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A protocol to evaluate the efficacy, perceptions, and cost of a cholesterol packaging approach to improve medication adherence

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ABSTRACT

Purpose: Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for cardiovascular disease (CVD), a leading cause of death in the United States. Despite clinical practice guidelines aimed at facilitating LDL-C control, many Veterans do not achieve guideline-recommended LDL-C levels.

Methods: We describe a study focused on VA healthcare system users at risk for CVD (i.e., LDL-C level >130 mg/dl and/or <80% cholesterol pill refill adherence in the last 12 months). We are conducting a two and a half year randomized controlled trial (i.e., intervention administered over 12 months) among Veterans with uncontrolled cholesterol receiving care at select VA-affiliated primary care clinics in North Carolina. We anticipate enrolling 250 diverse patients (10% women; 40% African American). Patients are randomized to an educational control group or intervention group. Intervention group participants' medication is provided in special blister packaging labeled for daily use that includes reminders; MeadWestvaco Corporation's pre-filled DosePak® contains standard doses of statins in accordance with the existing prescriptions.

Conclusions: Pre-filled blister packaging may provide an inexpensive solution to improve medication adherence. Our study enrolls a diverse sample and provides information about whether an adherence packaging intervention can: 1) improve medication adherence; 2) improve patients' LDL-C levels; 3) be well received by patients and providers; and 4) provide a cost effective solution to improve medication adherence.

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1. Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is a modifiable risk factor for cardiovascular disease (CVD). In 2013 the American Heart Association, in collaboration with the National Heart, Lung, and Blood Institute and others, released revised guidelines for cardiovascular risk reduction including LDL-C management [1]. This guideline changed recommendations about which patients are at high cardiovascular risk and should be prescribed a statin medication. Based on the new guidelines, most older Americans will be recommended to take statin drugs. The guidelines also removed target cholesterol levels from treatment recommendations (i.e., treat to target and lower is better strategy are not evidence-based).

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Because of the health implications of hyperlipidemia, the Centers for Medicare and Medicaid Services (CMS) established a quality goal. The goal ensured that Medicare Part D members who were prescribed statin medication for hyperlipidemia would fill their prescription often enough to cover 80% or more of the time they are supposed to be taking the medication. Not properly adhering to prescribed medications is associated with higher LDL-C, increased all-cause hospitalization, and increased all-cause mortality [2]. To improve LDL-C control, it is essential to improve medication adherence. The objective of this prescription medication refill goal is to facilitate patients' LDL-C control. Similarly, the Department of Veterans Affairs (VA) healthcare system has adopted the pill refill quality guideline, noting that the overarching goal is to properly treat each individual patient. Unfortunately, many Veterans are not achieving preferred LDL-C levels [3]. Because elevated LDL-C is a major modifiable risk factor for CVD, developing strategies to reduce LDL-C is critical. Reduction of LDL-C in high-risk patients is associated with a substantial reduction in morbidity, mortality, and costs.

Our study seeks to evaluate efficacy, clinical effectiveness, patient and provider perceptions, and cost effectiveness of an innovation prescription medication packaging approach. We posit that this special packaging will improve medication adherence rates among Veterans by addressing the modifiable risk factor of LDL-C. To achieve LDL-C risk reduction, we are conducting a clinical trial that tests the innovative adherence packaging relative to usual care. Specifically, we assess MeadWestvaco (MWV) Corporation's pre-filled DosePak® (i.e., a blister package system).

Innovative packaging of prescription medication could improve medication adherence through several mechanisms. The simple daily labeling may make it is easier to determine whether medications were taken, if there were any missed or skipped doses, and when missed doses occurred. Blister packaging may make medication-taking more convenient for patients by eliminating issues associated with traveling with medication, forgetting whether medications have been taken on a particular day, and other common problems of medication non-adherence. Additionally, this packaging approach may streamline professional monitoring of patients' adherence. Patient's provider or pharmacy staff could examine patient's DosePak® and straightforwardly assess whether and when patients have taken their medication. In general, our study addresses: 1) whether there are benefits of the special blister packaging that, despite additional costs, make it advantageous over a typical amber vial; and 2) for which patients the packaging is most beneficial.

2. Materials and methods

2.1. Study overview

The study that we describe is focused on the users of the VA healthcare system at risk for cardiovascular disease (CVD). Patients are considered to be at risk for CVD if the LDL-C level is greater than 130 mg/dl and/or they have less than 80% medication adherence in the last 12 months. We concentrate on the VHA and LDL-C risk reduction because, despite the availability of effective therapies for dyslipidemia in the VHA, many VA patients fail to meet cholesterol control recommendations [2,3]; only approximately 53% of VA patients who have concomitant diabetes mellitus and hypertension attain appropriate LDL-C values [3].

Patients are followed for 12 months and the study will be a two and a half year (i.e., the intervention will be administered over 12 months, but patients are monitored for up to 30 months to allow for longer-term assessment of whether improvements in medication adherence and LDL-C are sustained after the intervention is complete). This is a randomized controlled trial among Veterans with uncontrolled cholesterol receiving care at the Raleigh Community-based Outpatient Clinic (CBOC) and hospital-based primary care clinics associated with Durham VAMC to improve their CVD risk profile. This study is sponsored by a grant from MeadWestvaco (MWV) and is approved by the Durham VA Medical Center Institutional Review Board (clinicaltrials.gov registration number: NCT01744977).

2.2. Sample identification and eligibility criteria

Potential participants are identified through a data extraction from the VA electronic health record. In order to be eligible for inclusion in the study, patients must meet all of the following criteria: be enrolled in one of the three primary care clinics affiliated with the Durham VA Medical Center (e.g., the Durham VA Medical Center, Hillandale Outpatient Clinic, or Raleigh Community-Based Outpatient Clinic) for at least one year; had at least one visit to their primary care provider in the previous 12 months; have an outpatient diagnostic code for hypercholesterolemia; have uncontrolled LCL-C in the last 12 months (average >130 mg/dl) and/or poor LDL refill defined as <80% medication adherence in the last 12 months; and be prescribed simvastatin, rosuvastatin or pravastatin (e.g., 20 mg or 40 mg as described below). The study statistician identifies patients meeting initial inclusion criteria and randomly samples potential participants for additional screening and study recruitment. Patients are also screened for exclusion criteria at several stages throughout the recruitment process (Table 1).

2.3. Recruitment and randomization procedure

Patient recruitment takes place over the course of 18 months, with the goal of recruiting 8–10 patients weekly. Based on appointment information available in the electronic health record, study staff identify participants who have an upcoming medical appointment scheduled in the next two to three weeks. If insufficient patients are identified, additional patients meeting eligibility criteria who do not have an immediately scheduled upcoming appointment are contacted. An introductory recruitment letter signed by patient's provider is sent to participants that have been identified. Approximately one to two weeks after the introductory letter is mailed, study staff call potential participants to assess patient's interest in the study and determine whether they meet eligibility criteria. For patients interested and eligible, an in-person interview is scheduled. Patients are sent reminder letters up to three weeks prior to their scheduled appointments (e.g., six and 12 month follow-up appointments). During the initial in-person interview, patients are provided with full details of the study and provide written informed consent. Should a consented

Table 1
Eligibility screening phase and criteria.

Eligibility screening phase	Eligibility criteria
Phase 1: initial automated medical record review The study statistician will identify patients meeting initial inclusion criteria through the electronic health record and will randomly sample potential participants.	Patients must meet all of the following: • Enrolled in one of the three primary care clinics affiliated with the Durham VA Medical Center including the Raleigh Community-Based Outpatient Clinic for at least one year • Had at least one visit to their primary care provider in the previous 12 months • Have an outpatient diagnostic code for hypercholesterolemia • Have uncontrolled LCL-C in the last 12 months (average >130 mg/dl) and/or poor LDL refill defined as <80% medication adherence in the last 12 months • Be prescribed simvastatin, rosuvastatin or pravastatin (e.g., 20 mg or 40 mg pills which will fill in the special study packaging)
Phase 2: manual medical record review Prior to contacting potential participants, study staff will manually screen the electronic health record for additional eligibility criteria.	Patients will be excluded for any of the following[a]: • Diagnosis of metastatic cancer • Active diagnosis of dementia • Active diagnosis of psychosis with admission in the previous 30 days • Treated with dialysis • Hospitalized for a stroke, myocardial infarction, coronary artery revascularization in the previous month • Severely impaired hearing, speech or sight • Currently participating in another on-going cardiovascular disease risk management study • Prescribed specific statin medications that preclude the special study packaging.
Phase 3: patient inquiry Patients still meeting inclusion criteria are contacted via telephone. During the initial telephone or in-person interview, study staff screen for final eligibility criteria.	Patients will be excluded for any of the following: • Does not have access to a telephone • Resident in nursing facility that manages patients medications or receiving home health care for extended period (i.e., home health service for less than 30 days remain eligible) • Planning to leave the area prior to the anticipated end of participation in the study

[a] Patients can be excluded at any time (even after enrollment) if diminished mental capacity becomes a concern.

participant have to be excluded post-enrollment for any reason, that participant is provided with the study educational material.

The study statistician completed the study randomization in its entirety prior to the beginning of patient enrollment. In other words, the schematic of the randomization was created prior to the study. Patients were not fit into the next available slot until the time that they were randomized and they were systematically slotted into the next slot based on interview completion. Once a patient consents and completes the baseline patient assessment (described below), the research assistant randomizes the patient to one of the two groups. A blocked randomization technique is used to ensure rolling balance between groups. To prevent contamination, research assistants are blinded to block size. A computerized and centralized process that is integrated into the tracking database determines randomization assignments. The two arms include: 1) education only group, and 2) adherence packaging intervention group. Study flow is described in Fig. 1.

2.4. Baseline patient assessment and follow-up contacts

Participants complete three assessments (baseline, six, and 12 months), plus one optional qualitative, telephone-based interview. During the baseline patient assessment, trained study staff obtain participants' clinical information (i.e., weight, height, blood pressure) using a digital sphygmomanometer and digital scale according to a standard protocol. Laboratory values (i.e., lipids) are obtained following the appointment by the Durham VA Medical Center or Raleigh CBOC laboratory staff and directly entered into patients' hospital electronic medical record. Participants also undergo an in-person interview in which study staff inquire about patients' age, race, medical history, self reported LDL-C adherence, health knowledge, and understanding about CVD risk, lifestyle, changes in weight, and quality of life. Patients are asked about self-reported medication adherence and (for those randomized to the intervention arm) perceptions of the study packaging. To ensure data integrity, all outcome and lab data are double entered into the study database. To minimize loss to follow-up, research study staff may attempt to complete assessments via telephone for patients who are difficult to reach. In addition to reviewing VA medical records for adverse events, patients are asked about such events at each follow-up (e.g., at 6 and 12 months). If a patient reports an event it is documented in the study files and reported to the IRB per local protocols.

2.5. Intervention arms

The education only (i.e., control) group receives primary care and management of LDL according to the discretion of their provider. These patients receive generic educational information on LDL-C reduction and have no contact with the research pharmacist. Additionally, the control group receives written information on how to obtain medication refills and the importance of taking their cholesterol medications as prescribed. At follow-up study appointments patients are provided with further educational material addressing issues of hyperlipidemia. Using a health education control group enables an assessment of the cost benefit of the intervention and is

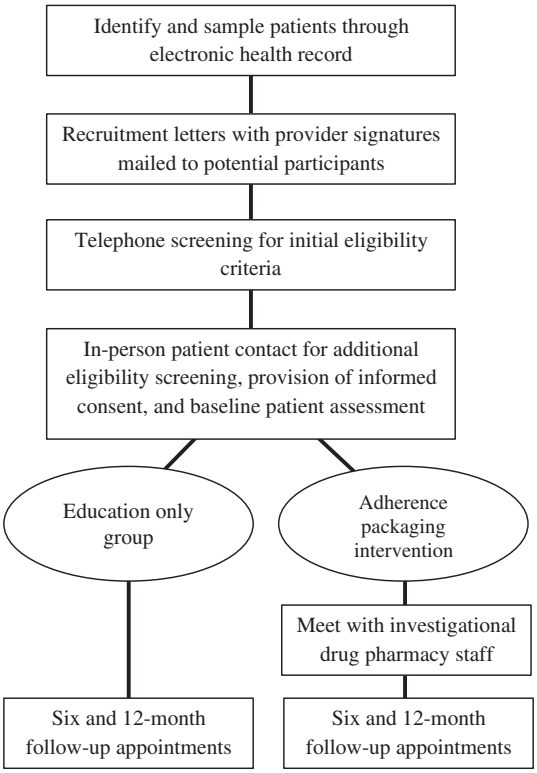

Fig. 1. Study flow.

comparable to the care typically provided in a traditional VA primary care clinic setting. Patients in the education only arm do not receive their medication in the special packaging.

Following the baseline assessment, participants randomized to the adherence packaging intervention group present to the VA study pharmacy for the initial fill of their statin medication. Intervention participants' medications are provided in a special packaging, the MeadWestvaco (MWV) Corporation's pre-filled DosePak® packaging containing standard doses statins (Fig. 2). The DosePak® medication flow (i.e., prescription fill and refill process) is described in Fig. 3. Pre-packaged DosePak® packages of: 1) simvastatin [20 mg or 40 mg tablets]; 2) pravastatin [20 mg or 40 mg tablets]; or 3) rosuvastatin [20 mg or 40 mg tablets] are provided to participants in accordance with their existing prescription. If patients are taking a half-tablet of statin medication prior to study enrollment, the investigational drug pharmacy service keeps participant's current dose but will provide it in a whole tablet. Over the course of the study, staff do not change patients' medications; at the end of patients' active participation in the study, their current prescription for statin is converted back to half tablets per pharmacy policy, if applicable. The medication in the DosePak® is the same medication and dose that patients were prescribed prior to study enrollment. Participant's primary care provider may adjust medications during the course of the study for better cholesterol control. Each package is labeled with the pre-approved patient education and the medication name and dose will be clearly labeled for each batch of medication received into pharmacy. When participants present to pharmacy services they receive a 3-month supply of their standard dose cholesterol medication in the DosePak® package. At the time of the first fill the pharmacist: 1) counsels the patient on the appropriate use of the DosePak®; 2) reviews the patient counseling points for statins included on the package; and 3) reviews how to obtain subsequent refills. Each medication fill for enrolled patients is labeled by pharmacy staff, then checked for accuracy and dispensed by a registered licensed pharmacist. Participants in the intervention group are contacted for an optional, telephone-based qualitative interview within 30 days after their final in-person interview. The objective of the qualitative interview is to evaluate participants' perception of the study packaging and evaluate the successes and challenges of the program.

For patients in both arms, the initial baseline visit takes up to 90 min. Subsequent visits at 6- and 12-months are comparable, but require approximately 60 min for completion. The baseline assessment requires slightly more time because the informed consent document will be reviewed in detail and at the end of the baseline assessment 10 cc of blood will be drawn for a lipid panel.

2.6. Compensation

Participants are paid $20 for participation in each interview (e.g., baseline, 6-, 12-month outcome, and qualitative; available to receive up to a total payment of $80). Therefore, individuals could receive a maximum compensation of $80.

2.7. Outcome measures

The study has three quantitative outcome measures: medication adherence, clinical LDL-C, and cost (Table 2). The primary outcome measure is medication adherence as assessed by the ReComp measure [4,5]. ReComp was developed in the Veterans Affairs healthcare system. It is an electronic

Fig. 2. MeadWestvaco (MWV) Corporation's Pre-filled DosePak® Packaging.

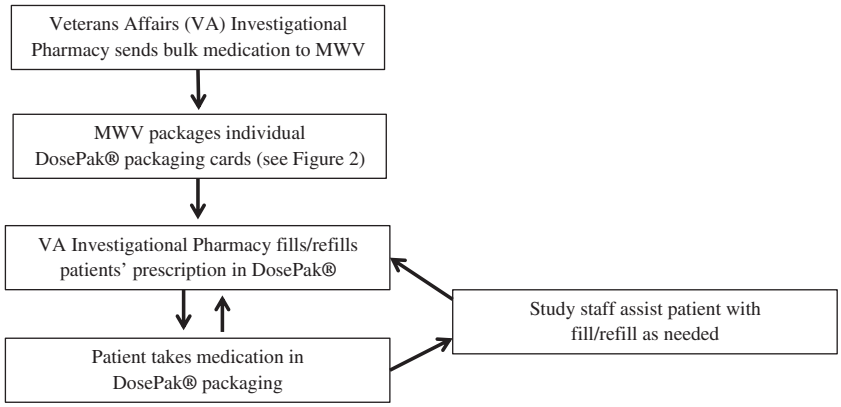

Fig. 3. MeadWestvaco (MWV) Corporation's Pre-filled DosePak® Medication Flow.

pharmacy-based prescription medication refill adherence algorithm and has been validated for multiple short observation periods. It compensates for the limitations of other existing methods of calculating medication adherence by taking into account both overstocking of prescriptions and days when patients have run out of medication. Thus, ReComp enables the examination of gaps in medication supply and oversupply [4]. We will dichotomize the ReComp measure, defining patients as either adherent or non-adherent. Patients who have medications available for at least 80% of each month will be considered adherent; otherwise, patients will be considered non-adherent. Per our statistical analysis described below, this will allow us to design models evaluating the association between adherence and the special blister packaging, as well for which patients the packaging is most beneficial.

The secondary clinical outcome measure is LDL-C. Total and High-Density Lipo-protein Cholesterol (HDL-C) will be obtained from a non-fasting lipid profile, measuring direct LDL-C. LDL-C is the component of total cholesterol used as a treatment target, and levels will both guide the intervention on cholesterol and be used as a secondary outcome. We will measure self-reported medication adherence, specifically to lipid lowering medications, using a valid, reliable measure [6]. With this outcome measure we will evaluate the impact of the intervention extending beyond medication adherence and into clinical patient outcomes.

The third outcome measure is cost from the healthcare system perspective. The cost of the blister package, relative to adherence improvements, will be evaluated. We will assess intervention-related costs (i.e., including cost of the blister

Table 2
Primary and secondary study outcomes.

	The outcome	Measurement	When measured	Variable type
Primary outcomes	Medication adherence	ReComp in a prescription medication refill adherence algorithm takes into account both overstocking of prescriptions and days when patients have run out of medication, enabling examination of gaps in medication supply and oversupply. We will dichotomize the ReComp measure, defining patients as either adherent (i.e., medications available for at least 80% of each month) or non-adherent.	Patient-reported adherence is ascertained during in-person interviews (i.e., baseline, 6-, and 12-months). Pharmacy data for the ReComp measure is obtained at the time of study completion.	Dichotomous (adherent vs. non-adherent)
Secondary outcomes	Total cholesterol and LDL-C	Total cholesterol and LDL-C level in milligrams per deciliter (mg/dl) is obtained from the VA laboratory. Uncontrolled LDL-C is defined as >130 mg/dl.	Laboratory values are obtained at 6 and 12 months.	Continuous and dichotomous
	Cost	Intervention-related costs (i.e., including cost of the blister packaging) and resource-utilization for larger health care costs. Health utilities will be captured using the Health Utilities Index Mark III to enable assessment in Quality-Adjusted Life Years (QALYs). Healthcare events will be obtained from VA electronic records and by querying participants about non-VA hospitalizations during their interviews.	Cost information will be obtained at the time of study completion.	Continuous
	Perceptions of the intervention	This will assessed using qualitative interview data.	The qualitative interview will be completed within 30 days after their final in-person interview.	Qualitative

packaging) and resource-utilization for larger health care costs. Health utilities will be captured using the Health Utilities Index Mark III to enable assessment of cost-effectiveness denominated in Quality-Adjusted Life Years (QALYs), which will serve as the secondary effectiveness measure for the cost-effectiveness analysis. Healthcare events (e.g., emergency room visits, urgent care, and hospitalizations) will be obtained from VA electronic records and by querying participants about non-VA hospitalizations during their interviews.

2.8. Sample size

We anticipate that at least 250 individuals will be randomized to the medication adherence program or control arm. We assume a baseline pill refill adherence rate of 50% in the control arm and expect that adherence will improve in the intervention arm by 10% over the 12-month intervention period. Using the estimates above, and a Type I error rate of 0.05, we anticipate having approximately 80% power for detecting a 10% difference in ReComp pill refill rates between groups. We anticipate little missing data since individuals' pill refill information is available through the electronic medical records.

2.9. Statistical methodology

Descriptive statistics, including graphical displays, will be used to summarize all study variables. We will construct individual and mean trajectory plots of the longitudinal outcome variables to understand their general trends over the study period. In addition, we will explore the variability and correlation structure of the longitudinal secondary outcome variables such as change in LDL-C over time. For some secondary results, we may not reach statistical significance; however, we will estimate the effect sizes and corresponding confidence intervals to help inform potential later research.

The primary analysis will examine whether Veterans who receive the intervention will have greater improvement of their cholesterol medication adherence as measured by pill refill at 6 and 12 months of follow-up as compared to the control group. Pill refill will be obtained for all patients at baseline, 6, and 12 months of follow up. A general linear mixed model will be used to estimate changes in ReComp over time and test the primary hypothesis. Linear models are a flexible and powerful analytic tool for repeated continuous measures. The predictors in the model will include a time effect and the treatment by time interaction; in the model, time will be a categorical variable to avoid making arbitrary assumptions about trends over time [7].

Secondary analyses will evaluate whether: 1) Veterans who receive the intervention will have improved LDL levels as compared to the control group over 12 months of follow-up; and 2) the cost effectiveness of the intervention. Relevant to the cost analysis, patient-level data will be available to estimate costs and effectiveness, so stochastic methods can be used to evaluate variability associated with the cost-effectiveness ratio. Discount and inflation rates of 3% will be applied to out-year costs, and sensitivity analyses will be conducted allowing these rates to range from 2% to 5%. We will conduct a number of sensitivity analyses to assess the robustness of our results, particularly in terms of examining different cost structures for the medication blister packaging. These data are expected to help inform future modeling and potentially larger studies directed at focusing on health care costs and health care utilization.

Qualitative analysis will be used to evaluate challenges and successes of the intervention. In order to formally evaluate the process of implementation of the packaging intervention, we plan to conduct a summative evaluation at 12 months. The goal of the evaluation is to optimize implementation to improve cholesterol adherence outcomes. Summative evaluation will be used to gather insights from both patients and providers who participated in the intervention program. We will also evaluate health care providers' perceptions regarding for which patients the blister package may be best suited (e.g., older adults, simple medication regimens). Similarly, we will examine whether individual patients' had challenges using the blister packages and if so, what were they and how can they be reduced? We will randomly select participants to interview at 12 months with the goal of contacting 25 unique individuals.

Qualitative analysis to examine the interviews will involve three phases: data coding, within-case analysis, and across-case analysis. In the data coding phase, we will use qualitative data analysis software (ATLAS.ti 5.0) to code the study data. The conceptual framework will provide a starting list of codes, which we will supplement with emergent codes as analysis proceeds. Using a common codebook, two investigators will conduct a pilot test by independently coding five transcripts. Based on the pilot test, the investigators will sharpen coding manual's definitions, decision rules, and examples. Research assistants will code the remaining documents. For within-case analysis, we will examine the relationship between themes within each case (i.e., patient interview) to develop a theory of what aspects of the intervention were most beneficial to participants. For across-case analysis, we will examine those relationships between cases to determine if they generalize.

3. Discussion

Medication adherence is a common and costly problem affecting the U.S. healthcare systems and patients [8]. On average, it is estimated that 50% of prescription medications are not taken in accordance with prescription instructions [9]. Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for cardiovascular disease (CVD). While the specific definition of elevated LDL-C and guidelines for CVD risk reduction evolve, there is a growing emphasis on the importance of statin therapy for those individuals with high CVD risk [1]. These changing definitions are potential limitations of the study. However, non-adherence with statin therapy for elevated LDL-C is a serious issue.

Our study addresses the efficacy of this innovative prescription packaging in a diverse patient population. Because the Durham VA Medical Center has one of the original Comprehensive Women's health clinics, we anticipate that approximately 10% of our sample will be women. Further, based on prior self-management studies [10–12] and because the selected clinics serve a large African American population, we anticipate that at least 40% of our sample will be African American. The racial and gender diversity of the study sample is anticipated to increase the potential generalizability of study findings.

During study enrollment, the VA National Formulary adjusted its coverage of rosuvastatin. Unless clinically contraindicated, patients prescribed rosuvastatin were converted to atorvastatin. Our study includes patients prescribed rosuvastatin, not atorvastatin, potentially reducing the sampling pool of eligible patients. Providers may choose to keep patients on rosuvastatin despite it not being on the formulary. Patients may remain eligible if providers choose to maintain their rosuvastatin regimen. We will evaluate the potential impact of this policy change when recruitment and baseline data collection is complete.

The planned analyses are robust — addressing not only medication adherence, but also improvements in clinical outcomes (e.g., LDL-C level), and cost effectiveness. While specific LDL-C targets have been removed from clinical guidelines [1], this decision is controversial [13]. Despite the recent guideline revisions, we assert that measuring improvements in LDL-C remains an important clinical outcome. Determining the cost effectiveness is critical to determining whether this intervention is feasible for broad scale implementation (i.e., scale-up to other primary care clinics or packaging of additional prescription medications) [14]. Our study will provide important information about the utility of an innovative prescription medication packaging approach on improved medication adherence.

4. Conclusions

The findings of this study will have important clinical implications. We posit that the special blister packaging will improve patients' medication adherence, subsequently leading to improved LDL-C control. Elevated LDL-C has been associated with increased all-cause mortality [15]. Conversely, improvements in LDL-C control have been associated with reduction in the risk for major cardiovascular events [16]. If the intervention is effective in facilitating patients' medication adherence and control of their LDL-C level, this medication packaging system could be ripe for broader dissemination by providing a low resource method to improve patient care.

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