Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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1. **Original Protocol**

   A. **ABSTRACT**

   Providing patients with financial incentives has been shown to promote exercise, weight loss, adherence to medical advice, and abstinence from smoking and other drug use. However, research on incentives to date has generally viewed them as if they were all-or-nothing, comparing behaviors in the presence versus the absence of incentives, and assuming that they worked similarly among different types of people. Yet, concepts from behavioral economics suggest that how and to whom incentives are delivered may affect their impact substantially. Thus, comparing incentive structures (e.g., should we create potential for gains vs. losses, or target individuals vs. groups?) and identifying patients for whom they work particularly well may elucidate mechanisms by which incentives alter behavior and inform the design of behavior-modifying interventions.

   This study will seek to compare 4 incentive structures that are based upon principles of behavioral economics, contingency management, and social network theory to promote smoking cessation. In this NIH funded trial, 2,185 CVS Caremark employees who smoke will be randomized to 5 different arms: (1) a usual care group consisting of web-based resources and free access to NRT if they were insured through CVS Caremark, (2) usual care + individual rewards (fixed payments for an individual’s success), (3) usual care + individual deposits (fixed losses for an individual’s failure), (4) usual care + collaborative rewards (payments to successful group members that increase with increasing group success rates), and (5) usual care + competitive deposits (redistribution of deposited money from group members who fail to group members who succeed). Our established partnership with CVS Caremark and our recent development of an NIH-supported, web-based infrastructure for behavioral research (Way to Health) will make such a large trial feasible.

   We will seek to determine the comparative and absolute efficacy and effectiveness of the 4 different incentive structures, which will each be grounded in behavioral economic principles. Additionally, we will measure rates of acceptance of each incentive structure as well as to examine participant characteristics that modify the effectiveness, efficacy, and acceptance of different incentive structures.

   B. **SPECIFIC AIMS**

   **Aim 1:** To compare the overall effectiveness of 4 financial incentive structures for improving “quit rates” (rates of prolonged smoking abstinence for 6 months): (a) individual reward, (b) individual deposit, (c) cooperative reward, and (d) competitive deposit.

   **Hypotheses:**

   1. Compared with usual care, all 4 incentive structures will increase quit rates significantly. Compared with individual rewards of equivalent size and schedule, individual deposit contracts, cooperative rewards, and competitive deposit contracts will each increase quit rates significantly.
   2. Group-oriented incentives will increase quit rates significantly more than individual-oriented incentives.
   3. Deposit-based incentives will increase quit rates significantly more than reward-based incentives.

   **Aim 2:** To compare smokers’ acceptance of 4 financial incentive structures for smoking cessation.
Hypotheses:

1. Acceptance rates of reward-based incentives will be higher than those of incentives involving deposit contracts.
2. Acceptance rates of group-oriented incentives will be higher than those of individual-oriented incentives.

Aim 3: To compare the specific efficacy of 4 financial incentive structures for improving “quit rates” using complier average treatment effect analyses.

Hypotheses:

1. Compared with usual care, reward-based and deposit-based incentives will be significantly more efficacious in promoting smoking cessation among participants who would accept these programs.
2. Deposit-based incentives will be more efficacious than reward-based incentives among participants who would accept either.

Primary outcomes: Rates of sustained smoking abstinence for 6 months as determined by salivary cotinine or anabasine (metabolites of nicotine) testing and acceptance rates of each of the 4 incentive structures.

Secondary outcomes: Salivary cotinine or anabasine testing at 14 days, 30 days, 6 months, and 12 months (follow-up) following patients’ selected target quit dates.

C. STUDY OVERVIEW

The overall aim of this study will be to determine the effectiveness, efficacy, and acceptance of 4 financial incentives for smoking cessation. Our hypotheses are that the 4 financial incentives will be more effective than usual care in promoting smoking cessation and that deposit contracts (and those based on group contingencies) will be more effective than an individual reward incentive program in promoting cessation. We also believe that reward-based incentives will be more acceptable than deposit-based incentives. These hypotheses will be tested in a randomized controlled trial (RCT). Following completion of a baseline assessment, 2,185 participants will be randomized to usual care or 4 incentive structures using an adaptive randomization approach. Participants can accept or decline their assigned intervention if they are assigned to one of the 4 incentive structures. If they decline, either by selecting an option stating that they did not want to receive this intervention or by not completing a deposit within 14 days if assigned to one of the arms requiring a deposit, participants will be treated as though they had been assigned to usual care, though still analyzed in their assigned arm.

The study will consist of a 6-month intervention period and a 6-month follow-up period following the participant’s self-selected quit date for a total of one year of participation (as indicated in Figure 1). Outcomes will be collected at 14 days, 30 days, 6 months and 12 months post quit date. During the intervention period, participants in the incentive groups could receive money at 14 days, 30 days, and 6 months post quit date for quitting smoking and remaining abstinent as verified by saliva cotinine or urine anabasine levels. If they fail to quit or test positive for smoking at these time points, their participation in the study will end. Participants will have access to free resources provided through their study portal or their insurance throughout the study. Email and/or text communications will be used throughout to remind participants of upcoming study tasks (sample submission, surveys, etc.) or to report tests results and/or earnings. Abstinence (as determined by biochemical verification) at 6-months and acceptance of interventions at intake will constitute primary outcomes for this trial. Secondary
outcomes will include biochemical verified abstinence at 14 days, 30 days, 6 months, and 12 months post quit date.

D. STUDY DESIGN CONSIDERATIONS

Although great potential exists to promote healthy behaviors through financial incentives, few studies have compared the efficacy, effectiveness, or acceptance (uptake) of different incentive structures. This is important because although financial incentives structured as rewards to individuals substantially improve rates of healthy behaviors, the absolute proportions of people adopting healthier behaviors remain low. Most patient-targeted incentive programs to date have relied upon the traditional economic assumption that the presence and/or size of incentives primarily determine their influence. However, a conceptual framework that integrates key behavioral principles (Figure 2) counters this assumption, suggesting instead that the ways in which similarly-sized incentives are structured may alter their effects without influencing their costs.

First, concepts from the field of behavioral economics, such as time discounting, prospect theory, loss aversion, and regret aversion lend substantial insights into optimal incentive structures. Each of the 4 incentive structures to be tested in the present study will incorporate several design elements based in behavioral economic theory. These structures will also differ in ways that behavioral economic theory would suggest are important, but for which optimal methods are unknown. For example, the fact that people tend to be loss averse – to avoid a potential loss more strongly than they would seek a potential gain of equal expected value– suggests that deposit contracts may be superior to positive rewards. A recent study published by members of our team in JAMA showed that deposit contracts improve short-term weight loss more than usual care. However, no studies to date have directly compared the effects of gains vs. losses for improving health behaviors.

Second, social network theory and corresponding observations that smoking, obesity, and alcohol consumption spread and cease within groups, suggests that intervening upon groups may modify behaviors more effectively than intervening upon individuals. Indeed, a recent systematic review found that group-oriented treatments for obesity, including one trial of group-oriented deposit contracts, were significantly more effective than individual-oriented treatments.
RCTs available for this review included a total of 336 people, and group-oriented incentives have not been tested in smoking or other health behaviors. If group-oriented incentives work, an essential next question is whether they would work better if built upon principles of collaboration vs. competition. Collaborative incentives, in which payouts to successful group members increase with the group’s overall success rate, may work by adding in dimensions of interpersonal accountability and teamwork. By contrast, competitive contracts, in which all group members’ up-front deposits are later distributed among those who succeed (similar to pari mutuel insurance schemes), may work because peoples’ loss aversions may be amplified by the regret they anticipate if others benefited directly from their failures (a phenomenon termed “social takeover” by one of our co-investigators, Dr. Loewenstein).

Optimizing incentive structures in the context of smoking cessation could have a dramatic impact on public health, because smoking remains the leading cause of preventable mortality in the United States, accounting for 443,000 deaths each year. Globally, the annual number of deaths attributable to smoking is 5 million and growing. Smoking has been linked to two-thirds of cancer deaths, half of respiratory illness deaths, and more than 15% of deaths from cardiovascular disease. Nonetheless, there are an estimated 1.2 billion people in the world who currently smoke, including 46 million (20.6%) American adults in 2008. More than 75% of current American smokers wish to quit. Forty-five percent do quit for at least a day each year, and anti-smoking policies, new pharmaceuticals, and behavioral modification programs offer promises to help them. Nevertheless, only 2-3% of smokers attain prolonged abstinence annually. Thus, although 2010 has passed, we remain far from achieving the Healthy People 2010 goal of having fewer than 12% of Americans smoke. Optimizing the delivery of the incentive-based approaches that we and others recently have shown to be effective therefore holds great promise to counter this major public health threat. Even if incentive programs for smoking cessation were expensive, they likely would rank among the most cost-effective of all preventive health services because most of their costs are conditional on success.

The comparative effectiveness of behavior-change programs depends on both (1) the programs’ comparative efficacy – that is, how well they work among people who use them – and (2) the programs’ comparative acceptance – that is, the probability that people targeted for participation will indeed use them. Despite proliferating research on financial incentives to promote behavior change, patients’ views of such programs are mixed, and their actual acceptance, or uptake, of such programs has rarely been studied. Among 176 obese patients randomly assigned to 1 of 6 deposit contracts for weight loss, patients were less likely to sign contracts requiring larger (vs. smaller) up-front deposits, and were
roughly equally likely to sign contracts with group-based (vs. individual-based) payout schemes. However, this study from nearly three decades ago was underpowered to detect important differences in the acceptance of these incentive programs, and we are not aware of subsequent studies evaluating financial incentive programs’ acceptance. The paucity of research on this critical question likely stems from the fact that studying comparative acceptance presents a dilemma for the investigator. Ideally, patients’ acceptance of different incentive programs would be examined in an RCT to mitigate the possibility that acceptance rates could be confounded by the characteristics of patients to whom different programs are offered. However, including potentially unacceptable incentive programs in RCTs is perilous because post-randomization losses due to nonacceptance could both limit power and introduce bias into analyses of interventions’ comparative efficacy. The present study is designed to examine incentive programs’ comparative acceptance without undermining our ability to study efficacy by using adaptive randomization and instrumental variable analyses to mitigate the potential risks of loss of power and introduction of bias, respectively.

In preparation for this study, our team developed the National Institute on Aging-supported WTH technology (RC2-AG036592). This web-based behavioral research infrastructure will substantially increase the efficiency of patient enrollment and tracking, data management, and incentive collection and disbursement, thereby enabling much larger studies than was possible previously. This platform will also create virtual social networks (akin to Facebook), enabling study of group interventions. Using this platform, we have conducted a pilot study of incentives among Walgreens employees to cease smoking. In this pilot study, we have tested not just the website, but also procedures for recruitment and saliva and urine sample collection. Therefore, our team has gained significant experience to conduct this full effectiveness RCT.

E. PARTICIPANTS

This study will be coordinated by investigators at Penn, but all participants who enroll will be full or part-time CVS employees and/or their family members or friends who smoke. We plan to enroll 2,185 participants who accept their assigned interventions through the Penn-run website WTH.

Inclusion Criteria

- At least 18 years old
- Smoke at least 5 cigarettes per day or use other tobacco products
- Have smoked for at least 6 months
- Have access to the internet
- Current full- or part-time employee of CVS
- Interested in quitting smoking
- Have no plans to leave CVS in next year

Exclusion Criteria

- Are unable or unwilling to access the internet
- Are unable to provide informed consent
- Fail the pre-screening for tobacco use (test negative for tobacco use)
F. RECRUITMENT

With assistance in coordination from CVS, we will recruit participants using: (1) postcards from CVS and the University of Pennsylvania to all employees, (2) in-store flyers, (3) announcements on in-store TV screens.

G. SCREENING

All recruitment messages will contain links to the WTH research portal, within which all subsequent enrollment and retention procedures will be coordinated. Upon entering the study website, participants will be presented with a brief consent form and required to click a button confirming their willingness to submit the results of the eligibility study to the research team. Each participant will then complete an eligibility survey. The web application will immediately check the results of the survey and notify the participant of his or her eligibility. Eligible participants will then be forwarded to the online consent process.

H. RANDOMIZATION

Participants will be randomized individually to 1 of the 5 arms using random number generation. We will not use cluster randomization (e.g., by worksite) because the competitive nature of arm 5 could be deleterious to workplace efficiency if people in the same store were competing. We will stratify randomization by 2 dichotomous variables: (1) participant income (above or below the CVS workforce median), and (2) participant insurance status (whether or not they are covered under the CVS insurance plan). Achieving balance across arms on each of these factors will minimize confounding and promote our ability to assess effect modification. Initial randomization probabilities will be 20% (usual care), 15% (individual rewards), 25% (individual deposits), 15% (cooperative rewards), and 25% (competitive deposits). This unbalanced randomization is intended to achieve equal numbers of accepting participants in each arm to maximize statistical power, accounting for hypothesized differences in acceptance rates across arms. To facilitate this goal, we will adapt these probabilities throughout enrollment based on the inverse of the accrued relative acceptance rates in each arm. Theses probabilities will be updated after every third participant enrolls and accepts or denies their intervention.

This form of adaptive randomization will achieve balance in the sample sizes among arms while retaining the virtues of randomization in minimizing confounding. On a rolling basis, participants assigned to the group-oriented incentive arms will be placed into 6-person cohorts with other participants sharing the most proximate quit dates to minimize delays in calculating and disbursing payments.

I. RETENTION

Following randomization and intervention acceptance, we will maintain retention in a number of ways using the WTH platform and payments for completing specific study-related tasks. To enhance participant retention across all 5 arms, and regardless of incentive acceptance, we will provide up to $160 in reimbursements as follows: $50 for completing the intake questionnaire, $20 reimbursements for cotinine/anabasine testing at 14 days, 30 days, 6 months, and 12 months (among those eligible), and an additional $30 for completing an exit questionnaire. We will also screen and pay a subset of participants for verification of smoking status prior to their participation. We will compensate these
participants $20. All such remunerations will be disbursed using checks through the WTH platform with assistance from Wells Fargo Bank upon confirmation of questionnaire completion or of a participant’s saliva or urine sample submission. Participants who do not complete these schedule submissions will be scored as continuing to smoke for purposes of analysis.

J. INTERVENTION

Participants will be randomized to 1 of 4 interventions based on behavioral economic principles and a usual care arm.

Usual Care

All aspects of this control arm will be made available to all consenting participants. They will be encouraged to enroll in the TrestleTree smoking cessation program offered by CVS to all employees. We will provide participants with links and step-by-step instructions for enrolling in this program through the WTH site. In addition, all participants will receive regular feedback on their progress towards quitting in their WTH portal, with personalized graphical data (updated daily) regarding the money they have (or would have) saved through smoking reduction and the associated health benefits accrued. Thus, the usual care arm will be comprised of the TrestleTree cessation program and regularly updated, web-based feedback regarding the economic and health-related benefits of smoking cessation. Every week the participant will receive an email or text message reminder to log in and complete a weekly smoking report. Fourteen days after their quit date, participants will report whether or not they have quit smoking by taking a survey. If they have quit smoking, they will receive instructions to submit either a saliva or urine sample. Subsequent to the sample submission, participants will receive $20 through the WTH website – regardless of the result. Once their smoking status has been verified, participants will be sent a message reporting this result. This process will be repeated 30 days and 6 months after the participants’ quit date. Twelve months after their quit date, all subjects will be emailed to prompt them to log into the web application to take a final smoking habits survey for $30. Participants who report having remained smoke free for the last month of the study will be asked to take cotinine or anabasine test to verify that they have quit. Participants who take a verification test will be compensated $20. Saliva or urine sample will be collected only from those participants who have declared themselves to have successfully quit smoking in the assessments on the WTH website.

Individual Reward

Participants assigned to this arm will receive the same usual care plan, plus be offered an incentive plan in which they can earn $600 for quitting smoking and a $200 bonus for achieving prolonged abstinence at 6 months. Participants in this arm will be informed of their eligibility to earn $200 if they quit smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. They will also be reminded of the $200 bonus for achieving abstinence at 6 months. Total earnings possible for this arm will be $800. All sample submission procedures, study related payments, and messaging will be identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment.

Individual Deposit

Participants assigned to this arm will receive the same usual care plan plus be offered an incentive plan where they were asked to deposit $150 of their own money for an opportunity to earn this money back and an additional $450 in incentives for quitting smoking. They could also earn a $200 bonus for achieving prolonged abstinence at 6 months. Participants in this arm will be informed of their eligibility to earn back $50 of their deposit and $150 in incentives if they quit smoking at each of 3 time points: 14
days, 30 days, and 6 months following their own target quit dates. They will also be reminded of the $200 bonus for achieving abstinence at 6 months. Total earning possible for this arm will be $650 in incentives and a $150 deposit refund. All sample submission procedures, study related payments, and messaging was identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment. To accept this assigned incentive plan will require saying they will accept it on the WTH platform and then making the $150 deposit via debit or credit card within 14 days.

**Collaborative Reward**

Participants assigned to this arm will receive the same usual care plan and an offer to be placed into a group with 5 other participants that will help determine their incentive earnings. In this arm, individual payouts will increase as more participants in each group quit. Participants can earn $100 for quitting smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. Individual payouts will increase as more members of the group quit, from $100 at each time point if 1/6 quits to $600 per person per time point if 6/6 quit. They will also receive a $200 bonus for achieving prolonged abstinence at 6 months. We will promote collaboration among these cohorts by linking group members via a Facebook-style chat room within the WTH infrastructure. Participants will be encouraged to use the chat room to help each other in their joint efforts to quit. Total earnings possible for this arm will be $2000. All sample submission procedures, study related payments, and messaging was identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment.

**Competitive Deposit**

Participants assigned to this arm will receive the same usual care plan plus an offer of an incentive plan in which they will be placed into a group with 5 other participants that will help determine their incentive earnings. In this arm, participants will be asked to deposit $150 of their own money for an opportunity to earn this money back and an additional $450 in incentives for quitting smoking. Participants in this arm will be informed of their eligibility to earn back $50 of their deposit and $150 in incentives if they quit smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. Individual payouts will increase as fewer members of the group quit, from $200 ($150 incentive and $50 return deposit) at each time point if 6/6 quits to $1,200 ($900 incentive and $300 of theirs and others’ deposits returned) per person per time point if 1/6 quit. They could also earn a $200 bonus for achieving prolonged abstinence at 6 months. Total earnings possible for this arm will be $3,800 ($2,900 in incentives and $900 deposit refund). All sample submission procedures, study related payments, and messaging will be identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment. To accept this assigned incentive plan will require saying they will accept it on the WTH platform and then making the $150 deposit via debit or credit card within 14 days.

**K. ASSESSMENTS**

The *primary outcome* will be sustained (or “prolonged”) abstinence, defined by the Society for Research on Nicotine and Tobacco as sustained abstinence (generally for 6 months) after an initial grace period (generally the first 2 weeks after quitting). Participants achieving this outcome will have had biochemically confirmed cessation at 14 days, 30 days, and at 6 months and will not have reported interval relapses or failures. *Secondary outcomes* will include:
(a) **Quit-rate point prevalence.** Because smokers who successfully quit for even a short period are more likely to quit long-term, we will measure the point prevalence of self-reported smoking cessation that is confirmed biochemically at 14 days, 30 days, and 6 months.\(^6\)

(b) **Relapse-free rate.** Fewer than 10% of people who quit for 6 months under natural conditions will relapse.\(^6\) However, it is possible that relapses could occur more commonly following the withdrawal of external incentives for smoking cessation.\(^6\) We will assess the proportion of participants achieving prolonged abstinence who remain abstinent 6 months after the intervention period (12 months following the quit date).

**Biochemical verification.** Salivary and urinary samples from those participants who have claimed to have quit smoking will be collected at CVS MinuteClinics by healthcare practitioners. If there are no geographically proximate MinuteClinics for sample collection, Hooper Holmes will contact participants and schedule appointments for remote urine and saliva sample collection. Saliva samples will be sent to the University of Pennsylvania where they will be tested using the NicAlert Saliva Nicotine Test, a semi-quantitative immunochromatographic assay test strip. Urine samples will be sent for anabasine testing at the ARUP Lab. Anabasine test results will then be sent to the Penn investigators via secure, HIPAA compliant fax.

**Outcomes related to acceptance of incentive structures.** The primary outcome for Aim II will be the acceptance rate, defined as the proportion of patients randomized to each of the incentive arms who, after learning the details of the incentive structure to which they were assigned, provide all necessary financial information to process payments, including their social security number and home address. For patients assigned to deposit contract arms, classification of acceptance will also require submission of the deposit via debit or credit card.

L. **DATA MANAGEMENT**

The WTH program includes senior personnel who, in conjunction with our project-specific team, will coordinate all data management and quality assurance. This managerial infrastructure is specifically designed to provide all of the services essential for the success of an RCT in compliance with all federal guidelines. All data will be stored in both a non-editable database and in a separate modifiable database, allowing researchers to correct mistakes while preserving the raw data for auditing purposes. Every data transaction, including accessing and changing data, will be logged for auditing purposes. Data will be entered into the database through several different mechanisms. Participants will enter their own personal information and respond to surveys through a PHP-based web interface. Researchers will have a separate interface that will allow them to manually enter the results from saliva and urine tests. Samples will be labeled using a participant ID or a study participant name if the participant chooses to use this as an identifier. Cotinine data will be linked by a programmer utilizing coded study IDs and operating behind a University firewall. The dataset will be blinded of all personally identifiable information when exported for analysis. The web application will automatically remove all identifiers when a researcher requests an analytic dataset. The only people with access to identifiable participant information will be prespecified coordinators responsible for contacting participants for follow-up. Personal information and research data will be stored in separate tables and will be linked by a computer-generated ID number.

We will prepare data annually for review by the Data Safety Monitoring Board that will be constituted. Board members will be Dr. Scott Sherman, Associate Professor of Medicine and Psychiatry, New York University, Dr. Peter Ubel, Professor of Medicine and Business, Duke University, and Dr. Michael Elliott, Associate Professor of Biostatistics, University of Michigan.
Descriptive analyses, using summary statistics, histograms, and other depictions will proceed throughout the work as components of standard data management. To evaluate the balance between groups achieved by randomization, baseline values of all variables will be compared across the 5 arms using t-tests or Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, and chi-square tests for comparisons of proportions.

M. QUALITY CONTROL

Dr. Halpern and the DSMB will provide oversight of all research activities to ensure proper consent and data collection. The WTH platform will ensure accurate delivery of incentives and interventions as well as accurate data collection. A manual of operations clearly describing the purpose of the study, eligibility criteria, and all study procedures will be provided to members of the study team to ensure standard and accurate implementation of the study protocol by all research personnel. All procedures and practices will be submitted for approval by the University of Pennsylvania’s Institutional Review Board prior to recruitment and implementation.

Quality Control in Data Collection

Standard procedures to ensure the accurate and reliable collection of data will include 1) protocol development with clear instructions, 2) training sessions with CVS MinuteClinics and Hooper Holmes associates to allow demonstration and practice pertaining to all sample collection procedures, 3) use of a web-based platform to collect all self-report information, and 4) on-going monitoring of all data collection activities. Protocols will be developed to ensure clarity and consistency and minimize human error. Retraining will be provided as needed. For quality control in the analysis of saliva cotinine results, two coordinators will score the NicAlert strip test separately. Retests will be conducted if there is a disagreement in result. ARUP labs will ensure the quality of urine anabasine tests they provide by crosschecking each sample.

Quality Control in Data Management

The data management system will be programmed with validation criteria, such as range and logic checks, to facilitate the data management process and reduce entry errors.

Quality Control in Implementing the Intervention

Methods to ensure the delivery of interventions to participants was established as part of a pilot study with Walgreens employees prior to this trial. In addition, the WTH platform has been used in several other incentive studies where quality of intervention delivery has been established.

N. STUDY TIMELINE

As shown in Table 1, the study will consist of a planning phase for developing standardized protocols and agreements, hiring and training staff, and testing the web-based portals. Over several years, we will conduct overlapping recruitment, enrollment, randomization, intervention, and follow-up phases.
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2. Final Protocol

A. ABSTRACT

Providing patients with financial incentives has been shown to promote exercise, weight loss, adherence to medical advice, and abstinence from smoking and other drug use. However, research on incentives to date has generally viewed them as if they were all-or-nothing, comparing behaviors in the presence versus the absence of incentives, and assuming that they worked similarly among different types of people. Yet, concepts from behavioral economics suggest that how and to whom incentives are delivered may affect their impact substantially. 1-4 Thus, comparing incentive structures (e.g., should we create potential for gains vs. losses, or target individuals vs. groups?) and identifying patients for whom they work particularly well may elucidate mechanisms by which incentives alter behavior and inform the design of behavior-modifying interventions. 5

This study will seek to compare 4 incentive structures that are based upon principles of behavioral economics, contingency management, and social network theory to promote smoking cessation. 6-19,20,21 In this NIH funded trial, 2,358 CVS Caremark employees who smoke will be randomized to 5 different arms: (1) a usual care group consisting of web-based resources and free access to NRT if they were insured through CVS Caremark, (2) usual care + individual rewards (fixed payments for an individual’s success), (3) usual care + individual deposits (fixed losses for an individual’s failure), (4) usual care + collaborative rewards (payments to successful group members that increase with increasing group success rates), and (5) usual care + competitive deposits (redistribution of deposited money from group members who fail to group members who succeed). Our established partnership with CVS Caremark and our recent development of an NIH-supported, web-based infrastructure for behavioral research, Way to Health (WTH), will make such a large trial feasible.

We will seek to determine the comparative and absolute efficacy and effectiveness of the 4 different incentive structures, which will each be grounded in behavioral economic principles. Additionally, we will measure rates of acceptance of each incentive structure as well as to examine participant characteristics that modify the effectiveness, efficacy, and acceptance of different incentive structures.

B. SPECIFIC AIMS

Aim 1: To compare the overall effectiveness of 4 financial incentive structures for improving “quit rates” (rates of prolonged smoking abstinence for 6 months): (a) individual reward, (b) individual deposit, (c) cooperative reward, and (d) competitive deposit.

Hypotheses:

4. Compared with usual care, all 4 incentive structures will increase quit rates significantly. Compared with individual rewards of equivalent size and schedule, individual deposit contracts, cooperative rewards, and competitive deposit contracts will each increase quit rates significantly.

5. Group-oriented incentives will increase quit rates significantly more than individual-oriented incentives.

6. Deposit-based incentives will increase quit rates significantly more than reward-based incentives.

Aim 2: To compare smokers’ acceptance of 4 financial incentive structures for smoking cessation.
Hypotheses:

3. Acceptance rates of reward-based incentives will be higher than those of incentives involving deposit contracts.
4. Acceptance rates of group-oriented incentives will be higher than those of individual-oriented incentives.

Aim 3: To compare the specific efficacy of 4 financial incentive structures for improving “quit rates” using complier average treatment effect analyses.

Hypotheses:

3. Compared with usual care, reward-based and deposit-based incentives will be significantly more efficacious in promoting smoking cessation among participants who would accept these programs.
4. Deposit-based incentives will be more efficacious than reward-based incentives among participants who would accept either.

Primary outcomes: Rates of sustained smoking abstinence for 6 months as determined by salivary cotinine or anabasine (metabolites of nicotine) testing and acceptance rates of each of the 4 incentive structures.

Secondary outcomes: Salivary cotinine or anabasine testing at 14 days, 30 days, 6 months, and 12 months (follow-up) following patients’ selected target quit dates.

C. STUDY OVERVIEW

The overall aim of this study will be to determine the effectiveness, efficacy, and acceptance of 4 financial incentives for smoking cessation. Our hypotheses are that the 4 financial incentives will be more effective than usual care in promoting smoking cessation and that deposit contracts (and those based on group contingencies) will be more effective than an individual reward incentive program in promoting cessation. We also believe that reward-based incentives will be more acceptable than deposit-based incentives. These hypotheses will be tested in a randomized controlled trial (RCT). Following completion of a baseline assessment, 2,538 participants will be randomized to usual care or 4 incentive structures using an adaptive randomization approach. Participants can accept or decline their assigned intervention if they are assigned to one of the 4 incentive structures. If they decline, either by selecting an option stating that they did not want to receive this intervention or by not completing a deposit within 30 days if assigned to one of the arms requiring a deposit, participants will be treated as though they had been assigned to usual care, though still analyzed in their assigned arm.

The study will consist of a 6-month intervention period and a 6-month follow-up period following the participant’s self-selected quit date for a total of one year of participation (as indicated in Figure 1). Outcomes will be collected at 14 days, 30 days, 6 months and 12 months post quit date. During the intervention period, participants in the incentive groups could receive money at 14 days, 30 days, and 6 months post quit date for quitting smoking and remaining abstinent as verified by saliva cotinine or urine anabasine levels. If they fail to quit or test positive for smoking at these time points, their participation in the study will end. Participants will have access to free resources provided through their study portal or their insurance throughout the study. Email and/or text communications will be used throughout to remind participants of upcoming study tasks (sample submission, surveys, etc.) or to report tests results and/or earnings. Abstinence (as determined by biochemical verification) at 6-months and acceptance of interventions at intake will constitute primary outcomes for this trial. Secondary
outcomes will include biochemical verified abstinence at 14 days, 30 days, 6 months, and 12 months post quit date.

D. STUDY DESIGN CONSIDERATIONS

Although great potential exists to promote healthy behaviors through financial incentives, few studies have compared the efficacy, effectiveness, or acceptance (uptake) of different incentive structures. This is important because although financial incentives structured as rewards to individuals substantially improve rates of healthy behaviors, the absolute proportions of people adopting healthier behaviors remain low. Most patient-targeted incentive programs to date have relied upon the traditional economic assumption that the presence and/or size of incentives primarily determine their influence. However, a conceptual framework that integrates key behavioral principles (Figure 2) counters this assumption, suggesting instead that the ways in which similarly-sized incentives are structured may alter their effects without influencing their costs.

First, concepts from the field of behavioral economics, such as time discounting, prospect theory, loss aversion, and regret aversion lend substantial insights into optimal incentive structures. Each of the 4 incentive structures to be tested in the present study will incorporate several design elements based in behavioral economic theory. These structures will also differ in ways that behavioral economic theory would suggest are important, but for which optimal methods are unknown. For example, the fact that people tend to be loss averse – to avoid a potential loss more strongly than they would seek a potential gain of equal expected value– suggests that deposit contracts may be superior to positive rewards. A recent study published by members of our team in JAMA showed that deposit contracts improve short-term weight loss more than usual care. However, no studies to date have directly compared the effects of gains vs. losses for improving health behaviors.

Second, social network theory and corresponding observations that smoking, obesity, and alcohol consumption spread and cease within groups, suggests that intervening upon groups may modify behaviors more effectively than intervening upon individuals. Indeed, a recent systematic review found that group-oriented treatments for obesity, including one trial of group-oriented deposit contracts, were significantly more effective than individual-oriented treatments. However, the 5
RCTs available for this review included a total of 336 people, and group-oriented incentives have not been tested in smoking or other health behaviors. If group-oriented incentives work, an essential next question is whether they would work better if built upon principles of collaboration vs. competition. Collaborative incentives, in which payouts to successful group members increase with the group’s overall success rate, may work by adding in dimensions of interpersonal accountability and teamwork. By contrast, competitive contracts, in which all group members’ up-front deposits are later distributed among those who succeed (similar to pari mutuel insurance schemes), may work because peoples’ loss aversions may be amplified by the regret they anticipate if others benefited directly from their failures (a phenomenon termed “social takeover” by one of our co-investigators, Dr. Loewenstein).

![Figure 2: Conceptual framework for the efficacy of incentive structures for smoking cessation. Solid lines = hypothesized main effects; dotted lines = hypothesized effect modifications.](image)

Optimizing incentive structures in the context of smoking cessation could have a dramatic impact on public health, because smoking remains the leading cause of preventable mortality in the United States, accounting for 443,000 deaths each year. Globally, the annual number of deaths attributable to smoking is 5 million and growing. Smoking has been linked to two-thirds of cancer deaths, half of respiratory illness deaths, and more than 15% of deaths from cardiovascular disease. Nonetheless, there are an estimated 1.2 billion people in the world who currently smoke, including 46 million (20.6%) American adults in 2008. More than 75% of current American smokers wish to quit. Forty-five percent do quit for at least a day each year, and anti-smoking policies, new pharmaceuticals, and behavioral modification programs offer promises to help them. Nevertheless, only 2-3% of smokers attain prolonged abstinence annually. Thus, although 2010 has passed, we remain far from achieving the Healthy People 2010 goal of having fewer than 12% of Americans smoke. Optimizing the delivery of the incentive-based approaches that we and others recently have shown to be effective therefore holds great promise to counter this major public health threat. Even if incentive programs for smoking cessation were expensive, they likely would rank among the most cost-effective of all preventive health services because most of their costs are conditional on success.

The comparative effectiveness of behavior-change programs depends on both (1) the programs’ comparative efficacy – that is, how well they work among people who use them – and (2) the programs’ comparative acceptance – that is, the probability that people targeted for participation will indeed use them. Despite proliferating research on financial incentives to promote behavior change, patients’ views of such programs are mixed, and their actual acceptance, or uptake, of such programs has rarely been studied. Among 176 obese patients randomly assigned to 1 of 6 deposit contracts for weight loss, patients were less likely to sign contracts requiring larger (vs. smaller) up-front deposits, and were
roughly equally likely to sign contracts with group-based (vs. individual-based) payout schemes.\textsuperscript{33} However, this study from nearly three decades ago was underpowered to detect important differences in the acceptance of these incentive programs, and we are not aware of subsequent studies evaluating financial incentive programs’ acceptance. The paucity of research on this critical question likely stems from the fact that studying comparative acceptance presents a dilemma for the investigator. Ideally, patients’ acceptance of different incentive programs would be examined in an RCT to mitigate the possibility that acceptance rates could be confounded by the characteristics of patients to whom different programs are offered. However, including potentially unacceptable incentive programs in RCTs is perilous because post-randomization losses due to nonacceptance could both limit power and introduce bias into analyses of interventions’ comparative efficacy.\textsuperscript{50} The present study is designed to examine incentive programs’ comparative acceptance without undermining our ability to study efficacy by using adaptive randomization and instrumental variable analyses to mitigate the potential risks of loss of power and introduction of bias, respectively.\textsuperscript{51-55}

In preparation for this study, our team developed the National Institute on Aging-supported WTH technology (RC2-AG036592). This web-based behavioral research infrastructure will substantially increase the efficiency of patient enrollment and tracking, data management, and incentive collection and disbursement, thereby enabling much larger studies than was possible previously. This platform will also create virtual social networks (akin to Facebook), enabling study of group interventions. Using this platform, we have conducted a pilot study of incentives among Walgreens employees to cease smoking. In this pilot study, we have tested not just the website, but also procedures for recruitment and saliva and urine sample collection. Therefore, our team has gained significant experience to conduct this full effectiveness RCT.

E. PARTICIPANTS

This study was coordinated by investigators at Penn, but all participants who enrolled were full or part-time CVS employees and/or their family members or friends who smoke. We planned to enroll 2,185 participants who accept their assigned interventions through the Penn-run website WTH. In light of observed acceptance rates, protocol modifications were made that resulted in the enrollment of a total of 2,538 participants, 1,528 of whom accepted their assigned intervention. These modifications are detailed in the Randomization section and in the Appendix: Summary of Amendments and Modification.

**Inclusion Criteria**

- At least 18 years old
- Smoke at least 5 cigarettes per day or use other tobacco products
- Have smoked for at least 6 months
- Have access to the internet
- Current full- or part-time employee of CVS and/or be a friend or family member of a current full- or part-time employee of CVS

**Exclusion Criteria**

- Are unable or unwilling to access the internet
- Are unable to provide informed consent
- Fail the pre-screening for tobacco use (test negative for tobacco use)
F. RECRUITMENT

With assistance in coordination from CVS, we will recruit participants using: (1) postcards from CVS and the University of Pennsylvania to all employees, (2) in-store flyers, (3) announcements on in store TV screens, (4) emails to cooperate employees, Human Resources, employees enrolled in wellness programs, and store managers, (5) on-site information tables for smoke-free campus announcement, (6) Human Resource presentations, (7) announcements in monthly benefits orientation, (8) announcement on employee health care centered website, (9) announcement on web based employee newsletter, (10) announcement in new hire section of web based employee newsletter, (11) paycheck messages, (12) announcements made through web based employee resources, (13) feature story in employee newsletter, (14) phone message from Chief Medical Officer, and (15) flyers and information tables at Benefit Fairs. Additional methods of recruitment include two sub-studies to boost enrollment. The objective of sub-study 1 is to examine two variations on how the current compensation amount of $50 is given to participants after completing enrollment. The first method is to offer potential participants $50 to complete the enrollment process for a limited amount of time after which they will only receive only $25 to complete. The second method is to offer potential participants $75 to complete enrollment for a limited time after which they will only be eligible for the original $50 for completion. This sub-study lasted for 6 weeks. The objective of sub-study 2 is to examine the effects of two lotteries on enrollment completion. One lottery is for an iPad3, the other lottery is for the direct cash equivalent. This lottery will be made available for all those who have already completed enrollment and for those who will complete enrollment by our pre-determined date. We also plan to vary email and postcard messages throughout the enrollment to examine the messages impact on recruitment.

G. SCREENING

All recruitment messages will contain links to the WTH research portal, within which all subsequent enrollment and retention procedures will be coordinated. Upon entering the study website, participants will be presented with a brief consent form and required to click a button confirming their willingness to submit the results of the eligibility study to the research team. Each participant will then complete an eligibility survey. The web application will immediately check the results of the survey and notify the participant of his or her eligibility. Eligible participants will then be forwarded to the online consent process.

H. RANDOMIZATION

Participants will be randomized individually to 1 of the 5 arms using random number generation.56 We will not use cluster randomization (e.g., by worksite) because the competitive nature of arm 5 could be deleterious to workplace efficiency if people in the same store were competing. We will stratify randomization by 2 dichotomous variables: (1) participant income (above or below the CVS workforce median), and (2) participant insurance status (whether or not they are covered under the CVS insurance plan).57,58 Achieving balance across arms on each of these factors will minimize confounding and promote our ability to assess effect modification. Initial randomization probabilities will be 20% (usual care), 15% (individual rewards), 25% (individual deposits), 15% (cooperative rewards), and 25% (competitive deposits). This unbalanced randomization is intended to achieve equal numbers of accepting participants in each arm to maximize statistical power, accounting for hypothesized differences in acceptance rates across arms. To facilitate this goal, we will adapt these probabilities throughout enrollment based on the inverse of the accrued relative acceptance rates in each arm.
Theses probabilities will be updated after every third participant enrolls and accepts or denies their intervention.

This form of adaptive randomization will achieve balance in the sample sizes among arms while retaining the virtues of randomization in minimizing confounding.\textsuperscript{52,53} On a rolling basis, participants assigned to the group-oriented incentive arms will be placed into 6-person cohorts with other participants sharing the most proximate quit dates to minimize delays in calculating and disbursing payments.

Several protocol deviations were made to the randomization process throughout enrollment to address observed disparities in acceptance rates across intervention arms. Acceptance in the intervention arms requiring a deposit were much lower than anticipated, causing the probability of being assigned to those arms to increase in such a way that we risked under enrolling in the remaining three arms (usual care, individual reward, and cooperative reward arms. On 11 April 2012, we implemented a 60%/40% split between [usual care + individual reward + collaborative reward arms] and [individual deposit + competitive deposit arms]. This meant that 60% of new participants would be adaptively randomized to the usual care, individual reward, or collaborative reward arms and 40% would be adaptively randomized to the individual deposit or competitive deposit arms. On 25 April 2012, we changed to an 80%/20% split between the same two groups. On 14 September 2012, we changed to a 50%/50% split between the same two groups. On 26 September 2012, we retained this 50%/50% split, continued the adaptive randomization for the deposit arms, but among the 50% of participants randomized to the group containing the other three arms, we fixed the allocation probabilities for the usual care (15%), individual reward (15%), and collaborative reward (70%) arms to bolster assignment to the latter.

I. RETENTION

Following randomization and intervention acceptance, we will maintain retention in a number of ways using the WTH platform and payments for completing specific study-related tasks. To enhance participant retention across all 5 arms, and regardless of incentive acceptance, we will provide up to $160 in reimbursements as follows: $50 for completing the intake questionnaire, $20 reimbursements for cotinine/anabasine testing at 14 days, 30 days, 6 months, and 12 months (among those eligible), and an additional $30 for completing an exit questionnaire. We will also screen and pay a subset of participants for verification of smoking status prior to their participation. We will compensate these participants $20. This amount was increased to $100 to increase compliance. All such remunerations will be disbursed using checks through the WTH platform with assistance from Wells Fargo Bank upon confirmation of questionnaire completion or of a participant’s saliva or urine sample submission. Participants who do not complete these schedule submissions will be scored as continuing to smoke for purposes of analysis.

J. INTERVENTION

Participants will be randomized to 1 of 4 interventions based on behavioral economic principles and a usual care arm.

**Usual Care**

All aspects of this control arm will be made available to all consenting participants. They will be encouraged to enroll in the TrestleTree smoking cessation program offered by CVS to all employees. We
will provide participants with links and step-by-step instructions for enrolling in this program through the WTH site. In addition, all participants will receive regular feedback on their progress towards quitting in their WTH portal, with personalized graphical data (updated daily) regarding the money they have (or would have) saved through smoking reduction and the associated health benefits accrued. Thus, the usual care arm will be comprised of the TrestleTree cessation program and regularly updated, web-based feedback regarding the economic and health-related benefits of smoking cessation. Every week the participant will receive an email or text message reminder to log in and complete a weekly smoking report. Fourteen days after their quit date, participants will report whether or not they have quit smoking by taking a survey. If they have quit smoking, they will receive instructions to submit either a saliva or urine sample. Subsequent to the sample submission, participants will receive $20 through the WTH website – regardless of the result. Once their smoking status has been verified, participants will be sent a message reporting this result. This process will be repeated 30 days and 6 months after the participants’ quit date. Twelve months after their quit date, all subjects will be emailed to prompt them to log into the web application to take a final smoking habits survey for $30. Participants who report having remained smoke free for the last month of the study will be asked to take cotinine or anabasine test to verify that they have quit. Participants who take a verification test will be compensated $20. Saliva or urine sample will be collected only from those participants who have declared themselves to have successfully quit smoking in the assessments on the WTH website.

Individual Reward

Participants assigned to this arm will receive the same usual care plan, plus be offered an incentive plan in which they can earn $600 for quitting smoking and a $200 bonus for achieving prolonged abstinence at 6 months. Participants in this arm will be informed of their eligibility to earn $200 if they quit smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. They will also be reminded of the $200 bonus for achieving abstinence at 6 months. Total earnings possible for this arm will be $800. All sample submission procedures, study related payments, and messaging will be identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment.

Individual Deposit

Participants assigned to this arm will receive the same usual care plan plus be offered an incentive plan where they were asked to deposit $150 of their own money for an opportunity to earn this money back and an additional $450 in incentives for quitting smoking. They could also earn a $200 bonus for achieving prolonged abstinence at 6 months. Participants in this arm will be informed of their eligibility to earn back $50 of their deposit and $150 in incentives if they quit smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. They will also be reminded of the $200 bonus for achieving abstinence at 6 months. Total earning possible for this arm will be $650 in incentives and a $150 deposit refund. All sample submission procedures, study related payments, and messaging was identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment. To accept this assigned incentive plan will require saying they will accept it on the WTH platform and then making the $150 deposit via debit or credit card within 30 days.

Collaborative Reward

Participants assigned to this arm will receive the same usual care plan and an offer to be placed into a group with 5 other participants that will help determine their incentive earnings. In this arm, individual payouts will increase as more participants in each group quit. Participants can earn $100 for quitting smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates.
Individual payouts will increase as more members of the group quit, from $100 at each time point if 1/6 quits to $600 per person per time point if 6/6 quit. They will also receive a $200 bonus for achieving prolonged abstinence at 6 months. We will promote collaboration among these cohorts by linking group members via a Facebook-style chat room within the WTH infrastructure. Participants will be encouraged to use the chat room to help each other in their joint efforts to quit. Total earnings possible for this arm will be $2000. All sample submission procedures, study related payments, and messaging was identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment.

**Competitive Deposit**

Participants assigned to this arm will receive the same usual care plan plus an offer of an incentive plan in which they will be placed into a group with 5 other participants that will help determine their incentive earnings. In this arm, participants will be asked to deposit $150 of their own money for an opportunity to earn this money back and an additional $450 in incentives for quitting smoking. Participants in this arm will be informed of their eligibility to earn back $50 of their deposit and $150 in incentives if they quit smoking at each of 3 time points: 14 days, 30 days, and 6 months following their own target quit dates. Individual payouts will increase as fewer members of the group quit, from $200 ($150 incentive and $50 return deposit) at each time point if 6/6 quits to $1,200 ($900 incentive and $300 of theirs and others’ deposits returned) per person per time point if 1/6 quit. They could also earn a $200 bonus for achieving prolonged abstinence at 6 months. Total earnings possible for this arm will be $3,800 ($2,900 in incentives and $900 deposit refund). All sample submission procedures, study related payments, and messaging will be identical to the Usual Care arm. Participants may accept or reject the assigned incentive plan; if they reject it, they will still receive the usual care treatment. To accept this assigned incentive plan will require saying they will accept it on the WTH platform and then making the $150 deposit via debit or credit card within 30 days.

**K. ASSESSMENTS**

The primary outcome will be sustained (or “prolonged”) abstinence, defined by the Society for Research on Nicotine and Tobacco as sustained abstinence (generally for 6 months) after an initial grace period (generally the first 2 weeks after quitting). Participants achieving this outcome will have had biochemically confirmed cessation at 14 days, 30 days, and at 6 months and will not have reported interval relapses or failures. Secondary outcomes will include:

(a) **Quit-rate point prevalence.** Because smokers who successfully quit for even a short period are more likely to quit long-term, we will measure the point prevalence of self-reported smoking cessation that is confirmed biochemically at 14 days, 30 days, and 6 months.

(b) **Relapse-free rate.** Fewer than 10% of people who quit for 6 months under natural conditions will relapse. However, it is possible that relapses could occur more commonly following the withdrawal of external incentives for smoking cessation. We will assess the proportion of participants achieving prolonged abstinence who remain abstinent 6 months after the intervention period (12 months following the quit date).

**Biochemical verification.** Salivary and urinary samples from those participants who have claimed to have quit smoking will be collected at CVS MinuteClinics by healthcare practitioners. If there are no geographically proximate MinuteClinics for sample collection, Hooper Holmes will contact participants and schedule appointments for remote urine and saliva sample collection. Saliva samples will be sent to the University of Pennsylvania where they will be tested using the NicAlert Saliva Nicotine Test, a semi-
quantitative immunochromatographic assay test strip. Urine samples will be sent for anabasine testing at the ARUP Lab. Anabasine test results will then be sent to the Penn investigators via secure, HIPAA compliant fax.

**Outcomes related to acceptance of incentive structures.** The primary outcome for Aim II will be the acceptance rate, defined as the proportion of patients randomized to each of the incentive arms who, after learning the details of the incentive structure to which they were assigned, provide all necessary financial information to process payments, including their social security number and home address. For patients assigned to deposit contract arms, classification of acceptance will also require submission of the deposit via debit or credit card.

L. DATA MANAGEMENT

The WTH program includes senior personnel who, in conjunction with our project-specific team, will coordinate all data management and quality assurance. This managerial infrastructure is specifically designed to provide all of the services essential for the success of an RCT in compliance with all federal guidelines. All data will be stored in both a non-editable database and in a separate modifiable database, allowing researchers to correct mistakes while preserving the raw data for auditing purposes. Every data transaction, including accessing and changing data, will be logged for auditing purposes. Data will be entered into the database through several different mechanisms. Participants will enter their own personal information and respond to surveys through a PHP-based web interface. Researchers will have a separate interface that will allow them to manually enter the results from saliva and urine tests. Samples will be labeled using a participant ID or a study participant name if the participant chooses to use this as an identifier. Cotinine data will be linked by a programmer utilizing coded study IDs and operating behind a University firewall. The dataset will be blinded of all personally identifiable information when exported for analysis. The web application will automatically remove all identifiers when a researcher requests an analytic dataset. The only people with access to identifiable participant information will be prespecified coordinators responsible for contacting participants for follow-up. Personal information and research data will be stored in separate tables and will be linked by a computer-generated ID number.

We will prepare data annually for review by the Data Safety Monitoring Board that will be constituted. Board members will be Dr. Scott Sherman, Associate Professor of Medicine and Psychiatry, New York University, Dr. Peter Ubel, Professor of Medicine and Business, Duke University, and Dr. Michael Elliott, Associate Professor of Biostatistics, University of Michigan.

Descriptive analyses, using summary statistics, histograms, and other depictions will proceed throughout the work as components of standard data management. To evaluate the balance between groups achieved by randomization, baseline values of all variables will be compared across the 5 arms using t-tests or Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, and chi-square tests for comparisons of proportions.

M. QUALITY CONTROL

Dr. Halpern and the DSMB will provide oversight of all research activities to ensure proper consent and data collection. The WTH platform will ensure accurate delivery of incentives and interventions as well as accurate data collection. A manual of operations clearly describing the purpose of the study, eligibility criteria, and all study procedures will be provided to members of the study team to ensure standard and accurate implementation of the study protocol by all research personnel. All
procedures and practices will be submitted for approval by the University of Pennsylvania’s Institutional Review Board prior to recruitment and implementation.

Quality Control in Data Collection

Standard procedures to ensure the accurate and reliable collection of data will include 1) protocol development with clear instructions, 2) training sessions with CVS MinuteClinics and Hooper Holmes associates to allow demonstration and practice pertaining to all sample collection procedures, 3) use of a web-based platform to collect all self-report information, and 4) on-going monitoring of all data collection activities. Protocols will be developed to ensure clarity and consistency and minimize human error. Retraining will be provided as needed. For quality control in the analysis of saliva cotinine results, two coordinators will score the NicAlert strip test separately. Retests will be conducted if there is a disagreement in result. ARUP labs will ensure the quality of urine anabasine tests they provide by crosschecking each sample.

Quality Control in Data Management

The data management system will be programmed with validation criteria, such as range and logic checks, to facilitate the data management process and reduce entry errors.

Quality Control in Implementing the Intervention

Methods to ensure the delivery of interventions to participants was established as part of a pilot study with Walgreens employees prior to this trial. In addition, the WTH platform has been used in several other incentive studies where quality of intervention delivery has been established.

N. STUDY TIMELINE

As shown in Table 1, the study will consist of a planning phase for developing standardized protocols and agreements, hiring and training staff, and testing the web-based portals. Over several years, we will conduct overlapping recruitment, enrollment, randomization, intervention, and follow-up phases.

<table>
<thead>
<tr>
<th>Task Description</th>
<th>YEAR 1</th>
<th>YEAR 2</th>
<th>YEAR 3</th>
<th>YEAR 4</th>
<th>YEAR 5</th>
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</table>
3. **Summary of Amendments and Modifications**

The most substantive protocol deviation, also described briefly in the manuscript text, was to the randomization process. Several modifications to the arms’ assignment probabilities were made during the enrollment period to address observed disparities in acceptance rates across intervention arms. Specifically, acceptance rates in the two intervention arms requiring deposits were much lower than anticipated, causing the probability of being assigned to those arms to increase in such a way that we risked depleting the total pool of potentially eligible participants, and thus under-enrolling in the remaining three arms (usual care, individual reward, and cooperative reward arms). Thus, on April 11, 2012, we implemented a 60%/40% split such that 60% of enrollees would be randomized to the three more acceptable arms (usual care + individual reward + collaborative reward) and 40% to the less acceptable arms (individual deposit + competitive deposit). Randomization probabilities among the first 3 arms still varied according to the same adaptive algorithm, as did randomization probabilities among the latter 2 arms; the only difference was that prior to implementing the adaptive randomization, we first ensured that a random sample of exactly 60% of new enrollees would go to the 3 more favorable arms and then get randomized among them. On April 25, 2012, in response to persistent overassignment to the less preferred arms, we changed to an 80%/20% split between the same two groups. This ultimately began to overcorrect the problem, so on September 25, 2012, we changed to a 50%/50% split between the two groups. Finally, on September 26, 2012, we retained this 50%/50% split, and continued the adaptive randomization among the two deposit arms, but among the 50% of participants randomized to the group containing the other three arms, we fixed the allocation probabilities for the usual care (15%), individual reward (15%), and collaborative reward (70%) arms to bolster assignment to the latter. These changes ultimately resulted in adequate enrollment in all 5 arms: a total of 2,538 participants, 1,528 of whom accepted their assigned intervention: Usual Care- 468 assigned (all accepted by default); Individual Reward- 498 assigned, 472 Accepted; Collaborative Reward- 519 assigned, 442 accepted; Individual Deposit- 582 assigned, 75 accepted; Competitive Deposit- 471 assigned, 71 accepted. Other modifications and amendments are listed in the table below.

<table>
<thead>
<tr>
<th>Protocol Version</th>
<th>Amendment or Clarification</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version 2.10</td>
<td>We retained a 50%/50% split between [usual care + individual reward + collaborative reward arms] and [individual deposit + competitive deposit arms], continued the adaptive randomization for the deposit arms, but among the 50% of participants randomized to the group containing the other three arms, we fixed the allocation probabilities for the usual care (15%), individual reward (15%), and collaborative reward (70%) arms to bolster assignment to the latter.</td>
<td>2012-09-16: IRB Approval</td>
</tr>
<tr>
<td>Version 2.9</td>
<td>We changed to a 50%/50% split between [usual care + individual reward + collaborative reward arms] and [individual deposit + competitive deposit arms]</td>
<td>2012-09-14: IRB Approval</td>
</tr>
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<td>Version 2.8</td>
<td>In this modification we proposed four different versions of the email messages sent to people who had created accounts but had yet to enroll. Two messages focused on the health benefits of quitting smoking while the other two placed some emphasis on the money that can be earned in this study. Across these messages we</td>
<td>2012-06-15: IRB Approval</td>
</tr>
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</table>
varied the subject line as well. One health focused email and one money-focused email had the subject line focused on health. The remaining messages had the subject line focused on money.

<table>
<thead>
<tr>
<th>Version 2.7</th>
<th>In this modification we proposed two different postcard messages for our recruitment. One message focused on the health benefits of quitting smoking while the other placed some emphasis on the money that can be earned in this study.</th>
<th>2012-05-30: IRB Approval</th>
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<td>Version 2.6</td>
<td>In this modification we proposed adding a sub-study to examine the effects of two lotteries on enrollment completion. One lottery was for an IPad3, the other lottery was for the direct cash equivalent. This lottery was available for all those who had already completed enrollment and for those who would complete enrollment by our pre-determined date. The eligibility criteria were updated for this modification: - The study was made available to individuals who use tobacco products, other than cigarettes. - Extended enrollment eligibility to friends of CVS employees. - We changed the randomization probabilities to an 80%/20% split between [usual care + individual reward + collaborative reward arms] and [individual deposit + competitive deposit arms]</td>
<td>2012-04-23: IRB Approval 2012-04-17: Registry update</td>
</tr>
<tr>
<td>Version 2.5</td>
<td>The following changes were made in this modification: - We extended the time frame allowed for participants to make a deposit for the deposit contract arms from 14 days to 30 days. - We increased the pre-screen payments for verification of smoking status prior to participation from $20 to $100 to appropriately compensate individuals for their time and effort.</td>
<td>2012-04-13: IRB Approval</td>
</tr>
<tr>
<td>Version 2.4</td>
<td>We implemented a 60%/40% split between [usual care + individual reward + collaborative reward arms] and [individual deposit + competitive deposit arms]. This meant that 60% of new participants would be adaptively randomized to the usual care, individual reward, or collaborative reward arms and 40% would be adaptively randomized to the individual deposit or competitive deposit arms.</td>
<td>2012-04-11: IRB Approval</td>
</tr>
<tr>
<td>Version 2.3</td>
<td>Made the following changes to the protocol: - To include additional recruitment opportunities at on-site Wellness Fairs CVS Caremark sponsors during their open enrollment period. - Report of a protocol deviation: Our study consists of online enrollment where participants are required to review and sign an informed consent electronically. A participant selected that they did not agree to the consent and thus</td>
<td>2012-03-27: IRB Approval 2012-03-08: Registry update</td>
</tr>
</tbody>
</table>
was not enrolled into the study. Upon further consideration this participant decided they wanted to participate and contacted us directly. In order to allow them to participate we elected to mail them two copies of the informed consent and asked them to mail back a signed copy. Upon receiving this signed consent we would allow this person to enroll into the study and participate.

- To include a sub-study aimed at bolstering enrollment for this study. The objective of this sub-study was to propose to study two variations on how the current compensation amount of $50 is given to participants after completing enrollment. The first method was to offer potential participants $50 to complete the enrollment process for a limited amount of time after which they would only receive only $25 to complete. The second method was to offer potential participants $75 to complete enrollment for a limited time after which they would only be eligible for the original $50 for completion. This sub-study lasted for 6 weeks.

**Version 2.2**

Added additional recruitment strategies: emails that were used to recruit and to solicit help with recruitment, announcements on CVS employee websites announcing the study, and a voicemail to announce this study to all CVS employees by the chief medical officer Troy Brennan.

**Version 2.1**

Made changes to protocol to:

- Include updated language that describes the availability of a chat room for participants in a collaborative rewards arm.
- Updated language describing the availability of nicotine replacement therapy and counseling through CVS for insured employees.

Updated eligibility survey to include new eligibility and inclusion criteria:

- Removed questions asking whether the participant is interested in quitting and whether they plan to leave CVS in the next year.
- Updated a question to ask whether the person is a CVS employee or family member of an employee rather than just a spouse.

**Version 2**

Several changes occurred with this study from the time of grant funding through the time at which the original protocol was approved by the IRB:

- We partnered with CVS Caremark for this study instead of Walgreens.
- We included spouses of CVS employees as eligible participants

2012-02-20: IRB Approval

2012-02-01: IRB Approval

2012-01-31: Clinical Trials Registration

2011-09-26: NCI Communication

2011-12-22:
- Recruitment strategies were expanded so that we could recruit from the entire CVS population of employees instead of targeting a population of known smokers.
- Incorporated a pre-screening strategy to verify smoking status in 10% of those recruited. This was done because we did not have prior knowledge of the smoking status of potential participants.
- Randomization stratification variables were changed to only include insurance status (did they have their insurance with CVS Caremark or not) and household income (above or below median).
- Sample collection would now be done with CVS MinuteClinics and a Hooper Holmes Health and Wellness, a biometric screening and collection agency.
- Saliva samples would now be tested for cotinine using NicAlert strip tests and Urine samples would be tested for anabasine using ARUP labs.

**Version 1.0 Grant Application**
The grant application was considered Version 1.0 of the protocol. The grant was awarded funding on September 29, 2010.

**2010-09-29 (Grant funded)**
4. Original Statistical Analytic Plan

A. ANALYTIC METHODS

The design of this study differs from a traditional RCT in two important ways. First, because the goal of this RCT is to focus on mechanisms of behavior change, we will conduct a per-protocol analysis designed to determine incentive structures’ efficacy by analyzing only participants who accept their assigned incentive structure at the time of randomization. However, because basic per-protocol analyses are subject to selection biases, we will model the randomization arm as an instrumental variable to mitigate potential selection bias.\(^{54,55}\) As in a traditional RCT, we will also analyze each incentive structures’ effectiveness using an intention-to-treat analysis that includes all randomized participants, regardless of whether or not they accept the randomly assigned arm. Below are details on each analysis [Note: please also see our analytic supplement for full details on the efficacy analyses].

We will use logistic regression as our primary analytic model to assess efficacy, effectiveness, and acceptance between and among the 5 groups. Although longitudinal models such as generalized estimating equations might be considered in light of the repeated measures among individual participants, logistic regression is preferred in this case because the primary outcome collapses most time points into a single dichotomous measure of prolonged abstinence.\(^{63}\) Participants who fail to complete follow-up will be evaluated as smokers in all analyses.

**Per-protocol and intention-to-treat analyses.** The efficacy of an intervention is a question of how well it works among those who accept it (or, in other contexts, “adhere” to it). By contrast, to be effective – that is, to have an impact on populations – requires that an intervention be both efficacious and accepted. We will use intention-to-treat analyses, in which all participants are analyzed as randomized (i.e., regardless of acceptance), to measure effectiveness.\(^{64}\) However, given our focus on the mechanisms by which different incentive structures modify behavior, we also will assess and report incentive structures’ efficacies using per-protocol analyses, excluding participants who do not accept their assigned intervention. Such per-protocol analyses may be subject to selection bias if smokers who do not accept a structure differ from those who do in ways that relate to their probabilities of quitting. Although this limitation is more fundamental to tests of effectiveness than to considerations of efficacy, we will use complier average treatment effect analyses, which use data from all patients and model the randomization arm as an instrumental variable, to mitigate such bias.

An instrumental variable is an independent variable that is only related to the outcome variable through relationships with one or more other independent variables. By virtue of this property, inclusion of a true instrumental variable in analytic models can substantially mitigate the potential for unmeasured confounding, thereby augmenting the ability to identify causal and mechanistic effects of interventions.\(^{55,65}\) Although true instrumental variables can be difficult to find in many contexts, in RCTs the randomization arm provides an excellent instrumental variable because it is very likely to satisfy the crucial assumption of not being related to unmeasured confounders. A randomization arm is also likely to meet other assumptions for instrumental variables, including the exclusion restriction (no direct relationship between randomized assignment and outcome except for that mediated by assignment acceptance) and the absence of interaction between the randomized group and the probability of acceptance or adherence.\(^{66}\) Thus, for the per-protocol analyses in this study, we will include the randomization arm as a covariate.\(^{66,67,68}\)

**Approach to missing data.** As in our prior studies where retention was excellent, we will provide carefully structured incentives to retain participants.\(^{16,69}\) However, as in nearly all smoking cessation studies, we will classify persons with incomplete follow-up data as smokers in both per-protocol and
intention-to-treat analyses. This approach generally will produce a conservative bias (i.e., towards the null). However, because the biases produced may be less predictable if differential dropout occurs among treatment arms and/or if relatively large (e.g., >10-20%) proportions of participants have missing outcome data, we will explore and potentially adjust for patterns of missingness by using pattern-mixture methods in secondary analyses.63,70

B. SAMPLE SIZE, POWER, AND DETECTABLE EFFECTS

Our calculations indicate that 2,185 participants would be needed – 437 in each of the 5 arms – to obtain 80% power to detect absolute differences ≥ 7.5 percentage points in prolonged abstinence rates between any one of the novel incentive structures (arms 3, 4, or 5) vs. the standard structure (arm 2). This calculation is based on (a) an assumed 6-month prolonged cessation rate of 14.7% in arm 2, as achieved in our prior study of this individual rewards structure, (b) 2-sided significance testing, (c) adjustment for multiple comparisons using the stepwise Hochberg method where the initial test is at α = 0.05 and subsequent tests are at progressively lower α levels, and (d) an allowance for imbalance across arms of up to 10%.71 This sample size also provides > 90% power to detect each structure’s absolute efficacy compared with usual care (estimated success rate of 5%6), and > 80% power in Aim II to detect differences in acceptance ≥ 7.5 percentage points between incentive structures, assuming ≥ 90% acceptance of the standard structure.72 An important strength of this proposed study is that, unlike prior RCTs of incentives, we will be specifically powered to determine how individuals vary in their responsiveness to or acceptance of financial incentives (Aim III). Presentation of power for detecting such interactions is complex, but can be conceptualized by a few key points. First, detecting an interaction of equivalent size to a main effect generally requires that sample size be increased by roughly 50%.73 Second, despite this, our power to detect interactions in this study will actually be greater than the power to detect main effects, because our hypothesized interactions utilize much larger sample sizes by combining trial arms. For example, we wish to determine whether the difference in acceptance between incentives framed as losses vs. rewards differs among people of varying incomes. This question entails a comparison of how the difference between acceptance of the loss frame (arms 3 + 5, or 974 participants) and the gain frame (arms 2 + 4, or 974 participants) varies across people with different incomes. Third, the ordinal nature of this effect modifier (income), and continuous nature of other hypothesized effect modifiers (e.g., number of substitute reinforcers), enhances power relative to what would be obtained with dichotomous effect modifiers. For these reasons, our overall goal sample size of 2,185 participants provides ≥ 80% power to detect hypothesized statistical interactions of magnitudes equal to 57-87% of the main treatment effect (7.5 percentage points) that we will be powered to detect. In the example above, if the gap in acceptance between loss vs. gain frames was 7.5 percentage points in the high-income group, we would be able to detect as significant an increase of roughly 5 percentage points to a gap of 12.5 percentage points among low-income participants.
5. Final Statistical Analytic Plan

A. ANALYTIC METHODS

The design of this study differs from a traditional RCT in two important ways. First, because the goal of this RCT is to focus on mechanisms of behavior change, we will conduct a per-protocol analysis designed to determine incentive structures’ efficacy by analyzing only participants who accept their assigned incentive structure at the time of randomization. However, because basic per-protocol analyses are subject to selection biases, we will model the randomization arm as an instrumental variable to mitigate potential selection bias.\textsuperscript{54,55} As in a traditional RCT, we will also analyze each incentive structures’ effectiveness using an intention-to-treat analysis that includes all randomized participants, regardless of whether or not they accept the randomly assigned arm. Below are details on each analysis [Note: please also see our analytic supplement for full details on the efficacy analyses].

We will use logistic regression as our primary analytic model to assess efficacy, effectiveness, and acceptance between and among the 5 groups. Although longitudinal models such as generalized estimating equations might be considered in light of the repeated measures among individual participants, logistic regression is preferred in this case because the primary outcome collapses most time points into a single dichotomous measure of prolonged abstinence.\textsuperscript{63} Participants who fail to complete follow-up will be evaluated as smokers in all analyses.

\textit{Per-protocol and intention-to-treat analyses}. The efficacy of an intervention is a question of how well it works among those who accept it (or, in other contexts, “adhere” to it). By contrast, to be effective – that is, to have an impact on populations – requires that an intervention be both efficacious and accepted. We will use intention-to-treat analyses, in which all participants are analyzed as randomized (i.e., regardless of acceptance), to measure effectiveness.\textsuperscript{64} However, given our focus on the mechanisms by which different incentive structures modify behavior, we also will assess and report incentive structures’ efficacies using per-protocol analyses, excluding participants who do not accept their assigned intervention. Such per-protocol analyses may be subject to selection bias if smokers who do not accept a structure differ from those who do in ways that relate to their probabilities of quitting. Although this limitation is more fundamental to tests of effectiveness than to considerations of efficacy, we will use complier average treatment effect analyses, which use data from all patients and model the randomization arm as an instrumental variable, to mitigate such bias.

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6. Summary of Amendments and Clarifications to Statistical Analytic Plan

No changes were made to the analytic plan during the course of this research.
7. Literature Cited

35. Hoelzl E, Loewenstein G. Wearing out your shoes to prevent someone else from stepping into them: Anticipated regret and social takeover in sequential decisions. Organizational Behavior and Human Decision Processes 2005;98:15-27.