates of birth, and genders will be sent to them so that we can obtain a dataset that only contains study participants healthcare utilization information.
- → P'unk Ave., LLC, a software development company designing the Way to Health website. P'unk Ave. will not store any of the patients' PHI, but they will have access to de-identified patient information, for the purposes of website administration and development.
- → Wells Fargo, the company which processes study-related payments. Patients' addresses and account balances will be stored on their secure computers.

- → Twilio, Inc., the company which processes some study-related messages. Twilio will store patients' phone numbers on their secure computers.
- → Qualtrics, Inc., the company which processes most study-related surveys. Qualtrics will house de-identified answers to these surveys on their secure servers.
- → Quest Diagnostics, Inc., a company which will process some study-related laboratory checks. Patients' names, addresses and the results from these laboratory checks will be stored on their secure computers.
- → The National Institute on Aging, the study sponsors. Representatives from the National Institute on Aging would have access to all study-related PHI in case of an audit.
- → 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
- → Mixed Methods Research Lab (MMRL) at the University of Pennsylvania. Patients' names, gender (when applicable for accurate gender identification), phone numbers(s) will be sent to the MMRL for the conduct of patient telephone interviews via Penn+Box.

28.3.4. Data Protection

The following PHI identifiers may be collected and stored as part of this research:

☒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
☐Certificate/license numbers
☐Vehicle identifiers and serial numbers, including license plate numbers
☐Device identifiers/serial numbers
☐Web addresses (URLs)
☐Internet IP addresses

☐Biometric identifiers, incl. finger and voice prints
☐Full face photographic images and any comparable images
☐Any other unique identifying number, characteristic, or code
☐None

28.4. Populations Vulnerable to Undue Influence or Coercion

There are no highly vulnerable populations such as prisoners that will be enrolled in this study. The physician participants will be employees of Penn and Geisinger. We will be careful to make sure we don't induce any undue influence to enroll in the study by having trained study staff who are not colleagues or supervisors of the potential participants carry out the recruitment efforts and study procedures.

The following populations may be vulnerable to undue influence or coercion. Vulnerable populations recruited to the study are marked below:

☐Children (refer to SOP 501 for definition of children)
☐Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus)
☐Fetuses and/or Neonates
☐Prisoners
☐Other
☒None of the above populations are included in the research study

28.5. Data and Safety Monitoring

28.5.1. Data and Safety Monitoring Plan

The entire data and safety monitoring plan, including the members of the Data and Safety Monitoring Board (DSMB), will be submitted to the study sites' IRBs and subsequently to the funding IC for approval prior to the accrual of human subjects. Individual-level data for participants will be kept confidential and will only be stored on highly secure servers available for patient-level data. Only authorized project personnel will have access to the data and the data will be stored on servers only and not stand-alone PCs or laptops. All data will be reported at units of aggregation which make impossible the identification of individual patients and physicians and project managers. However, because we are contacting patients after their initial enrollment, there is an obvious need to have data with identifiers and contact information from the master enrollment files for each study. Study personnel who work with

this data will have undergone all of the required human subjects training. They will work with the data in password protected files and once interviews or focus groups are completed the responses will be separated from the identifying information.

The DSMB has been constituted and is listed below, under Data and Safety Monitoring Board.

This Data and Safety Monitoring Plan, including the composition of the DSMB, will require approval of the IRBs and the funding IC and will be modified as needed based on the review of these groups. The data and safety monitoring plan will have 3 parts. First, the BMIC will develop and implement methods of verifying entered data and of quality control. Second, the PIs will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the IRBs and funding agency promptly, as appropriate. They will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB (described below) at least biannually (and more frequently if there are serious adverse events). Unanticipated adverse events that occur at any participating site – Penn, HVMA, or Geisinger -- will be reported immediately to the Multiple PIs. Interim analyses are not planned. Third, there will be a DSMB responsible for monitoring the trial. Modifications to the protocol initiated by any participating site –Penn, HVMA, or Geisinger -- that affect the study procedures or increase the risk to participants will be submitted to all participating sites' IRBs. The Project Director, in collaboration with the three site Project Managers, will initiate the process of communicating protocol modifications between the sites and will ensure current site IRB approvals are obtained.

28.5.2. Data and Safety Monitoring Board

The DSMB will be composed of experts in cardiology, clinical trials, epidemiology, general internal medicine, and biostatistics, along with project PIs, Drs. Asch and Volpp, and statistician, Dr. Troxel, as non-voting members. The PIs will be responsible for maintaining communication between the DSMB and the individual project staff. We consider the proposed trial to be relatively low risk. Therefore, we have arranged for a monitoring committee that is assigned to review the study and staff training protocols, monitor the trial for safety and adverse events, and conduct bi-annual meetings. These members will not be involved directly with the trial. The members that we propose to serve on this committee and their activities are: 1. Donald Lloyd-Jones, MD, ScM is Chair of the Department of Preventive Medicine at Northwestern University's Feinberg School of Medicine; Director of the Program in Risk Estimation, Communication and Prevention; and an Associate Professor in Preventive Medicine and Medicine. Dr. Jones is a trained cardiologist and epidemiologist who participates in multiple NIH panels rewriting the cardiovascular disease clinical practice prevention guidelines. Dr. Jones will

serve as Chair of this project's DSMB. 2. Constantine Gatsonis, PhD is Professor of Medical Science (Biostatistics), Acting Head of the Biostatistics Section, and Director of the Center for Statistical Sciences at Brown University. Dr. Gatsonis conducts research in the design and analysis of clinical trials, as well as in methods in medical technology assessment, health services research and outcomes research. 3. Eugene Oddone, MD, MHSc is Professor of Medicine, Director of the Center for Health Services Research in Primary Care at the Durham Veterans Affairs Medical Center and Chief of General Internal Medicine at Duke University. He has previously served on multiple DSMBs. The DSMB will perform several duties. First, they will review and approve the research protocol and plans for data and safety monitoring prior to the study. Second, they will evaluate the progress of the trial. This will include assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and study outcomes. This assessment will be performed at meetings every 6 months during the clinical trial and more frequently if needed. Third, they will make recommendations to ensure that all of the issues above are appropriately addressed. Drs. Asch and Volpp as the study PIs will be responsible for responding to all recommendations of the DSMB and submitting DSMB reports to the UPENN IRB.

28.6. Risk/Benefit

28.6.1. Potential Study Risks

28.6.1.1. Risks Involved in the Main Study

There is minimal risk to subjects participating in this trial. For physicians, prescribing behavior will be monitored and financial incentives awarded if their study enrolled patients achieve improvement in cholesterol control. As prescribing behavior at this level is not usually monitored for physicians there is a risk of disclosure and breach of confidentiality. For all subjects, there is a risk of breach of confidentiality and privacy for completion of study surveys. Participants will be prescribed a cholesterol-lowering medication and treated with that medication only in accordance with standard clinical care. The interventions in this study attempt to improve adherence with prescribing what is standard of care on the part of physicians and taking medication among patients. In designing the intervention, we considered whether incentives might result in over-prescribing or overdosing to get higher incentives. These risks are mitigated by tying the incentives to reaching target LDL and maintaining it. Physicians or patients will receive no incentives for incremental decreases in LDL below target goal, and the amount of the incentive payment will not change based on incremental decreases in LDL below target goal in a given quarter. For patients, medication adherence behavior will be monitored and financial incentives awarded to those on some arms of the study if they

achieve a 10 mg/ dl reduction in LDL cholesterol over baseline or the previous quarters goal. Of note is that the use of the GlowCaps may facilitate a patient's adherence to physician recommended medication regimen(s).

Completion of the pre- and post-intervention assessment and survey by the patient as well as the pre- and post-intervention phlebotomy poses minimal risk. Risk involved is limited to that of discomfort, disclosure and breach of confidentiality.

28.6.1.2. Risks Involved in Process Evaluation and Cost-Effectiveness Analysis

The immediate benefits of this study for participants are minimal; however, as mentioned, so are the risks. Overall the risk benefit ratio is favorable given the long-term potential of this study to significantly contribute to our knowledge of financial incentive programs, and their impact on health and health-related behaviors

28.6.2. Potential Study Benefits

There are no anticipated benefits to physicians other than the financial incentives that they receive for study participation. There may be no benefits to patients other than the financial incentives that they receive for study participation. However, some patients may achieve better cholesterol control, which would lower their risk of a heart attack, as a result of participation in this study.

28.6.3. Alternatives to Participation

To not participate in the study.

28.6.4. Risk/Benefit Assessment

There is important knowledge to be gained from this project. The impact of financial incentives in general is only beginning to be understood and much remains to be learned about how best to design financial incentives as well as the applications for which they are best suited. While financial incentives have been tested in other health care applications there has yet to be an application that simultaneously targets patients and physicians. While improving care quality has been a national priority for decades, methods to achieve large and robust improvements in

quality of care have remained elusive, and significant quality deficits remain in U.S. health care. Although educational programs and life-style counseling are fundamental to effective cholesterol management, adherence to and titration of pharmaceutical therapy represents a major strategy by which cholesterol control can be achieved among patients at high risk of CVD. We have designed an innovative, theoretically-grounded financial incentive program that is potentially scalable and cost-effective through the leveraging of existing and emerging informatics infrastructure to address both medication adherence and titration. Study participation presents minimal risks to both providers and their patients.

Changes to Protocol

Summary of Amendments and Modifications

There were three substantive protocol amendments, all motivated by challenges in patient recruitment. On April 12, 2012, we eliminated two of the originally planned six arms of this cluster randomized trial (the choice architecture arm that involved nurse-practitioner management of lipids, and the physician outcome-based incentive arm without glowcaps feedback). These two arms were felt to be the least critical to the central goals of the study and were removed with the approval of the DSMB. At the same time, we widened the inclusion criteria to accept patients with lower baseline levels of LDL cholesterol. For similar reasons, on October 25, 2012 we added Harvard Vanguard Medical Associates (HVMA) as a site for physician and patient recruiting to supplement Penn and Geisinger.

Most other protocol modifications involved changes to recruitment strategies (for example, using the Geisinger call center for assistance with recruiting all patients regardless of site); minor changes to survey instruments and consent procedures; adding and deleting investigators to the study team, including the decision to use the Mixed Methods Research Laboratory (MMRL) at the University of Pennsylvania to facilitate the process analyses.

A list of protocol modifications is presented below.

Date: 11/22/11
Subject: Resubmission of Amendments, originally submitted 11/21/11
IRB Status: Approved 12/1/11

Summary of Change	Rationale for Change
Proposal to use Geisinger Survey Research Unit	To enhance the efficiency of patient recruitment

Date: 12/7/11
Subject: Submission of Amendments
IRB Status: Tabled 12/8/11

Summary of Change	Reason for Change
Minor revisions to the Way to Heart Health content list	**Minor revisions to our IRB-approved WTH content list**
Renaming of section 6 title	Non-substantive change to the name of an IRB-approved content list section to better describe the content of the content list section
Re-wording of content list text	Non-substantive change to the text of an IRB-approved content list section;

(under section 6 heading)	Further clarifying because participants complained about the ambiguity of existing content list text
Re-wording of a message sent to ineligible patient participants (Section 6C)	Non-substantive change to the text of an IRB-approved content list section; Further clarifying because participants complained about the ambiguity of an existing message sent to ineligible participants
Addition of address as a disclosed identifier	**To facilitate Geisinger Health System's mailing of baseline enrollment packets to Penn patients**
Addition of text regarding the disclosure of patient address information (section A3)	Addition of text describing the need for the disclosure of patient mailing address information to staff at Geisinger Health System
Ticking of box next to "Street Address, Apartment #, Precinct, or other geocode more geographically specific than zip code" (Section B)	To indicate that Street Address and Apartment # will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Ticking of box next to "City/Town, State and Zip Code" (Section B)	To indicate that City/Town, State and Zip Code will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Un-ticking of box next to "None of the Indirect Identifiers noted above will be collected" (Section B)	To indicate that indirect identifiers (City/Town, State and Zip Code) will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Minor revisions to the baseline/12-month patient survey	**Minor revisions to our IRB-approved patient survey**
Addition of question "Do you take any prescribed medications to lower your cholesterol?"	To facilitate the lottery override discussed in the revised protocol
Addition of skip logic to the "Thinking over the past 2 weeks, were there any days when you did not take your medicine(s) for such reasons?"	Further refined survey design, because it does not make sense to ask "Thinking over the past 2 weeks, were there any days when you did not take your medicine(s) for such reasons?" to patients who answer "no" to the question "Do you sometimes deliberately not take your medicine(s) to save money (for example, skipping a pill to make a prescription last longer)?"; To minimize respondent burden
Addition of text describing a lottery	**Because not all patients taking a medication to lower their cholesterol will**

override system	**have a medication to lower their cholesterol active in their Epic electronic medical record, and this study would like to make all participants who may be taking a medication to lower their cholesterol eligible for the lottery**
Minor revisions to the patient phone script	**Minor revisions to our IRB-approved script: All revisions are noted on the "Summary of Script Changes" document, and all changes are non-substantive changes wherein the flow of the call is refined with respect to the originally-submitted script, with the following exceptions:**
SCR_1A, SCR_2A and SCR_3A deleted	Because the medical monitor will follow up directly with patients and their PCPs to determine eligibility for the study; because patients answering "yes" to SCR_3 will always be excluded from participating in the study
RA_START, RABUSY, RAOINT, RAEXP, RAPHONE, and RAGOVT variables deleted	To minimize respondent burden and in an effort to recruit only interested subjects
Changing D6 response options and adding D6_1	In an effort to accurately collect race/ethnicity data
Adding variables FINI_1, FINI_2, FINI_2A, FINI_2B, FINI_3, and FINI_4	To streamline the recruitment process
Submission of Geisinger Agreement for Disclosure of PHI for Research	**Per protocol, PHI disclosure agreements will be submitted to the UPenn IRB**

Date: 12/8/11

Subject: Resubmission of Amendments, originally submitted 12/7/11

IRB Status: Approved 12/13/11

Summary of Change	Reason for Change
Minor revisions to the Way to Heart Health content list	**Minor revisions to our IRB-approved WTH content list**
Renaming of section 6 title	Non-substantive change to the name of an IRB-approved content list section to better describe the content of the content list section
Re-wording of content list text (under section 6 heading)	Non-substantive change to the text of an IRB-approved content list section; Further clarifying because participants complained about the ambiguity of existing content list text
Re-wording of a message sent	Non-substantive change to the text of an IRB-approved content list section;

to ineligible patient participants (Section 6C)	Further clarifying because participants complained about the ambiguity of an existing message sent to ineligible participants
Addition of address as a disclosed identifier	**To facilitate Geisinger Health System's mailing of baseline enrollment packets to Penn patients**
Addition of text regarding the disclosure of patient address information (section A3)	Addition of text describing the need for the disclosure of patient mailing address information to staff at Geisinger Health System
Ticking of box next to "Street Address, Apartment #, Precinct, or other geocode more geographically specific than zip code" (Section B)	To indicate that Street Address and Apartment # will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Ticking of box next to "City/Town, State and Zip Code" (Section B)	To indicate that City/Town, State and Zip Code will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Un-ticking of box next to "None of the Indirect Identifiers noted above will be collected" (Section B)	To indicate that indirect identifiers (City/Town, State and Zip Code) will be disclosed to Geisinger Health System, to facilitate Geisinger's mailing of baseline enrollment packets to Penn patients
Minor revisions to the baseline/12-month patient survey	**Minor revisions to our IRB-approved patient survey**
Addition of question "Do you take any prescribed medications to lower your cholesterol?"	To facilitate the lottery override discussed in the revised protocol
Addition of skip logic to the "Thinking over the past 2 weeks, were there any days when you did not take your medicine(s) for such reasons?"	Further refined survey design, because it does not make sense to ask "Thinking over the past 2 weeks, were there any days when you did not take your medicine(s) for such reasons?" to patients who answer "no" to the question "Do you sometimes deliberately not take your medicine(s) to save money (for example, skipping a pill to make a prescription last longer)?"; To minimize respondent burden
Addition of text describing a lottery override system	**Because not all patients taking a medication to lower their cholesterol will have a medication to lower their cholesterol active in their Epic electronic medical record, and this study would like to make all participants who may be taking a medication to lower their cholesterol eligible for the lottery**

Minor revisions to the patient phone script	**Minor revisions to our IRB-approved script: All revisions are noted on the "Summary of Script Changes" document, and all changes are non-substantive changes wherein the flow of the call is refined with respect to the originally-submitted script, with the following exceptions:**
SCR_1A, SCR_2A and SCR_3A deleted	Because the medical monitor will follow up directly with patients and their PCPs to determine eligibility for the study; because patients answering "yes" to SCR_3 will always be excluded from participating in the study
RA_START, RABUSY, RAOINT, RAEXP, RAPHONE, and RAGOVT variables deleted	To minimize respondent burden and in an effort to recruit only interested subjects
Changing D6 response options and adding D6_1	In an effort to accurately collect race/ethnicity data
Adding variables FINI_1, FINI_2, FINI_2A, FINI_2B, FINI_3, and FINI_4	To streamline the recruitment process
Submission of Geisinger Agreement for Disclosure of PHI for Research	**Per protocol, PHI disclosure agreements will be submitted to the UPenn IRB**

Date: 12/20/11

Subject: Submission of Amendments

IRB Status: Approved 12/22/11

Summary of Change	Reason for Change
Patients with a history of side effects to statins will not be enrolled to the study, instead of not enrolling patients with a history of side effects to *any* cholesterol-lowering medications	Although the study does not require a specific lipid lowering therapy, we want to ensure that statins are a treatment option given their particular effectiveness, more so than other pharmacological options, at reducing LDL.
Revised exclusion criteria text to screen out patients with "side effects" to statins, rather than patients with an "allergy" to statins	To clarify the screening question for patients
Patients with a history of side effects to statins will only be enrolled if the medical monitor reviews the patient's medical record and he/she determines that	Further refined subject safety procedures since the original protocol submission

the patient may safely participate in the study	
Patients with ALT > 80 U/L will not be enrolled to the study; eliminating AST study exclusion criteria	Further refined subject safety procedures since the original protocol submission; Because ALT is a more specific marker of hepatic injury than AST.
Patients with an active or progressive liver disease will not be enrolled to the study	Revised text for better clarification
Specified that the UPENN primary care Clinical Practices group is called the "Clinical Practices of the University of Pennsylvania" (CPUP)	Improving the clarity of study documents
Minor revisions to the patient phone script	Minor revisions to our IRB-approved script
Data and Safety Monitoring Plan	Further developed the safety monitoring plan, which also includes the role of the medical monitor, relative to the original protocol safety monitoring text
Submission of protocol and instructions for physicians' review of patient lists	Changes have been made after working with the privacy office in response to a subject complaint

Date: 1/10/12

Subject: Submission of Multiple Amendments

IRB Status: Approved 1/18/12

Summary of Change	Rationale for Change
Addition of Antonette Frasch, MD as a member of study staff	Addition of Antonette Frasch, MD to the study staff. She will perform the role of medical reviewer.
Submission of Patient Account Recovery Link letter	Addition of Account Recovery Link letter in order to instruct patients how to access their WTH profile if they enrolled over the phone. After a patient enrolls over the phone, consents, and is found eligible for the study, we create a participant profile for them on WTH.

	The profile monitors study progress and patients can use the link to access their account and follow their study progress online.
Minor revision to Call Center Recruitment Script	Revised the introduction section for clarification, explaining that we are working with their practice where they receive care, and that their primary care physician is also participating in the study. To facilitate the success of our recruitment efforts.
Submission of Inclusion/Exclusion CRF	Addition of a Case Report Form, titled "Inclusion/Exclusion From" for documenting patient eligibility criteria.
Submission of Patient Online Tracking Form	For tracking the online enrollment process.
Submission of Physician Enrollment Visit Tracking Form	For documenting the elements of the physician enrollment visits.

Date: 1/31/12
Subject: Submission of Multiple Amendments
IRB Status: Approved 2/2/12

Summary of Change	Rationale for Change
Submission of DSMB minutes	Per Penn Manual for Clinical Research
Revisions to the HIPAA Waiver	Providing 'sex' in the file we will send to Geisinger (in addition to patient's name), to help Geisinger staff identify the patient's gender when calling the patient. Provide name of practice and physician name, in accord with our recently revised and approved "introduction section " of the telephone script

No longer using the StageCoach card	Because of operational issues with the StageCoach card
Submission of arm-specific Vitality GlowCap instructions	To provide detailed instructions for the use of the GlowCap
Revisions to the patient introduction letter	To collect information from patients regarding any potential medical issues due to statin use during the study

Date: 2/2/12
Subject: Exception to protocol
IRB Status: Approved 2/8/12

Summary of Change	Rationale for Change
Submission of documents related to a protocol exception allowing for an interpreted conversation between study staff and a potential participant	A participant is hearing impaired and wishes to enroll in the study over the phone

Date: 1/31/12
Subject: Submission of Multiple Amendments
IRB Status: Tabled 2/13/12

Summary of Change	Rationale for Change
Minor edits to the consent forms	To clarify who will receive access to PHI generated during the course of the study
Minor Revision to the patient introduction letter	Clarifying when patients should contact the study staff

Date: 2/13/12
Subject: Re-submission of amendments first submitted 1/31/12

Supplement to: Effect of financial incentives to physicians, patients, or both on lipid levels: a cluster-randomized clinical trial

IRB Status: Approved 2/17/12

Summary of Change	Rationale for Change
Edits to the consent forms and plans to re-consent	To include details about electronic medical records

Date: 2/21/12
Subject: Merging two separate protocols
IRB Status: Approved 3/1/12

Summary of Change	Rationale for Change
Merging the Grant Research Strategy Appendix with the Study Protocol	For greater simplicity and ease of pursuing future amendments

Date: 3/1/12
Subject: Revision to patient recruitment letter
IRB Status: Tabled 3/2/12

Summary of Change	Rationale for Change
Revised Patient Recruitment Letter	Simplifying letter and making study sound more appealing to patients

Date: 3/2/12
Subject: Revision to patient recruitment letter
IRB Status: Approved 3/6/12

Summary of Change	Rationale for Change
Revised Patient Recruitment Letter incorporating IRB suggestions	Simplifying letter and making study sound more appealing to patients

Date: 4/12/12
Subject: Study Design Change
IRB Status: Approved 4/16/12

Summary of Change	Rationale for Change
Based on slower than anticipated patient recruitment to date, we have had extensive discussions with our Data Safety Monitoring Board (DSMB) and our project officer at the National Institute on Aging (NIA) and they have given us two important recommendations to revise the study. 1. Drop 2 study arms (NP arm and the physician incentive without GlowCaps feedback arm). 2. Their recommendation is to allow the highest risk patients (10-year CVD risk of >20% or CAD equivalent) with LDLs of >120 mg/dL (as opposed to the current 140 mg/dL) and people with a 10-year CVD risk of 10-20% with LDLs of >140 mg/dL (as opposed to the current 170 mg/dL) to participate in the study. We would plan to keep the official goals (LDL<100 mg/dL and LDL<130 mg/dL, respectively) the same, and to provide the maximum incentive to anyone who achieved either a 10 point reduction in LDL cholesterol relative to the last quarter's goal, or who have reached the 100 or 130 mg/dL threshold.	While interesting, neither of these are of central importance and this would change our recruitment target to 1,400

Date: 4/26/12
Subject: Submission of Multiple Amendments
IRB Status: Tabled 5/1/12

Summary of Change	Rationale for Change
Submission of an e-mail recruitment letter	To reach out to a broader array of participants while using multiple and simultaneous recruitment methods
Minor edits to the Split Incentives GlowCap Instruction Sheet	Correcting a typographical error
Propose additional text in the opening sentence in the patient recruitment letter. “Are you interested in lowering your cholesterol and earning $405 along the way?”	To enhance our recruitment efforts

Date: 4/30/12
Subject: Resubmission of Amendments
IRB Status: Approved 5/16/12

Summary of Change	Rationale for Change
Further clarification regarding the request for text listed above	

Date:5/25/12
Subject: Submission of Multiple Amendments
IRB Status: Approved 6/1/12

Summary of Change	Rationale for Change
Staffing Change	Removal of Amanda Parant from the list of study personnel
Staffing Change	Addition of Lisa Wesby to the list of study personnel
Revisions to the physician recruitment letter	Reflecting recent protocol changes

Date: 6/20/12
Subject: Submission of Multiple Amendments
IRB Status: Approved 6/26/12

Summary of Change	Rationale for Change
Revisions to the letters for GlowCap Mailings	Further clarifying and simplifying patient-oriented study materials
Staffing Change	Addition of Lisa Wesby to the list of key study personnel
Revisions to the paper patient recruitment letter	To enhance uniformity among existing approved editions of the recruitment letter
Revisions to the e-mail recruitment letter	To enhance uniformity among existing approved editions of the recruitment letter
Submission of DSMB Meeting Minutes	Per Penn Manual for Clinical Research
Submission of 6-month Patient Followup Letter	Submission of Patient-Oriented Study Materials

Date: 7/18/12
Subject: Additional staff
IRB Status: Approved 8/7/12

Summary of Change	Rationale for Change
Staffing Change	Addition of Cristina Novak to the list of study personnel

Date: 8/5/12
Subject: Additional text in 6 month reminder letter for PHI being sent to CC
IRB Status: Approved 8/7/12

Summary of Change	Rationale for Change
Penn patients PHI to call center for 6 mo. survey	We are including additional text in the reminder letter for the small number of patients who were phone screened by the Penn team before the Geisinger call center was operating for our study. Therefore, this group of patients wasn't sent the version of the recruitment letter, which informs them in advance that the Geisinger Survey Research Unit's call center will be calling them on our behalf, unless they contact us in advance to opt out. The 6-month followup letter will now include text to clarify that the Geisinger Survey Research Unit's call center will call them to complete their 6-month survey, which was also previously approved by the IRB in November 2011.

Date: 9/1/12
Subject: Submission of Multiple Amendments
IRB Status: Approved 9/12/12

Summary of Change	Rationale for Change
Revisions to the 6-month patient survey (phone version)	Addition of Health Utilities Index questions & Resource Utilization

	questions, as stated in our original protocol and paralled to the IRB approved online version which was submitted on 7/25/11 and approved on 8/25/11.
Additional Staff	Addition of Beth Stearman and Kate Volpicelli to the study staff team. Kate Volpicelli will need to be added as key personnel, as she will need access to HSERA
Removal of key personnel	Gabriel Schwartz is no longer working on our research study

Date: 9/17/12
Subject: Patients switching to another physician
IRB Status: Approved 9/27/12

Summary of Change	Rationale for Change
Enrolled patients switching physicians within the practice: 1. Keep the patient in the same arm that they were enrolled in irrespective of what study arm their new study physician was randomized to. 2. In the event a patient may switch to a physician who is not enrolled in the study, we plan to keep this patient in his/her originally enrolled study arm	To preserve the patient's experience in the study

Date: 10/25/12
Subject: Addition of HVMA
IRB Status: Approved 11/28/12

Summary of Change	Rationale for Change	Document	Affected Page
Adding HVMA as an additional site.	To improve recruitment efforts, we are adding HVMA as an additional site.	• Revised protocol – Tracked changes • Revised protocol – Clean copy • Tom Sequist's CITI Training For re-submission: • HVMA IRB approval letter • amended BAA	Entire Doc

Date: 12/14/12; Resubmission: 2/12/13
Subject: Multiple Amendments
IRB Status: Approved 2/28/13

Summary of Change	Rationale for Change	Document	Affected Page
Adding John Mitt Coats and Caroline Carney to study personnel and removing Beth Stearman.	Submission of additional staff via HSERA as required by IRB. Previously received verbal approval for each to start working on the study by Christine Davison. Beth Stearman is no longer involved in the study.	CITI Training Certificate uploaded for Caroline Carney.	Entire Doc
Agreement for Disclosure of PHI – HVMA & Penn	Execution of Agreement for disclosure of PHI between HVMA & Penn per HVMA's request.	Fully executed Agreement for Disclosure of PHI between HVMA & Penn	Entire Doc
Fully executed Amendment to the HIPAA Business Associate Agreement	This is version contains signatures from key personnel at all three sites.	Amended BAA with designated signatories	Entire Doc

~~Email Version of the Patient Recruitment Letter~~ **[Removed on 2.12.13 – no longer necessary]**	~~Additional language added to the IRB approved email recruitment letter, as recommend by OACP and the IRB when potential subjects will be recruited via e-mail.~~	~~Email Version of Recruitment Letter (v12.12.12)~~	~~Entire Doc~~
Patient Reminder Letter for Screening Labs	A reminder letter to be mailed to participants who have consented, but have not yet completed the screening labs.	Patient reminder letter for screening labs 12.11.12	Entire Doc
Patient 12 Month Survey – Online & Phone Versions	The addition of Post Study System Usability Questionnaire (PSSUQ) questions to the patient 12-month survey. We have an online version and a phone version which will be administered depending on how the patient initially enrolled in our study.	▪ Patient 12 month survey online version 12.13.12 clean ▪ Patient 12 month survey online version 12.13.12 track changes ▪ Patient 12 month survey phone version 12.13.12 clean ▪ Patient 12 month survey phone version 12.13.12 track changes	Entire Doc

Date: 2/04/13
Subject: Protocol Deviations
IRB Status: reviewed and acknowledged on 3/14/13

Summary of Change	Rationale for Change	Document	Affected Page
Protocol deviation: inadvertent disclosure of PHI		• Clean copy • Copy reviewed by UPHS chief privacy officer • HSERA deviation submission (submitted 3.13.13)	

Date 3/11/13
Subject: Addition of Jay Lewis
IRB status: Approved 3/12/13

Summary of Change	Rationale for Change	Document	Affected Page
Addition of study personnel	Research coordinator will assist with study operations	• CITI training certificate	Entire Doc

Date: 3/12/13
Subject: Reminder Insert & CPUP Provider Recruit Letter
IRB Status: Approved 3/21/13

Summary of Change	Rationale for Change	Document	Affected Page
CPUP Provider Recruitment Letter	The letter used to recruit CPUP providers; similar to the letter used for CCA providers that was already IRB approved.	• CPUP Provider Recruitment Letter – Clean Copy • CPUP Provider Recruitment Letter – Tracked Changes	Entire Doc
Reminder/Enrollment Near Completion Insert	Insert to be included in initial mailings to remind participants that they should complete the screening process as soon as possible.	Reminder/Enrollment Near Completion Insert	Entire Doc

Date: 4/25/13
Subject: Study Enrollment Closing
IRB Status: Approved 4/25/13

Summary of Change	Rationale for Change	Document	Affected Page
Letter to patients	Patients needed to begin screening labs. The letter will include patient lab order and information on completing screening labs.	• Letter to patient	Entire Doc

Date: 4/29/13
Subject: Addition of Kai Xu
IRB Status: Approved 4/30/13

Summary of Change	Rationale for Change	Document	Affected Page
Addition of study personnel	Dr. Kai Xu will be joining our study team as an interim Medical Monitor. Our current Medical Monitor, Dr. Antonette Frasch, will be going on maternity leave from May – August 2013.	• CITI training certificate	Entire Doc

Date: 6/14/13
Subject: Addition of Lin Yang. DSMB minutes
IRB Status: Approved 6/17/13

Summary of Change	Rationale for Change	Document	Affected Page
Addition of study personnel	Lin Yang will be joining the data analysis team.	• CITI training certificate	Entire Doc
Submission of DSMB meeting minutes from meeting on April 19,2013	Meeting occurred and minutes need to be submitted.	• DSMB meeting minutes	Entire Doc

Date: 8/1/13
Subject: Revised GCC script at 12 Months

IRB Status: Approved 8/8/13

Summary of Change	Rationale for Change	Document	Affected Page
Revision of the Geisinger call center script (excluding survey) for the 12 M time point. This document provides clarification to patients about when the end of the study is.	Patients were unclear about whether the study ended after 12 or 15 months.	• Track changes • Clean copy of script	Entire Doc

Date: 8/27/13

Subject: Addition and removal of study personnel

Status: Approved 8/29/13

Summary of Change	Rationale for Change	Document	Affected Page
Adding Kelsey Gangemi as a Research Coordinator and as a study contact.	Kelsey joined the team as a Research Coordinator	• CITI training certificate for Kelsey Gangemi	Entire Doc
Removing the following personnel: Sarah Windawi, John Coats, Dawn Tice who no longer work on the study.	Personnel no longer work on study	N/A	
Removing Lisa Wesby from a study contact and add to key personnel.	Lisa's duties have changed	N/A	

Date: 9/26/13

Subject: Move David Shuttleworth from key study personnel list to study personnel list

Status: Approved 10/2/13

Summary of Change	Rationale for Change	Document	Affected Page
We are moving David Shuttleworth from the" key study personnel list" to the "study personnel list."	David will need access to HSERA for IRB submissions.	• None	Entire Doc

Date: 10/21/13

Subject: Utilization of the MMRL for post-study survey
Status: Approved 10/23/13

Summary of Change	Rationale for Change	Document	Affected Page
We will be utilizing the Mixed Methods Research Lab at the University of Pennsylvania, Department of Family Medicine, for the conduct and analysis of post-study patient interviews.	The Mixed Methods Research Lab (MMRL) is a comprehensive qualitative analysis department. The research lab is staffed with personnel who are experts in qualitative data collection, data management, and data analysis.	• Revised protocol – track changes • Revised protocol – clean copy • Patient Invitation letter • Patient phone script, including written statement of research for obtaining verbal consent • Confidentiality and Nondisclosure Agreement from ADA Transcription • ShareFile Security Overview	Entire Doc

Date: 11.19.13
Subject: HVMA pilot study
Status: Approved 12/2/13

Summary of Change	Rationale for Change	Document	Affected Page
A pilot study, stemming from protocol # 812701 will be conducted at the Harvard Vanguard Medical Associates site, a sub-site associated with the main trial. This pilot study is directly related to the RC4 protocol, which is looking at medication adherence and its relationship to financial incentives and health outcomes in populations at risk for CVD.	• Extra grant money used towards multiple pilot studies	• HVMA IRB Approval Letter • Protocol Summary	Entire Doc

Date: 12/3/13
Subject: PI Change
Status: Approved 12/19/13

Summary of Change	Rationale for Change	Document	Affected Page
Addition of Dr. Thomas Isaac: Dr. Thomas Isaac will be replacing Dr. Thomas Sequist as PI at the HVMA site.	• PI is leaving the HVMA site so new PI is added	• CITI training certificate for Thomas Isaac	Entire Doc
Omission of Dr. Thomas Sequist who will no longer act as PI at the HVMA site.	• PI is leaving the HVMA site	N/A	

Date: 12/20/13
Subject: DSMB meeting minutes
Status: Approved 12/23/13

Summary of Change	Rationale for Change	Document	Affected Page
Meeting minutes were submitted for the DSMB meeting that occurred on 12/6/13	• DSMB meeting occurred	• DSMB meeting minutes	Entire Doc

Date: 1/9/14
Subject: Addition of Wenli Wang
Status: Re-submitted with the addition of Wenli in HSERA and Approved 1/14/14

Summary of Change	Rationale for Change	Document	Affected Page
Wenli Wang will join the team as a data analyst	• Addition of study personnel	• CITI training certificate	Entire Doc

Date: 1/23/14
Subject: Addition and removal of PI at GHS and amended BAA and Agreement for Disclosure of PHI for pilot; addition of MMRL staff

Status: Approved 1/31/14

Summary of Change	Rationale for Change	Document	Affected Page
The addition and removal of Primary Investigators at Geisinger Health System.	• New PI (Annemarie Hirsch) will join GHS since previous PI (Walter Stewart) left GHS	• CITI training certificate for Annemarie Hirsch	Entire Doc
The submission of the amended Business Associate Agreement and Agreement for Disclosure of PHI for Research for an already IRB approved pilot study which will be conducted at Harvard Vanguard Medical Associates, a sub-site of the RC4 main trial.	• The pilot study, stemming from protocol # 812701 will be conducted at the Harvard Vanguard Medical Associates site, a sub-site associated with the main trial. The existing Business Associate Agreement and the existing Agreement for Disclosure of PHI has been amended, to include the additional pilot study.	• Amended Business Associate Agreement • Amended Agreement for Disclosure of PHI for Research between HVMA and Penn	Entire Doc
We are also adding the following staff personnel, from the Mixed Methods Research Lab, who may be working on our study: Shimrit Keddem, Breah Paciotti, Lisa Jacobs, Katie Kellom, Aderinola Adejare, Samuel Katz, Miles Davison, Ebony Easley, Karen Vaccaro, Dan Brooks, Charles Samuel Robinson, Eva Bugos	• Staff members at MMRL will be conducting post-study phone interviews with study participants	• N/A	

Date: 3/10/14
Subject: Addition of Emin Tahirovic
Status: Approved 3/12/14

Summary of Change	Rationale for Change	Document	Affected Page
Emin Tahirovic will join the team as a data analyst	• Addition of study personnel	• CITI training certificate	Entire Doc

Date: 4/04/14
Subject: Revisions to the post-study interview script for the MMRL
Status: Approved 4/9/14

Summary of Change	Rationale for Change	Document	Affected Page
• Revisions to the patient post-study interview script with the MMRL	• Minor revisions made for participant clarification	• CITI training certificate	Entire Doc

Date: 5/8/14
Subject: Additional question added to the physician interview script
Status: Approved 5/21/14

Date: 5/16/14
Subject: Revised PCP exit survey – one additional question added regarding incentives
Status: Approved 6/5/14

Date: 7/8/14
Subject: Addition of Darra Finnerty
IRB Status: Approved 7/15/14

Summary of Change	Rationale for Change	Document	Affected Page
Addition of study personnel	Research coordinator will assist with study operations.	• CITI training certificate	Entire Doc

Date: 7/29/14
Subject: Submission of DSMB minutes & addition of study staff, Michael Kopinski
IRB Status: Approved 7/30/14

Original Statistical Analysis Plan

1. Analysis Plan

28.7. Statistical Considerations

LDL cholesterol is strongly associated with CVD outcomes—so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dl change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The study has been powered for two phases of hypothesis testing. In the first, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms.

We will accrue 2100 participants evenly randomized across the 6 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (<10% per year) at both sites. Physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.01 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests in the second phase will vary from a maximum of 10 (if all five active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement).

Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between 80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

28.8. Potential Limitations

We will minimize data loss by reimbursing all participants for study visits and mailing/emailing reminders plus follow-up phone calls for participants for their follow-up visits. We will address selection bias using sensitivity analyses about the characteristics of the larger, target population, making extreme assumptions about the variables that drive selection in different directions and determining their effect upon inference. Contamination is possible but should not be problematic because our outcomes are individual, lipid management is not typically addressed in acute care visits by cross-covering providers, and we pay incentives only to incentive arm participants. The Hawthorne effect can improve outcomes in observed groups if participants are more likely to achieve goals than if they had not been observed, but this should be mitigated by a usual care control group that is similarly observed. We have guarded against Type I error by employing a conservative Bonferroni procedure for the five primary hypotheses as well as the Tukey honest significant difference approach to test the comparative effectiveness of the active interventions. A study period longer than 3 years would have allowed for better evaluation of sustainability post-active phase of intervention; however, we have included a 3 month post-intervention observation period that will give us considerable information on adherence given the daily GlowCaps information.

28.9. Data Analysis Plan

Prior to analysis, we will produce data summaries including graphical methods to assess data quality, examine central tendencies and distributional assumptions and randomization success. The primary analysis will consist of unadjusted intent-to-treat hypothesis tests for the significance of coefficients associated with treatment assignment in linear models of change in LDL; these models will adjust for the clustering of patients within physicians. We will also estimate regression models adjusted for the stratification variables and other covariates of interest (such as patient sex, income, race, baseline LDL, and study site), retaining these given evidence of confounding or predictive ability. We will employ a confounder selection method based on "change in estimate" criterion. We will assess interaction terms between the a priori potential effect modifiers such as study site, income level, race, and baseline LDL. All hypothesis tests will be two-sided and use adjusted Type I error rates as described above to maintain control of false positive test results. Models will be assessed using standard diagnostic techniques. We will assess the normality of the outcome and use transformations to improve the approximation if necessary or robust regression techniques, if suitable transformations cannot be found. Handling of missing data is an important issue in all RCTs. Follow-up data will be missing if participants miss visits and do not have labs taken. We anticipate low levels of loss to follow-up, but will conservatively assume that these patients fail to achieve any reduction in LDL and are non-adherent. We will compare dropout

rates by arm for both patients and physicians, will attempt to find the reasons for missing data and will 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. The analyses for secondary outcomes in Aims 1 and 2 will parallel those for the primary outcome.

28.10. Cost-Effectiveness Analysis

To assess the cost-effectiveness of the interventions, we will use analytic methods for economic evaluations in clinical trials. Our approach will be similar to Specific Aims 1 and 2 using cost as the outcome. We will use generalized linear models to adjust for the stratification variables and other factors. Cost-effectiveness ratios will be calculated as the difference in costs divided by the difference in LDL calculated under Specific Aims 1 and 2 for the within-trial analysis, with parametric 95% CIs for the cost per percentage point increase in adherence and acceptability curves. Standard errors and the correlation of the difference in cost and effect will be obtained using a bootstrap procedure. A further cost-effectiveness analysis from the societal perspective will be conducted to assess the impact of the LDL cholesterol reductions on CVD events measured as cost per QALY gained. To address uncertainty in the micro simulation model, we will also conduct a probabilistic sensitivity analysis (PSA) by defining probability distributions for the variables in the model used to calculate costs and effectiveness. We will use the results of the PSA to calculate confidence (or credible) intervals and acceptability curves. This research study will request Pennsylvania Health Care Cost Containment Council (PHC4) administrative discharge data for all the patients in the study, and this will be used to measure hospitalizations and resource utilization as part of the study's cost effectiveness analysis. In requesting this data, the study will transfer PHI (in this case, patients' social security numbers, dates of birth, genders and ID numbers, unique from the patients' study ID numbers) to and from PHC4 in a secure manner, and information regarding this transfer of PHI will be included in the patient informed consent/HIPAA documents.

28.11. Process Evaluation

To improve the design of future interventions, we will engage in a qualitative process evaluation throughout the study to learn why some study participants succeed in changing behavior and others do not, and what elements of the approach were acceptable to participants.

28.12. Patient Interviews

We will conduct two waves of interviews:

[1] 180 (30 per arm) participants who were the least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm. The least and most successful participants

will be offered $25 for completing the phone interview. Examples of topics that will guide full script development include: motivations for enrolling, perceived benefits and barriers to participation, and the impact of financial incentives.

Procedures

Potential participants will be mailed an invitation letter sent by the study team (attached as a separate document). Patients will be provided opt-out instructions detailed in the invitation letter, prior to being contacted by study personnel. Study personnel will contact patient subjects by phone and ask whether they would like to participate in a post-study phone interview. Personnel will follow a detailed phone script (attached as a separate document), explaining the elements of the interview. Verbal consent will be obtained prior to conducting the phone interview. The original signed consent form contains information regarding the post-study interview, therefore patients are aware in advance they may be contacted for a post-study interview. The phone interviews are expected to last approximately 30 minutes..

Analysis

All phone interviews will be digitally recorded and sent to a transcription service (ADA Transcription) to be transcribed. ADA Transcription is a transcription agency located in Mount Holly, NJ. (http://www.adatranscription.com/). Identifying patient information will be de-identified prior to sending to ADA Transcription. The purpose of the analysis will be to extract themes and narratives relevant to the research questions. Audio recordings of the interviews will be uploaded to ADA Transcription's website. ADA Transcription uses a file transfer program called Citrix Sharefile. All communications between Citrix ShareFile and the user are encrypted using either Secure SocketLayer (SSL) or Transport Layer Security (TLS) encryption protocols and up to AES 256-bit encryption, a level of encryption that is similar to what banks use (which is higher than most medical facilities). The data will be encrypted during uploads and downloads, and ShareFile also encrypts stored files when they are at rest on our servers for an additional layer of security. ADA password protects all audio files and can track users' access to the data. All audio is only stored for set periods of time and then purged completely from the system. Transcripts are returned in password-protected Word files via email. The data will be sent back to the study sites via Penn+Box, as described in the section above.

Subject Confidentiality

All computerized study databases will be housed on a secure server. The server is also protected by a firewall to limit unauthorized access to study information. Study personnel will use a confidential subject identification number to identify all subject study data in research databases. Once the interviews are completed, no personally identifiable information will be associated with participant's responses or their

data. In addition to these measures, all information that is collected as part of this study will not be shared with other groups or investigators who are part of the research team, except as required by the Institutional Review Board for the protection of human subjects. Further, data that are prepared for statistical analyses will be de-identified and will be stored in study databases using a confidential identification number.

Subject Privacy

Each participant will be assigned a unique ID number. The link between name and ID number will be kept in a separate database that is accessible only to the key study personnel. Names of participants will not be included on the transcripts that derive from the interviews. After each digital recording has been transcribed, it will be destroyed. We will take extensive precautions to protect the privacy of subjects. A key containing information will be kept in locked file cabinets until study interviews are completed and the data have been checked for completeness and accuracy.

Consent Process Overview

Prior to participation, all participants will be asked to provide verbal consent. These documents will be read aloud by the individual conducting the interview. It will be made clear to all subjects that all information will be kept confidential and that their participation is entirely voluntary and they are allowed to leave or withdraw consent at any time.

Potential Study Risks

There are minimal risks involved in participating in the phone interviews. There is a slight risk of potential breaches of confidentiality for subjects participating in the phone interviews. Every effort will be made to maintain subject privacy and confidentiality.

Potential Study Benefits

From the perspective of those interviewed, there are few individual benefits from participating in the interviews than being given an opportunity to voice their personal experiences and opinions about participating in the Way to Heart Health Study. Interview participants might also benefit from feeling that their efforts will affect positive change in patient health outcomes.

28.13. Provider interviews

During year 3, Dr. Shea and staff will conduct 30 in-depth interviews with physician participants, using a written script, similar to the patient post-study interview script. We will examine how participation in this intervention influenced interactions with patients and solicit narratives describing patient experiences that provide a deeper understanding of the impact of trial arms on provider patient

interactions. We will ask how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Participants will be offered RVU credit incentives.

28.14. Exit Surveys

At trial end, all provider and patient participants will complete exit surveys administered on the telephone or through the Way to Health platform (dependant on initial choice in enrollment mechanism). These surveys will systematically assess acceptability of the study and its various components, as well as possible effects in other domains including conditions other than cardiovascular risk, and effects other than health care. We will conduct surveys on attitudes towards using incentives, and trust in physicians, at baseline and at completion of the study. As noted above, patients will receive $25 after completing the baseline visit (of which the survey forms a part).

At conclusion all physicians will be asked the same set of general questions, and those in the incentive arms a modified version of the specific questions, to ascertain if participation in the study has led to a change in attitudes. As noted above, physicians will be paid by RVU credit for completion of the baseline visit.

28.15. Qualitative Data Analysis and Management of Focus Groups

All patient interviews and focus groups will be audio-taped, transcribed, and content analyzed, with analyses based on the grounded theory approach. We will use NVivo 8.0 to manage the data. Two independent reviewers will code the transcripts; Drs. Shea and Metlay will resolve discrepancies.

Final Statistical Analysis Plan

1. Analysis Plan

1.1. Statistical Considerations

LDL cholesterol is strongly associated with CVD outcomes—so much so that even small movements in LDL are clinically meaningful. We use a 10 mg/dl change as our threshold, based on a meta-analysis by the Cholesterol Treatment Trialists (CTT) Collaboration on 90,000 patients from 14 trials in which such a change would equal about a 5% reduction in CVD events. Based on preliminary data from Geisinger and Penn the standard deviation of LDL is approximately 40 mg/dl at both sites and the intraclass correlation (ICC) of LDL measurements for patients within providers ranges from 0.01 (Geisinger) to 0.04 (Penn). While repeated assessments of LDL within patients are likely correlated, we do not incorporate any correlation since the assessments from which the change will be determined are quite far apart in time (12 months). To the extent that these assessments are correlated, power will be increased. The study has been powered for two phases of hypothesis testing. In the first, we will determine which of the active arms show a significant improvement over the control condition. In the second, we will compare the successful active arms to one another. For the second phase, we require sufficient power to detect a difference of at least 10 mg/dl. In the first phase, we require sufficient power to detect a difference of at least 15 mg/dl, since we anticipate greater differences between the active and control arms than among any two intervention arms.

We will accrue 1400 participants evenly randomized across the 4 arms of the study. While we recognize that some participants (patients and/or physicians) may drop out of the study, we have not inflated the sample size to accommodate dropout. Instead, we plan to conservatively assume that patient participants who drop out failed to achieve any reduction in their LDL; patient participants whose physician drops out will be encouraged to maintain study visits. Because we are randomizing physicians but treating the patient as the unit of analysis, we also incorporate a conservative ICC estimate of 0.04 to allow for a higher correlation in the study sample than the overall population. We have based our power calculations on having 150 physician subjects; however, to be conservative we will target an initial enrollment of 200 physicians. Turnover rates are low (<10% per year) at both sites. Physicians provide an average cluster size of about 14 patients per physician. Together, these assumptions result in a design effect of approximately 1.5. If we have more than 150 physicians and smaller cluster sizes, the power will increase. Because we are testing multiple hypotheses in each phase, we use several multiple comparisons corrections to maintain control of the family-wise Type I error rate (alpha). We use a Type I error rate of 0.017 in the first phase of testing, in which each active arm is compared to the control arm; 350 subjects per arm provide more than 90% power to detect a difference of 15 mg/dl in LDL decrease. In the second phase, we will use Tukey's honest significant difference approach to test all pairwise comparisons among any active arms that show significant improvement over control in the first phase. The number of hypothesis tests in the second phase will vary from a maximum of 3 (if all three active arms show significant improvement) to a minimum of 2 (if only two active arms show improvement). Using simulations to characterize a wide variety of scenarios, 350 subjects per arm provide between

80% and 85% power to detect a difference of 10 mg/dl in average LDL decrease between active intervention arms.

1.2. Potential Limitations

We will minimize data loss by reimbursing all participants for study visits and mailing/emailing reminders plus follow-up phone calls for participants for their follow-up visits. We will address selection bias using sensitivity analyses about the characteristics of the larger, target population, making extreme assumptions about the variables that drive selection in different directions and determining their effect upon inference. Contamination is possible but should not be problematic because our outcomes are individual, lipid management is not typically addressed in acute care visits by cross-covering providers, and we pay incentives only to incentive arm participants. The Hawthorne effect can improve outcomes in observed groups if participants are more likely to achieve goals than if they had not been observed, but this should be mitigated by a usual care control group that is similarly observed. We have guarded against Type I error by employing a conservative Bonferroni procedure for the three primary hypotheses as well as the Tukey honest significant difference approach to test the comparative effectiveness of the active interventions. A study period longer than 3 years would have allowed for better evaluation of sustainability post-active phase of intervention; however, we have included a 3 month post-intervention observation period that will give us considerable information on adherence given the daily GlowCaps information.

1.3. Data Analysis Plan

Prior to analysis, we will produce data summaries including graphical methods to assess data quality, examine central tendencies and distributional assumptions and randomization success. The primary analysis will consist of unadjusted intent-to-treat hypothesis tests for the significance of coefficients associated with treatment assignment in linear models of change in LDL; these models will adjust for the clustering of patients within physicians. We will also estimate regression models adjusted for the stratification variables and other covariates of interest (such as patient sex, income, race, baseline LDL, and study site), retaining these given evidence of confounding or predictive ability. We will employ a confounder selection method based on "change in estimate" criterion. We will assess interaction terms between the a priori potential effect modifiers such as study site, income level, race, and baseline LDL. All hypothesis tests will be two-sided and use adjusted Type I error rates as described above to maintain control of false positive test results. Models will be assessed using standard diagnostic techniques. We will assess the normality of the outcome and use transformations to improve the approximation if necessary or robust regression techniques, if suitable transformations cannot be found. Handling of missing data is an important issue in all RCTs. Follow-up data will be missing if participants miss visits and do not have labs taken. We anticipate low levels of loss to follow-up, but will conservatively assume that these patients fail to achieve any reduction in LDL and are non-adherent. We will compare dropout rates by arm for both patients and physicians, will attempt to find the reasons for missing data and will

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. The analyses for secondary outcomes in Aims 1 and 2 will parallel those for the primary outcome.

1.4. Cost-Effectiveness Analysis

To assess the cost-effectiveness of the interventions, we will use analytic methods for economic evaluations in clinical trials. Our approach will be similar to Specific Aims 1 and 2 using cost as the outcome. We will use generalized linear models to adjust for the stratification variables and other factors. Cost-effectiveness ratios will be calculated as the difference in costs divided by the difference in LDL calculated under Specific Aims 1 and 2 for the within-trial analysis, with parametric 95% CIs for the cost per percentage point increase in adherence and acceptability curves. Standard errors and the correlation of the difference in cost and effect will be obtained using a bootstrap procedure. A further cost-effectiveness analysis from the societal perspective will be conducted to assess the impact of the LDL cholesterol reductions on CVD events measured as cost per QALY gained. To address uncertainty in the micro simulation model, we will also conduct a probabilistic sensitivity analysis (PSA) by defining probability distributions for the variables in the model used to calculate costs and effectiveness. We will use the results of the PSA to calculate confidence (or credible) intervals and acceptability curves. This research study will request Pennsylvania Health Care Cost Containment Council (PHC4) administrative discharge data for all the patients in the study, and this will be used to measure hospitalizations and resource utilization as part of the study's cost effectiveness analysis. In requesting this data, the study will transfer PHI (in this case, patients' social security numbers, dates of birth, genders and ID numbers, unique from the patients' study ID numbers) to and from PHC4 in a secure manner, and information regarding this transfer of PHI will be included in the patient informed consent/HIPAA documents.

1.5. Process Evaluation

To improve the design of future interventions, we will engage in a qualitative process evaluation throughout the study to learn why some study participants succeed in changing behavior and others do not, and what elements of the approach were acceptable to participants.

1.6. Patient Interviews

We will conduct two waves of interviews:

[1] 120 (30 per arm) participants who were the least and most successful in improving LDL. Likely, saturation will be achieved with 15-30 interviews per arm. The least and most successful participants will be offered $25 for completing the phone interview. Examples of topics that will guide full script

development include: motivations for enrolling, perceived benefits and barriers to participation, and the impact of financial incentives.

The research team will utilize the Mixed Methods Research Lab, a comprehensive qualitative analysis department at the University of Pennsylvania's Department of Family Medicine, for the conduct of patient interviews. The research lab is staffed with personnel who are experts in qualitative data collection, data management, and data analysis.

Procedures

All study sites will send patient contact information securely to MMRL in order to conduct the patient interviews. All study sites will be sending patient information to the MMRL via The University of Pennsylvania's SecureShare system, a HIPPA compliant transfer system that allows University members to share PHI.

Potential participants will be mailed an invitation letter sent by the study team (attached as a separate document). Patients will be provided opt-out instructions detailed in the invitation letter, prior to being contacted by the Mixed Method Research Lab. Personnel from the MMRL will contact patient subjects by phone and ask whether they would like to participate in a post-study phone interview. Personnel will follow a detailed phone script (attached as a separate document), explaining the elements of the interview. Verbal consent will be obtained prior to conducting the phone interview. The original signed consent form contains information regarding the post-study interview, therefore patients are aware in advance they may be contacted for a post-study interview. The phone interviews are expected to last approximately 30 minutes. All access to audio is password protected by the MMRL and is HIPAA compliant. All audio is only stored for set periods of time and then purged completely from the system.

Analysis

All phone interviews will be digitally recorded and sent to a transcription service (ADA Transcription) to be transcribed. ADA Transcription is a transcription agency located in Mount Holly, NJ. (http://www.adatranscription.com/). Identifying patient information will be de-identified prior to sending to ADA Transcription. The purpose of the analysis will be to extract themes and narratives relevant to the research questions. The data will be sent from the MMRL to ADA Transcription. Audio recordings of the interviews will be uploaded to ADA Transcription's website. ADA Transcription uses a file transfer program called Citrix Sharefile. All communications between Citrix ShareFile and the user are encrypted using either Secure SocketLayer (SSL) or Transport Layer Security (TLS) encryption protocols and up to AES 256-bit encryption, a level of encryption that is similar to what banks use (which is higher than most medical facilities). The data will be encrypted during uploads and downloads, and ShareFile also encrypts stored files when they are at rest on our servers for an additional layer of security. ADA password protects all audio files and can track users' access to the data. All audio is only stored for set periods of time and then purged completely from the system. Transcripts are returned to

the Mixed Methods Research Lab in password-protected Word files via email. The data will be sent back to the study sites via Penn+Box, as described in the section above.

Subject Confidentiality

All computerized study databases will be housed on a secure Windows NT server. The server is also protected by a firewall to limit unauthorized access to study information. The MMRL will use a confidential subject identification number to identify all subject study data in research databases. Once the interviews are completed, no personally identifiable information will be associated with participant's responses or their data. In addition to these measures, all information that is collected as part of this study will not be shared with other groups or investigators who are part of the research team, except as required by the Institutional Review Board for the protection of human subjects. Further, data that are prepared for statistical analyses will be de-identified and will be stored in study databases using a confidential identification number.

Subject Privacy

Each participant will be assigned a unique ID number. The link between name and ID number will be kept in a separate database that is accessible only to the key study personnel. Names of participants will not be included on the transcripts that derive from the interviews. After each digital recording has been transcribed, it will be destroyed. We will take extensive precautions to protect the privacy of subjects. A key containing information will be kept in locked file cabinets until study interviews are completed and the data have been checked for completeness and accuracy.

Consent Process Overview

Prior to participation, all participants will be asked to provide verbal consent. These documents will be read aloud by the individual conducting the interview. It will be made clear to all subjects that all information will be kept confidential and that their participation is entirely voluntary and they are allowed to leave or withdraw consent at any time.

Potential Study Risks

There are minimal risks involved in participating in the phone interviews. There is a slight risk of potential breaches of confidentiality for subjects participating in the phone interviews. Every effort will be made to maintain subject privacy and confidentiality.

Potential Study Benefits

From the perspective of those interviewed, there are few individual benefits from participating in the interviews than being given an opportunity to voice their personal experiences and opinions about participating in the Way to Heart Health Study. Interview participants might also benefit from feeling that their efforts will affect positive change in patient health outcomes.

1.7. Provider interviews

During year 3, Dr. Shea and staff will conduct 30 in-depth interviews with physician participants, using a written script, similar to the patient post-study interview script. We will examine how participation in this intervention influenced interactions with patients and solicit narratives describing patient experiences that provide a deeper understanding of the impact of trial arms on provider patient interactions. We will ask how the intervention could be modified to increase likelihood of success, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. Participants will be offered RVU credit incentives.

1.8. Exit Surveys

At trial end, all provider and patient participants will complete exit surveys administered on the telephone or through the Way to Health platform (dependant on initial choice in enrollment mechanism). These surveys will systematically assess acceptability of the study and its various components, as well as possible effects in other domains including conditions other than cardiovascular risk, and effects other than health care. We will conduct surveys on attitudes towards using incentives, and trust in physicians, at baseline and at completion of the study. As noted above, patients will receive $25 after completing the baseline visit (of which the survey forms a part).

At conclusion all physicians will be asked the same set of general questions, and those in the incentive arms a modified version of the specific questions, to ascertain if participation in the study has led to a change in attitudes. As noted above, physicians will be paid by RVU credit for completion of the baseline visit.

1.9. Qualitative Data Analysis and Management of Focus Groups

All patient interviews and focus groups will be audio-taped, transcribed, and content analyzed, with analyses based on the grounded theory approach. We will use NVivo 8.0 to manage the data. Two independent reviewers will code the transcripts; Drs. Shea and Metlay will resolve discrepancies.

Summary of Changes to Statistical Analysis Plan

Two study arms were removed. As a result, the sample size was reduced from 2100 to 1400. The Bonferroni-corrected alpha level for the first phase of hypothesis testing was adjusted from 0.01 to 0.017. The maximum number of hypothesis tests in the second phase of testing was adjusted from 10 to 3.