The Use of Mobile Health Technology and Behavioral Economics to Encourage Adherence to Statins and Blood Pressure Lowering Medication in Adolescents with Familial Hypercholesterolemia or Hypertension: Protocol for Pre-Post Comparison Study

Jacob Hartz, Hannah Palfray, Sarah de Ferranti, Tiffany Powell-Wiley

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Jacob Hartz[1, 2] MD, MPH; Hannah Palfray[1, 2]; Sarah de Ferranti[1, 2] MD, MPH; Tiffany Powell-Wiley[3, 4] MD, MPH

[1]Department of Cardiology Boston Children's Hospital Boston US
[2]Department of Pediatrics Harvard Medical School Boston US
[3]Social Determinants of Obesity and Cardiovascular Risk Laboratory, Building 10-CRC 5-5332 Cardiovascular Branch, Division of Intramural Research National Heart, Lung, and Blood Institute, National Institutes of Health Bethesda US
[4]Intramural Research Program, National Institute on Minority Health and Health Disparities National Institutes of Health Bethesday US

Corresponding Author:
Jacob Hartz MD, MPH
Department of Cardiology
Boston Children's Hospital
300 Longwood Ave.
Boston
US

Abstract

Background: Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in the United States, with risk factors such as hypertension and elevated LDL cholesterol originating in childhood. While statins and blood pressure-lowering medications can mitigate these risks, adherence is often poor, particularly among youth. Innovative solutions, such as monetary incentives via smartphone applications, may enhance adherence, but evidence in youth is lacking.

Objective: This study aims to evaluate the efficacy of a smartphone application (Wellth®) offering financial incentives to improve adherence to statins and blood pressure-lowering medications among youth aged 12-19 at risk for cardiovascular disease.

Methods: We initially designed a randomized controlled trial to compare the efficacy of two different incentive structures in youth treated with a statin for familial hypercholesterolemia with inadequate adherence. After facing recruitment challenges, the study protocol was changed to evaluating a single incentive in a pre-post design, The primary outcome was the change in adherence rate over the 60-day incentive period compared to the adherence rate during the 14-day “run-in” period. The secondary outcome was a change in LDL cholesterol level. Adjustments to the protocol were made in response to recruitment challenges during the COVID-19 pandemic, simplifying the incentive structure and expanding eligibility criteria.

Results: The study is currently undergoing recruitment and collection of data from the first participants. The study has faced recruitment challenges exacerbated by the COVID-19 pandemic, necessitating protocol modifications. Detailed analysis of adherence rates and LDL cholesterol changes is ongoing.

Conclusions: This study explores the efficacy of monetary incentives delivered through a smartphone application to improve medication adherence in youth at risk for CVD. The findings will be used to build upon the existing literature in an effort to improve medication adherence throughout the life-course and ultimately reduce CVD.

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Authors: Jacob Hartz, MD, MPH[1,2]; Hannah Palfrey,[2] Tiffany M. Powell-Wiley,[3,4] MD, MPH; Sarah de Ferranti MD, MPH[1,2,]

Affiliations
[1]Department of Pediatrics
Harvard Medical School
Boston, MA 02115

[2]Department of Cardiology
Boston Children's Hospital
Boston, MA 02115

[3]Social Determinants of Obesity and Cardiovascular Risk Laboratory, Building 10-CRC 5-5332
Cardiovascular Branch, Division of Intramural Research
National Heart, Lung, and Blood Institute, National Institutes of Health
Bethesda, MD 20892.

[4]Intramural Research Program, National Institute on Minority Health and Health Disparities National Institutes of Health
Bethesda, MD 20892.

Corresponding Author
Jacob Hartz, MD, MPH
300 Longwood Ave.
Department of Cardiology
Boston Children's Hospital
Phone: 617-355-09555, Fax (617) 355-0955
Jacob.hartz@cardio.chboston.org

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ABSTRACT

Background

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in the United States, with risk factors such as hypertension and elevated LDL cholesterol originating in childhood. While statins and blood pressure-lowering medications can mitigate these risks, adherence is often poor, particularly among youth. Innovative solutions, such as monetary incentives via smartphone applications, may enhance adherence, but evidence in youth is lacking.

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Methods

We initially designed a randomized controlled trial to compare the efficacy of two different incentive structures in youth treated with a statin for familial hypercholesterolemia with inadequate adherence. After facing recruitment challenges, the study protocol was changed to evaluating a single incentive in a pre-post design. The primary outcome was the change in adherence rate over the 60-day incentive period compared to the adherence rate during the 14-day “run-in” period. The secondary outcome was a change in LDL cholesterol level. Adjustments to the protocol were made in response to recruitment challenges during the COVID-19 pandemic, simplifying the incentive structure and expanding eligibility criteria.

Results

The study is currently undergoing recruitment and collection of data from the first participants. The study has faced recruitment challenges exacerbated by the COVID-19 pandemic, necessitating protocol modifications. Detailed analysis of adherence rates and LDL cholesterol changes is ongoing.

Conclusion

This study explores the efficacy of monetary incentives delivered through a smartphone application

to improve medication adherence in youth at risk for CVD. The findings will be used to build upon the existing literature in an effort to improve medication adherence throughout the life course and ultimately reduce CVD.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and disability in the United States. It leads to $216 billion in direct costs and an additional $147 billion in indirect costs each year.[1] While the presentation of CVD events primarily occurs in adulthood, the significant risk factors for CVD, including hypertension and elevated low-density lipoprotein (LDL) cholesterol, have their antecedents in childhood.[2,3] With the use of statins[4-17] and blood pressure-lowering medications,[18] substantial reductions in this risk are possible.

However, adherence to statins and blood pressure-lowering medications is needed to accrue these potential benefits. Unfortunately, medication adherence is frequently poor, with up to 50

percent of adults not taking all their prescribed medications.[19-23] In adults, nonadherence is associated with an increased risk for CVD events and all-cause mortality,[20,24] as well as almost $44 billion annually in additional healthcare costs.[25,26] Although studies are limited, adherence to statins and blood pressure-lowering medications also has been shown to be inadequate in youth.[27-30] Youth seem to be particularly vulnerable to nonadherence,[31] even in diseases in which the consequences of nonadherence can lead to rapid disease progression or severe, acute symptoms, such as bipolar disorder,[32] human immunodeficiency virus,[33] or asthma.[34]

Multiple factors impact adherence **(Figure 1),** including patient-related factors (e.g., beliefs and expectations), socioeconomic factors, medication-related factors (e.g., complexity of the regimen and adverse effects), the disease being treated, and the health care system.[35] Unfortunately, successful interventions to improve medication adherence overall are rare in both adults[36] and youth.[36,37] Further, there are no formally tested interventions to improve adherence to statins or blood pressure-lowering medications in youth. One potential solution to improve adherence is to provide monetary incentives. Traditional economic theory suggests that providing individuals with incentives to complete an action will lead to increased frequency of the occurrence of the desired action. Studies in adults have shown monetary incentives to be modestly successful in certain diseases[38-40] , but not all studies have shown positive results.[41] Further, it is unclear if these findings translate to youth.

To address this gap, we planned a study using a smartphone application (Wellth®) to provide financial incentives to improve medication adherence in youth at risk of CVD. Smartphone applications are promising interventional tools as they are familiar to most youth.[42,43] Data suggests using smartphone applications in a healthcare setting is of interest to youth[44] across a diverse set of socioeconomic and cultural backgrounds.[42] The Wellth application is designed to improve medication adherence through reminders and by providing monetary rewards for taking a medication as prescribed.

The objective of this manuscript is to describe the original study design, recruitment methods, outcomes, analysis plan, strengths, and limitations. In addition, we highlight modifications to the design and recruitment strategies because of the social distancing requirements related to the COVID-19 pandemic and to improve recruitment.

INTERVENTION

Study Design

Use of Mobile Health Technology and Behavioral Economics to Encourage Adherence to Blood Pressure-Lowering Medications and Statins in Youth at Risk for Cardiovascular Disease was designed as a randomized control trial to compare the efficacy of two interventions on improving medication adherence to statins in youth ages 12-19 years old using a smartphone application **(Figure 2)**. The 104-day study consisted of a 14-day "run-in" period, two periods of 30 days in which subjects received incentives, and a 30-day "follow-up" period in which subjects were asked to record adherence but did not receive any incentives. During the "run-in" and "follow-up" periods, all features of the Wellth® application were available, except that the subjects did not receive any monetary incentives during these periods. This was included to isolate the effect of the monetary incentive from the other features of the application and to provide an objective baseline measure of adherence. After the 14-day "run-in," subjects were eligible to receive incentives during two 30-day incentive periods. Incentives were dispersed at the end of Period 1 (Day 44) and Period 2 (Day 74). In addition, we also measured the patient's adherence in the 30-day period after the incentive periods to determine if the effect of the intervention had sustained effects.

Eligibility Criteria

The original eligibility criteria are described in **Table 1**. Patients were eligible to participate if they were 12 to 19 years old, had a diagnosis of familial hypercholesterolemia (FH), were prescribed a statin, and reported less-than-ideal statin adherence. The diagnosis of FH was based on genetic testing or if the patient met the National Lipid Association recommendations, which are an LDL

cholesterol greater than or equal to 160 mg/dL or a non-HDL cholesterol greater than or equal to 190 mg/dL in patients <20 years old.[1119,20,45]

Recruitment

We recruited patients from a tertiary care hospital and its satellite outpatient clinics. Recruitment took place at outpatient clinic visits in a Preventive Cardiology Clinic. The study clinicians approached eligible patients and provided a brief overview of the study. If the participant was interested, the clinician would determine the patient's eligibility based on self-report adherence rate. If the patient was eligible and agreed to participate, then the clinician conducted the informed consent and enrollment.

We supplemented clinic recruitment by recruiting patients with FH treated with a statin by phone using a database maintained by the Preventive Cardiology Program, which includes approximately 400 patients. We estimated that 20 patients per month who met the eligibility criteria would be seen. If 50 percent of those patients agreed, we expected to complete the recruitment of 30 patients in 6 months (power calculation below).

Outcomes

The primary outcome was medication adherence as measured by the Wellth application and defined as the proportion of doses taken per doses prescribed. The adherence rate used in the analysis would be measured over one 14-day period and three 30-day periods (Day 1-14; Day 15-44; Day 45-74; Day 75-104). Secondary outcomes included changes in the LDL cholesterol levels from baseline until the end of the intervention period (Day 74). LDL cholesterol was considered a baseline measurement if it was obtained within 60 days from the day of consenting to the study. The covariates we included in the analysis were gender, age, and race/ethnicity.

Description of Wellth Application

The Wellth application was the primary tool used in the study to promote medication adherence. Patients used the application to receive reminders, make check-ins (i.e., document

adherence), check their reward balance, and view their adherence history. Participants would download the application to their smartphone without any additional software or encryption needed. In order to prevent patients from being excluded based on the costs of the necessary hardware, we provided a smartphone and data plan free of charge to patients. Wellth monitored application use and uploaded photos through a secure, customized analytics dashboard for data monitoring and customer support.

Structure of Incentive

Initially, subjects were to be randomized to one of two incentive structures. The first structure of the incentive was based on the principles of present bias and loss aversion. The incentive structure used in this protocol was based on the principles of Present Bias and Loss Aversion. Present Bias refers to the tendency of individuals to prefer more immediate rewards and outcomes and to discount future risks. [46] For instance, studies suggest that even small rewards, if provided frequently and immediately after a participant completes a desired task, can improve adherence in adults and may be more effective at promoting behavior change than larger rewards provided in the distant future.[36,47,48] The principle of Loss Aversion was included to help strengthen the incentive and is based on findings from studies that suggest individuals place more value on money or objects that they have than on new objects of the same value.[49]

Subjects would receive $30 at the beginning of each of the two 30-day periods but only were able to access money at the end of the 30-day periods. However, subjects could view their balance within the application at any time. For each missed check-in, the subject would lose $2 from the amount to be paid out at the end of the 30-day period. Subjects who missed more than 15 check-ins would not receive any money receive at the end of the 30-day period.

In the second incentive approach, subjects would not receive rewards for each “check-in” but instead receive the “chance” to receive a reward of varying amounts. This incentive structure is similar to that of a slot machine. As in the first incentive structure, the total amount a subject could

receive over the two 30-day periods was $60. However, subjects would not lose money if a “check-in” was missed, but rather they would lose an opportunity to receive a reward. The random distribution of the reward was structured so that a fully adherent subject would be ensured to receive a full $60 over the study period. However, in this arm of the study, it was also possible that a subject could receive $60 even if they were not fully adherent.

Power

Power calculations were performed for the primary outcome variable adherence rate at the end of the 60-day period. The mean difference in adherence rates at 60 days after the start of the intervention (Day 74) would be compared to 0%, which was the value that would be expected if there was no difference between the two interventions using a two-sided paired t-test conducted at the 0.05 level of significance. The mean adherence rate was hypothesized to be 80% when patients receive small frequent awards and 74% when receiving a large, randomly delivered reward, suggesting a mean within-patient difference of 6%. The standard deviation of the adherence rate was assumed to be 10% at each time point,[27] and the correlation between the two measures of adherence was assumed to be 0.50, resulting in a standard deviation of differences in adherence rate of 10%. If the correlation between measurements of adherence was conservatively assumed to be 0.30, the standard deviation of differences in adherence rate was estimated to be 11.8%. We expected to enroll 30 patients.

Statistical Analysis

Data would be analyzed on an intention-to-treat basis. Baseline patient characteristics measured prior to randomization would be compared between the two intervention groups to look for imbalances. Primary and secondary outcomes would be compared between groups on Day 44, Day 74, and Day 104. Continuous variables would be compared using the two-sample t-test or Wilcoxon rank sum test. Differences in categorical variables would be assessed using Fisher’s exact test. Analyses of the primary outcome variables (i.e., percent change in LDL cholesterol and proportion of

days adherent) would use a significance level of 0.025 at each follow-up time point; all other comparisons would be performed at the 0.05 level of significance. If differences in baseline characteristics were detected between the two groups, linear regression would be used to perform additional comparisons of the primary and secondary outcomes, controlling for these potential confounders. Transformations would be applied to continuous outcomes that were not normally distributed.

ADJUSTMENTS TO PROTOCOL

COVID-19 Pandemic

Our initial protocol and recruitment strategy had to be modified in response to the challenges that arose during the COVID-19 pandemic. In the original proposal, we planned to recruit patients seen during routine outpatient visits. However, in the early months of the pandemic, outpatient clinic appointments were limited to those with "urgent" concerns, which rarely included patients with dyslipidemia. Enrolling subjects remotely, though, posed several challenges. The first was connecting the patient to our research assistant. Unlike an in-person clinic visit in which the research assistant is readily available, connecting the research assistant with the patient during a remote encounter required arranging additional contact with the patient. We found that if there were any delays in connecting to the research assistant, eligible subjects seemed to quickly lose interest.

A second problem arose in obtaining written consent from subjects seen via telehealth visits. Unfortunately, the infrastructure for obtaining an electronic signature was initially unavailable and written consent was required by our institution. The written consent was rarely completed during the course of a virtual visit. Instead, families typically planned to send the signed consent forms that evening or the next day, which often did not occur despite repeated attempts to contact eligible patients. In addition, errors in the consent, such as missed signatures or illegible handwriting, often led to patients not participating, as obtaining corrected consent forms was challenging.

The third barrier that arose was related to technical issues signing patients up for the Wellth

application. While configuring the application for the patient was not cumbersome, and there were no complaints by subjects enrolling in the study, adding study-related information (e.g., participant identification number and study codes) was sometimes technically challenging. We could not have the subject download the smartphone application until the consent was finalized, which often meant arranging a separate time to get the application operational, and some subjects dropped out after signing the consent because of the additional time commitment.

Low Recruitment

Recruitment for the trial was more difficult than expected, in part related to the COVID-19 pandemic. We were concerned that the complexity and duration of the trial were deterrents. Over the first year, we made several sequential changes to simplify the intervention.

First, we decided to use only the first intervention, which involved small, frequent rewards, while removing the second intervention, which entailed random, variable rewards. This was based on our perception that the first intervention was conceptually easier for pediatric subjects to understand. Since we would no longer be comparing two types of incentive structures, we also removed randomization and created a pre-post-study design **(Figure 2)**. Adherence measures collected via the app during the 14-day “run-in” period would be used as the baseline adherence measure to be compared to adherence recorded on Day 44, Day 74, and Day 104.

The second modification was to shorten the trial duration by removing the 30-day follow-up period. We received feedback from potential subjects during recruitment that the length of the trial prevented them from participating. As this portion of the trial was predominantly included to assess the sustainability of the incentive, it made more sense to remove it rather than shorten the incentive period.

Third, we expanded the protocol to include patients with hypertension and prescribed a blood pressure-lowering medication (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, diuretics, or calcium channel blockers) to increase the pool of eligible

participants. We did not change the incentive structure, even for those patients who were prescribed regimens with twice-daily dosing. In these patients, we required both doses to be taken to earn the reward. The diagnosis of hypertension was based on chart review (i.e., ICD-9 or -10 diagnosis hypertension associated code) and was not based on blood pressure-specific thresholds.

DISCUSSION

This research protocol will test whether providing incentives that leverage the principles of behavioral economics to improve medication adherence in youth with FH and hypertension. Understanding the effectiveness of different types of incentives is crucial to improve medication adherence. The incentive structure in regard to the type of reward, frequency of receiving the award, and timing of delivery of the reward can lead to different responses. In fact, there is evidence that inappropriate reward structures can serve as a negative enforcer.

In addition, this proposal will harness the power of digital health technology, taking advantage of the fully-developed Wellth® application to reduce costs and simplify the intervention. Digital health applications allow for the automation of patient-provider interactions, improved monitoring using cameras with embedded metadata (e.g., date and time), and reduce the complexity of interventions, allowing for more widespread distribution of interventions.

Patients with FH and hypertension provide an ideal cohort to explore the role of different incentive packages. FH is rarely symptomatic in youth, and treatment is typically well-tolerated. One critical factor is that missed doses do not generally lead to acute complications in either disease. Therefore, providers and caretakers can safely distance themselves from interfering, which prevents adding biases introduced by frequent provider engagement.

It should be acknowledged that there are important differences between those prescribed lipid-lowering therapy for an inherited condition and those treated for hypertension, which is typically an acquired condition. Further, blood pressure-lowering medications have a different side effect profile than statins and may be prescribed more than once daily, which may impact adherence.

CONCLUSION

This proposal will elicit information critical for creating developmentally appropriate incentive structures to improve medication adherence in youth with risk factors for CVD. However, the efficacy of monetary incentives is extrapolated from adult studies, and it remains to be seen if they are ideal for youth.

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Figures

Figure 1. Five components of medication adherence as proposed by the World Health Organization.[35] The green curved arrows indicate components expected to respond to incentives, while the dashed black arrows are components that are less likely to respond.

Figure 2. Final Study Timeline. The fasting lipid profile included a total cholesterol, triglyceride level, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Table 1. Eligibility and Exclusion Criteria

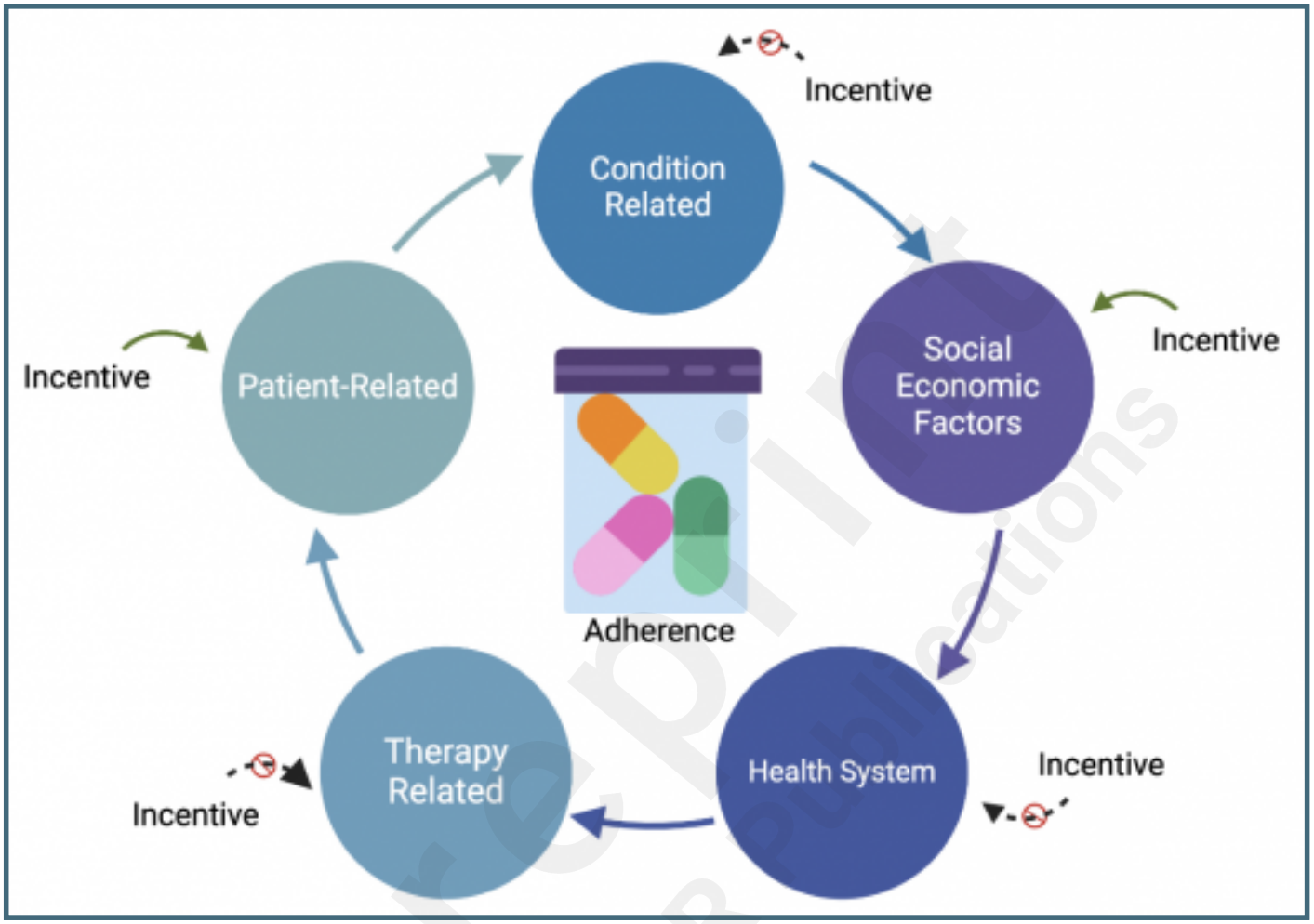
Eligibility Criteria	Exclusion Criteria
Less than ideal adherence by self-report	1. Homozygous FH
1. Ages 12 – 19 years	
2. Diagnosis of FH based on NLA criteria and/or genetic testing or a diagnosis of hypertension	2. Residence in a long-term care facility where medications are administered
3. Prescribed a statin or blood pressure-lowering medication	3. Pregnant or may become pregnant
4. Be able to provide written, informed consent or have a parent/guardian provide written, informed consent	4. History of adverse effect or allergy to a statin or blood-pressuring lowering medication, or any ingredient in one of these medications.

FH, familial hypercholesterolemia; NLA, National Lipid Association.

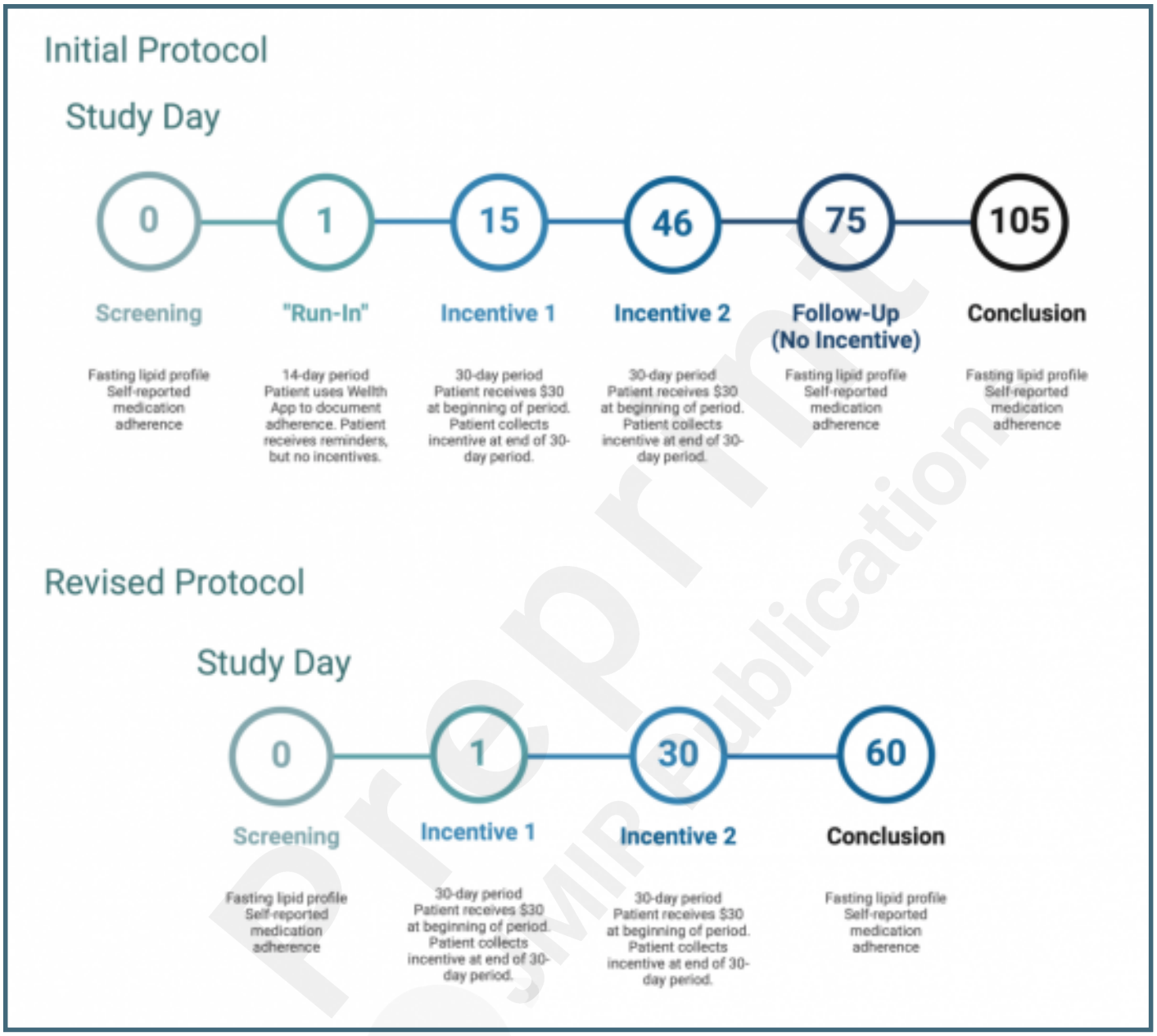
Supplementary Files

Figures

Five components of medication adherence as proposed by the World Health Organization.35 The green curved arrows indicate components expected to respond to incentives, while the dashed black arrows are components that are less likely to respond.



Final Study Timeline. The fasting lipid profile included a total cholesterol, triglyceride level, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.



Multimedia Appendixes

Previous comments by reviewers.
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