CIRB 16-02

Secondary Event Prevention using Population Risk Management After PCI and for Anti-Rheumatic Medications (SEPPRMACI-ARM)

Funding Agency: Department of Veterans Affairs

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Principal Investigator/Study Chair: Dr. Caplan

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Abstract

Optimal treatment of veterans requires the consistent use of a number of medications. The failure to adhere to prescribed medication regimen results in higher health care costs and poor outcomes, including greater rates of hospitalization across a wide spectrum of health conditions.[1]

In the case of ischemic heart disease (IHD), for example, optimal treatment can require a number of medications to maintain or improve cardiovascular health. These medications include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins"), beta adrenergic receptor antagonists ("beta-blockers"), aspirin, and thienopyridines ("platelet inhibitors") such as clopidogrel. Non-adherence to medications, however, is common[2] and increases the risk of subsequent adverse cardiovascular events (CVE; i.e., cardiac death, myocardial infarction [MI], unstable angina).[3] Our pilot data demonstrate that gaps in statin refills (i.e., an indicator of medication non-adherence) occur frequently in the year following percutaneous coronary intervention (PCI). Similarly, for the rheumatic diseases, optimal treatment requires the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs), which are often used in combination. Non-adherence to DMARDs is also associated with poor outcomes in the rheumatic diseases.[4]

To improve medication adherence rates, we propose to test a multi-faceted, targeted, patient-centered medication adherence intervention using a novel, modified stepped-wedge study design in two common and clinically important scenarios: 1) for patients with IHD following PCI and 2) for patients with chronic rheumatic diseases requiring DMARD therapy. By testing in two unrelated conditions, we hope to demonstrate the generalizability of our findings.

This intervention will consist of: proactive real-time adherence monitoring of patients and targeting of individuals only when they have exhibited non-adherence behavior (i.e., if patients have not refilled their medication more than 4 or 7 days after it was due to be refilled). The intervention will employ a tailored, escalating-intensity approach which begins with some combination of personalized short messaging service (SMS) text messages and interactive voice response (IVR) telephone technology, depending on patient preference. Patients failing SMS and then IVR by not refilling their medication (or declining SMS and failing IVR) escalate to a trained research interventionalist (typically, a clinical pharmacist). The interventionalist will contact the patient and address adherence barriers based on the dimensions outlined by the World Health Organization (WHO) that are specific to each patient.

We will test the intervention on IHD patients who have recently undergone PCI–a cardiac procedure commonly used among IHD patients to improve the heart's blood flow. We will also separately test the intervention on patients seen for chronic rheumatic conditions such as rheumatoid arthritis and spondyloarthritis followed in rheumatology outpatient clinics. The intervention will recruit from four Veterans Affairs Medical Centers (VAMCs) with VA Cardiac Catheterization Laboratories (CCLs) and rheumatology clinics, while 12 sites with CCLs and rheumatology clinics will serve as usual care controls. This novel approach provides greater statistical power by supplementing the pre-intervention/usual care observation periods of a stepped-wedge design with concurrent usual care observation periods from 12 additional sites.

List of Abbreviations

IHD – Ischemic Heart Disease

CVE – Cardiovascular Events

PCI – Percutaneous Coronary Intervention

DMARDs – Disease Modifying Anti-Rheumatic Drugs

SMS – Short Messaging System

IVR – Interactive Voice Response

WHO – World Health Organization

VAMCs – Veterans Affairs Medical Centers

CCLs – Cardiac Catheterization Laboratories

PDC – Proportion of Days Covered

ICE – Incremental Cost Effectiveness

ICERs – Incremental Cost Effectiveness Rations

ACS – Acute Coronary Syndrome

CART – Clinical Assessment, Reporting and Tracking Program

RCT – Randomized Controlled Trial

CONSORT – Consolidated Standards of Reporting of Trials

CDW – Corporate Data Warehouse

MI – Myocardial Infarction

CABG – Coronary Artery Bypass Graft

VSF – Vital Status File

ICD-9-CM – International Classification of Diseases, 9th Revision, Clinical Modification

CPT – Current Procedural Terminology

SD – Standard Deviation

ISPOR – International Society for Pharmacoeconomics and Outcomes Research

CHEERS – Consolidated Health Economic Evaluation Reporting Standards

PBM – Pharmacy Benefits Management

CITI – Collaborative IRB Training Initiative

DSMB – Data Safety Monitoring Board

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1.0 Study Personnel

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2.0 Introduction

IHD and rheumatic diseases are both pervasive, expensive, and results in grave health consequences. IHD affects an estimated 15.4 million Americans ≥20 years of age—representing 6.4% of the adult population.[5] The direct and indirect cost of IHD has been estimated at $195.2 billion,[6] with a doubling of cost projected by 2030.[5] Similarly, the direct cost to the U.S. workforce for rheumatoid arthritis alone approaches $5.8 billion yearly.[7]

Widely-accepted national evidence-based guidelines support the use of cardio-protective medications to reduce the risk of adverse consequences resulting from IHD and DMARDs to reduce the risk of adverse consequence in rheumatic diseases. For example, numerous

rigorously conducted randomized trials show that statins improve outcomes and reduce mortality in patients with established cardiovascular disease (i.e., secondary prevention),[8,9,10] including those undergoing PCI.[11,12] The use of statins and beta-blockers have been repeatedly demonstrated to be cost-effective in lowering CVE event rates, in part by their effects on cholesterol[13,14,15,16] and blood pressure, respectively.[17,18] Accordingly, the most recent VA performance measures and American Heart Association guidelines encourage the use of statins in patients with atherosclerotic disease; beta-blockers in subjects with left ventricular systolic dysfunction (ejection fraction ≤40%), prior MI, or blood pressure of 140/90 or greater; and clopidogrel following any acute coronary syndrome (ACS) or PCI with stent.[19] The rheumatology literature provides similar evidence for the benefit of DMARDs in rheumatic diseases,[20],[21] and guidelines strongly endorse their use.[22]

Unfortunately, non-adherence to medications is common,[2,23,24] and increases the risk of poor outcomes.[3,25] Our 2011 national preliminary data from VA CCLs demonstrate that over 6300 patients experienced at least one refill gap of >= 7 days for statins in the year following PCI. The mean PDC for these patients was only 75%—below the PDC threshold of 80% that typical defines adherent patients, based on the empiric evidence for effectiveness of medications at this cut-point.[26] Non-adherent patients were present at all CCLs without substantial variation in mean PDC by center, suggesting a global problem.

Systematic problems underlie and contribute to non-adherence to medications. Usual care of IHD and rheumatic disease patients is encumbered by systematic deficiencies including: passive monitoring (contact with patients only when initiated by the patient) and inefficiency (time-consuming patient-by-patient approach, rather than through population management). The proposed intervention addresses both the complex patient-specific factors (emphasizing forgetfulness and carelessness) and the systematic inadequacies using a multi-modal, escalating approach.

3.0 Objectives

1. To assess the effectiveness of a multi-faceted patient-centered intervention versus usual care in improving medication adherence as measured by proportion of days covered (PDC, primary outcome). This will be tested among IHD patients for statins, beta-blockers and clopidogrel in the year after PCI and among rheumatology clinic patients chronically prescribed DMARDs. Hypothesis: The PDC for patients in the intervention arm will exceed the PDC for the usual care arm by a 10% absolute difference.

2. (Secondary outcome): To determine the effectiveness of a multi-faceted patient-centered intervention versus usual care in reducing secondary CVEs (myocardial infarction [MI], repeat revascularization [PCI or coronary bypass graft], and all-cause mortality) among IHD patients at 18 months post-PCI and progressive erosive disease demonstrated on plain film radiographs in patients with rheumatic diseases (i.e. “radiographic progression”). Hypothesis: The rate of CVEs and radiographic progression will be 5% relatively lower for patients in the intervention arm compared with usual care.

3. (Secondary outcome): To establish the cost to implement and maintain the intervention, above the cost of usual care, as well as the incremental cost effectiveness (ICE; e.g. cost to achieve at 10% improvement in PDC; cost per CVE prevented). Hypothesis: This aim does not posit a hypothesis as the objective is descriptive. The available funding for this project limits this outcome to IHD patients (no rheumatic disease patients will be analyzed according to cost).

4.0 Resources and Personnel

Dr. Liron Caplan is the Principal Investigator of the study. Dr. Caplan will focus on the design, logistic, and analytic aspects of the study. He will have access to protected health information and will perform data analysis. Denver - Grade 15.

Dr. Michael Ho is the Co-Principal Investigator of the study. Dr. Ho will focus on the clinical and design aspects of the study. He will have access to protected health information and will perform data analysis. Denver - Grade 15.

Dr. Tom Maddox is a Co-Investigator for the study. As Director of the VA's Clinical Assessment, Reporting, and Tracking (CART) Program, Dr. Maddox will focus on clinical aspects of the study and recruitment. He will have access to protected health information and will perform data analysis. Denver - Grade 15.

Dr. Steve Zeliadt is a Co-Investigator for the study. As a health economist, Dr. Zeliadt will focus on designing and supervising the cost analyses. He will have access to protected health information and will perform data analysis. Seattle - Grade 14.

Dr. Keith McInnes is a Co-Investigator for the study. As an infomatician, Dr. McInnes will focus on the design of the texting and interactive voice response (IVR) telephone calls. Bedford - Grade 13.

Dr. Anna Baron is a biostatistician. Dr. Baron will focus on designing and supervising the analysis of the main outcomes for the intervention. She will have access to protected health information and will perform data analysis. Denver - IPA at a level compatible with Grade 14.

Eric Gunnink is an Analyst. Eric will focus on executing the cost analyses. He will have access to protected health information and will perform data analysis. Seattle - Grade 14.

Dennis Plomondon is a consultant for the study. Dennis will focus on development of the IVR/SMS intervention. He will have access to protected health information and will perform data analysis. Denver

Thomas Glorioso is an Analyst. Thomas will focus on executing the randomization and analysis of the main outcomes for the intervention. He will have access to protected health information and will perform data analysis. Denver - IPA at a level compatible with Grade 12.

Colin O'Donnell is an Analyst. Colin will focus on executing the randomization and analysis of the main outcomes for the intervention. He will have access to protected health information and will perform data analysis. Denver - IPA at a level compatible with Grade 13.

Gary Grunwald is an Biostatistician. Dr. Grunwald will focus on designing and supervising the analysis of the main outcomes for the intervention. He will have access to protected health information and will perform data analysis. Denver - IPA at a level compatible with Grade 14.

Ryan Duong is a Collaborator of the study. He will have access to protected health information and will perform data entry and data cleaning. Denver - Grade 2.

Kyle Brees is the Study Coordinator. He will have access to protected health information and will perform data analysis, particularly related to tracking of recruitment and data quality checks. Denver - IPA at a level compatible with Grade 7.

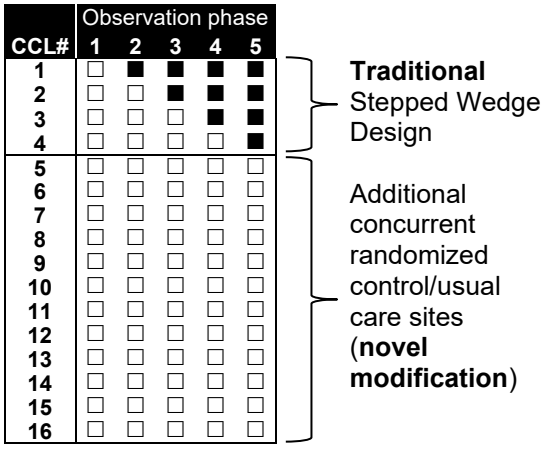
Local site investigators. The local site investigator (LSI) will be the Cardiac Catheterization Lab Director or Clinic Director at each study site. The LSI will attend the training session during which the research interventionalist will be educated and trained. The LSI will 1) serve as a local resource for additional training needs by the interventionalist, 2) provide local administrative oversite (i.e. obtain and maintain local R&D approval, and 3) guarantee the inclusion of the Patient information Sheet in the discharge paperwork for all local subjects.

5.0 Study Procedures

5.1 Study Design

This is essentially two concurrent 4-year multi-site cluster stepped-wedge RCTs that tracks each subject for 18 months. The RCTs are executed simultaneously in two conditions (IHD and chronic rheumatic disease) at the same VAMCs, with enrollment periods ("observation phases") of 6 months' duration. At the 4 intervention sites, which will be rolled-out through 4 phases (see Figure 1), subjects undergo prospective monitoring for med refill gaps, with deployment of a multifaceted, tailored program. The program assists veterans using SMS, and if necessary, escalates to IVR, and then to research interventionalists. The intervention will determine the specific reasons for non-adherence for each veteran and then, based on the individual's needs: facilitate drug refills, counsel patients on correct medication usage, simplify drug regimens, provide low literacy instructional

Figure 1: Study Design



CCL = Cardiac Catheterization Laboratory (number randomly assigned)
☐ = control period of observation
■ = intervention period of observation
Each empty or full box represents a recruitment cohort of 30 additional subjects, on average.

materials, facilitate communication with providers for adverse drug reactions, and engage in conversation about changing non-adherent behavior Twelve control sites, matched according to PCI volumes & baseline adherence (median PDC), will deliver usual care.

Our investigation employs modifications to the classic stepped-wedge trial design by collecting data from concurrent controls/usual care sites (CCL#5-16 in Figure 1, as well as the rheumatology clinics at these sites) in addition to the typical pre-intervention/usual care observation periods (open boxes, CCL#1-4 in Figure 1). Because the infrastructure already exists to collect pharmacy data from patients treated at all CCL's, we are able to obtain this additional control data. Our statistical simulations suggest this will enhance the power of our study.

For the first clinical scenario (IHD), patients discharged after PCI at any one of the four intervention sites who fill at least one prescription from one of the three qualifying medication classes (statins, beta-blockers, thienopyridines) will be monitored for medication refill gaps. The monitoring will occur daily through automated queries of pharmacy dispensing data, leveraging the considerable infrastructure of the VA's Clinical Assessment, Reporting, and Tracking (CART) Program. We have already developed these queries to identify when patients will need to refill their medications, based on the most recent medication refill date and the number of days supplied, but have not previously incorporated this in a real-time intervention. In the current study, patients with a refill gap (4 days for clopidogrel, 7 for all other medication classes) will be contacted in a manner that allows for simple refilling of their medication, thereby addressing a common cause of missed doses.[22] The intervention modality will escalate through increasingly more intensive components, including SMS (only if patient opts in to allow SMS during an initial IVR call), then IVR, then research interventionalist assistance (clinical pharmacist), then notification of Primary Care Provider or Patient Aligned Care Team. Further, in order to make study subjects' primary care team aware of a subjects' participation in the study, a note will be included in the participants' electronic medical record indicating their participation in the study.

For the second clinical scenario (rheumatic diseases), patients followed in rheumatology clinics with diseases such as rheumatoid arthritis and spondyloarthritis who have recently filled at least one DMARD prescription will be monitored for medication refill gaps. The monitoring will occur weekly through automated queries of pharmacy dispensing data, as developed by analysts associated with the local pharmacy service. Since all VAMCs with Cardiac Care Laboratories also have rheumatology clinics, the rheumatology intervention will be conducted simultaneously with the IHD-intervention and at the same VAMC sites, based on the randomization assignment used for the IHD-intervention (described below). This approach to randomization is necessary because it simplifies an already complicated randomization procedure and allows for more efficiency by hiring interventionalists/clinical pharmacists at fewer sites than if the IHD and rheumatology site assignments are performed independently. The intervention approach (SMS, IVR, and pharmacist) will be identical to that of the IHD intervention, but with content adapted to DMARDs.

To protect confidentiality, whenever possible, study records will identify patients only by unique study number. The only exception will be the tracking database that will include the patient's name, SSN, and telephone number which will be used to obtain pharmacy data from the CDW following PCI and to validate CV events in the medical record. Access to the database and study records will be limited to research staff. All paper records will be maintained in locked file cabinets within locked offices. Electronic data files will be encrypted/password-protected and user-restricted on computers maintained in a secure environment behind the VA firewall per VA security regulations. All data will be maintained in accordance with the VHA Records Control schedule 10-1 (v.January 2016).

5.2 Recruitment Methods

This study will employ an approach to consent similar to SDP-179 Hybrid Effectiveness-Implementation Study to Improve Clopidogrel Adherence which has previously been approved by CIRB (CIRB Protocol #12-12) The study will enroll all subjects undergoing PCI or using DMARDs at 16 VA Medical Centers (conservatively estimated at n~300 subjects from intervention periods at 4 sites and n~2100 at control sites for each intervention: IHD and rheumatic diseases; n=4800 subjects total for both RCTs). These Medical Centers are all tertiary referral hospitals within their respective VISN and provide a full spectrum of cardiac and rheumatologic care services.

Recruitment/Consent for clusters (CCLs)*:* The National Program Director for Cardiology, Director of the National CART Program, Chair of the VA Rheumatology Field Advisory Committee, and President of the VA Rheumatology Consortium all strongly endorse this proposal and have committed to assist with recruitment of sites. Over sixty CCLs/rheumatology clinics are available from which to select the 16 study sites, CCL and Rheumatology Clinic Directors will provide formal "site-level consent" --i.e. commitment in writing to institute the protocol--that submits their catheterization laboratory to randomization.

Recruitment/Consent for individual veterans*:* For the IHD intervention, following their PCI and prior to discharge from the CCL, patients at intervention sites will be informed of the study. This will be achieved through a written Information Sheet that is distributed to all patients; it will consist of an IRB-approved document explaining the purpose of the study and intervention details. Individuals at the intervention site will be given the information sheet and will be called by a member of the study team within a few days to see if the potential participant is interested in participation in the study. If the individual is interested in participating then the elements of consent will be reviewed at that time with verbal consent if the patient agrees to participate (Waiver of Documentation of Informed Consent and Waiver of HIPAA are requested). For the rheumatic disease intervention, patients will be informed of the study by receiving a written Information Sheet at the end of their regularly scheduled clinic visits and will be called by a member of the study team to undergo the same verbal consent process used in the IHD intervention group if there is interest in participating.

For the control group sites, a waiver of HIPAA authorization and a Waiver of Informed Consent for access and use of the data will be requested.

Randomization

Unit of randomization: In order to prevent cross-contamination of the intervention, a clustered design is being used with randomization at the level of CCL, rather than at the patient level. Rheumatology Clinic assignment follows CCL assignment; that is, rheumatology clinics at each site allocated to the same treatment arm (intervention or control) as the CCL at that site.

Procedures: CCLs Directors and Rheumatology Clinic Directors will agree in writing that their CCLs (and the associated rheumatology clinic at each VAMC) will be randomized to intervention or control/usual care. A two-stage randomization procedure will be employed. First, consented CCLs will be grouped with the most similar sites, in terms of baseline PDC and PCI volumes. Using the median PDC and median PCI volume for all consented CCLs, each site will be assigned to one of four groups: high PDC/high PCI volume, high PDC/low PCI volume, low PDC/high PCI volume and low PDC/low PCI volume. From each group of 4 consented CCLs, one site will be randomized to intervention and three will be randomized to control. In the second stage, the four intervention sites will undergo randomization to determine the order that sites roll-out the intervention, as is typical of stepped-wedge designs.

Sequence Generation: Randomly permuted blocks with four centers per block (matched according to annual PCI volumes and center PDC) will be generated using computer-derived assignments.

5.3 Informed Consent Procedures

For the Intervention sites, we are submitting a Waiver of Documentation of Informed Consent and utilizing a verbal consent processas described above. For the Control sites, a Waiver of Informed Consent will be requested.

5.4 Inclusion/Exclusion Criteria

Eligibility for clusters (CCL sites)*:* In order to qualify for inclusion in the study, CCLs must have performed 20 PCIs within the prior year (to ensure adequate study power). In addition, the Directors of the local CCL and Rheumatology Clinic must agree to institute the intervention if randomized to the intervention arm. CCLs and rheumatology clinics with on-going interventions to improve med adherence will be excluded.

Eligibility for individual veteran participants*:* Patients will qualify for inclusion if they 1) undergo PCI or are prescribed a DMARD; 2) are prescribed any of the following medications: a statin, beta-blocker, or thienopyridines (IHD intervention) and hydroxychloroquine, oral methotrexate, sulfasalazine, azathioprine, leflunomide, or tofacitinib (rheumatic disease intervention) [Note: as a study focused on adherence, we will NOT address the appropriateness of prescribed medications, which is an important, but separate issue]; 3) receive their care from the VA. This is defined by the presence of a VA-assigned-PCP in the year prior to PCI or in the year following PCI (IHD intervention) or in the year prior to or following index DMARD prescription (rheumatic disease intervention). Patients will be excluded under the following circumstances: 1) undergoing only diagnostic catheterization; 2) receive their index medicines (listed in item 2 above) from a non-VA source; 3) discharge to nursing home or

skilled nursing facility; 4) individuals with impaired decision making capacity, prisoners, or pregnant women, or the terminally ill

5.5 Study Evaluations

Data sources*:* Data sources for this project are described in Table 1 on the following page.

Procedural Outcomes/RE-AIM framework: To assess the potential for broader implementation of the intervention following this study we will use the Reach-Efficacy-Adoption-Implementation-Maintenance (RE-AIM) framework. Major items in the RE-AIM framework are mapped to specific aspects of the study, as described below.

Reach: Measurements of intervention delivery will be tracked by summarizing the numbers/proportion of enrolled subjects, number of excluded subjects, reason for exclusion and representativeness of subjects at intervention sites compared to a) control sites and b) the national population of veterans receiving PCIs or DMARDs.

Table 1: Data sources

Source	Data/Variables
Clinical Assessment Reporting and Tracking (CART)	Indication for PCI (ACS/non-ACS), demographic data (age, gender), IHD risk factors
Pharmacy Benefits Management (PBM)	National drug price data, Proportion of Days Covered for target medication classes
VA Vital Status File (VSF)	CV events
VA's Corporate Data Warehouse (Inpatient, Outpatient, Pharmacy, Vital Signs, Laboratory production domains)	CV events IHD and rheumatic disease risk factors (e.g. diabetes, hypercholesterolemia for IHD; smoking for rheumatic diseases)
IVR technology database and clinical pharmacists	Veterans' preferences for various communication modalities CV events outside the VA system PHQ-9 and GAD-7 results. Training time for staff Research interventionalist (clinical pharmacist) time to administer interventions, reasons for non-adherence, and specific actions taken to ameliorate non-adherence
VA Electronic Medical Record (CPRS, CAPRI, VistaWeb) containing annual radiographs	Presence of radiographic progression

Efficacy: The primary measures of efficacy appear below for Aims 1-2 under the sub-title "Outcomes" (page 13). We will also perform a sub-analysis specifying the incremental benefit (% adherence achieved) for each intervention component. As a descriptive study, Aim 3 does not include measures of Efficacy.

Adoption: We will report the absolute number, proportion, and representativeness of CCLs and rheumatology clinics willing to initiate the program.

Implementation: At least 3 procedures will assess the fidelity of the study execution and intervention protocol at both the level of CCLs/rheumatology clinics and individual subjects, including:

1. Site visits to intervention CCLs/rheumatology clinics by the study PIs or study coordinator occurring annually to monitor study documentation and performance of the intervention.

2. Centralized enrollment monitoring consisting of monthly downloads of PCI procedural volumes using CART data or DMARDs using CDW for intervention and control sites and comparison of volumes with each CCL or rheumatology clinic's historical volumes. Numbers of SMS, IVR, and research interventionalist activities will be complied each month using centralized tracking software compared to PCI and DMARD volumes to gauge use of the intervention. External sites will enter data using secure logins. Specifically, they will employ user-restricted remote access from their VA workstation to the research server located at the Denver VAMC which contains the data. All of this will occur behind the VA firewall.

3. Assessment of research interventionalists' performance will be done by having a mock patient contact each interventionalist every 3 months. The mock patient will be the study coordinator. The study coordinator will describe a real-world barrier to adherence and the interventionalists' actions will be reviewed. Research interventionalists will be unaware of which patients serve in the capacity (to avoid the "Hawthorne effect"[23]) and the barrier described will vary over the course of the study, such that all domains of the WHO framework are represented.

Maintenance: The PDC effect size will be compared for subjects in the first 6 months after PCI and greater than 6 months after PCI. In the final 6 months of the project, we will survey the CCLs directors at intervention sites to determine whether they intend to continue the intervention after the study terminates and if not, the reasons for discontinuation. We will also assess the persistence of the intervention by reporting subjects' PDC after the 18 month active intervention period for a period up to 3 years post-PCI, until the termination of the last observation period.

Outcomes:

Determination of outcome for Aim 1 (Proportion of Days Covered, PDC) The PDC for the targeted medication classes will be calculated for patients with any 4 day (clopidogrel) or 7 day (other medication classes) gap at both intervention and control sites using Corporate Data Warehouse (CDW) pharmacy files that are regularly exported into the CART system (i.e. an intention to treat analysis) and available to analysts affiliated with the principal investigator. Thus, if the median PDC from all control observation periods was 75%, then a median PDC of 85% from intervention periods would meet the primary end point (85-75=10). PDC is a measure of med adherence based on fill dates and days' supply for each fill of a prescription that adjusts for overlapping scripts. The PDC provides logistical advantages over other measures of adherence in that it summarizes data from multiple medications[27], has established cut-points based on empiric evidence[26], and is endorsed by the Pharmacy Quality Alliance.[28]

A historical data pull (including medication, labs, vitals, inpatient and outpatient visits) will go back three years to establish baseline comorbidities and adherence levels at each site. This data will only include retrospective information, rather than prospective results that reflect the potential impact of the intervention.

Determination of outcome for Aim 2 (CVEs for IHD patients; radiographic progression for rheumatic disease patients) For the IHD intervention, the outcome will consist of CV events including hospitalization for myocardial infarction (MI) or unstable angina, coronary artery bypass graft (CABG), or all-cause mortality at 18 months following index PCI. CVEs will be reported as a cumulative binary (yes/no) variable for each patient and will be censored after the initial post-PCI event. CVEs will be identified through a number of mechanisms: 1) case finding based on administratively coded data derived from the VA's CDW; 2) search of CART records; 3) queries of the VA Vital Status File (VSF); 4) keyword text searches via the VA's national electronic medical record-based interface (i.e. VISTA CAPRI)), and 5) an IVR call placed at the end of the observation period to the patient's home to identify CVE's not occurring in the VA system.. The administrative data queries will search for *International Classification of Diseases, 9th and 10th Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes, and *Current Procedural Terminology (CPT)* codes in these data sources (see Table 2). We have previously published on the validation of these coding algorithm approaches. The coding for each event will be based on previously published algorithms, which we have validated.[29],[30]

Table 2: Coding algorithms used in present study for definition of CV event and related comorbidity

Outcome	Reference	ICD-9-CM and CPT codes								Cost
MI	[31] [32]	410.x	411.x	412.x	413.x	414.x	429.2	v45.81		$29800 [33],[34]
PCI	[37]	36.01	36.02	36.05	36.06	36.07	36.09	0.66	99.10	$10000 [35],[36]
CABG	[37]	36.1x								$45,358 [38]

ICD-9-CM=International Classification of Disease-9; CPT=Current Procedural Terminology; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft.

We rationalized our choice of outcome time interval (18 months observation period), based on the fact that the benefits of aggressive medical management can become apparent in a relatively short interval.[39]

For the rheumatic disease interventions, patients' regular annual radiographs will be classified by a rheumatologist blinded to group assignment as either "progressive erosive disease" compared with most recent baseline plain film radiographs or "stable". This assessment will be based on the appearance of new boney erosions or worsening severity of existing boney erosions. This assessment, based on chart reviews, will be determined for a random sampling of 100 intervention subjects and 100 control subjects with rheumatic diseases.

Sensitivity analyses will assess the potential impact of CVEs or radiographic progression not captured by VA data sources due to deaths occurring outside the health system and the results at 18-24 months following index PCI or DMARD prescription for patients with available follow-up.

Exploratory outcome: Depression and anxiety will be assessed in a random sampling of 100 intervention subjects for each clinical scenario (100 out of the 300 intervention IHD subjects and 100 out of the 300 rheumatic disease subjects). Specifically, the Patient Health Questionnaire-9 (PHQ-9) and GAD-7, administered via IVR call to the patient's home at the end

of the observation period will be used to determine if patients with more frequent texts, IVR calls, and pharmacist intervention are more likely to perceive themselves as experiencing depression and/or anxiety. Patients endorsing suicidality on any call or via the PHQ-9 responses will be immediately referred to the VA Suicide Prevention Hotline. The research coordinator or PI will call the patient directly and then, with patient consent, establish a 3-way call with the Hotline. All study staff, including interventionalists, will review the VA's National Mental Health Safety Plan as part of the study training.

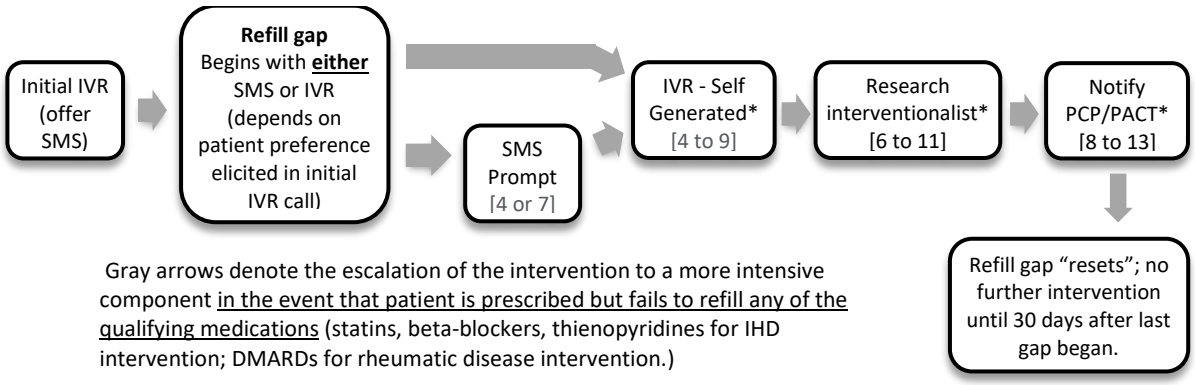
Determination of outcome for Aim 3 (Cost) The cost of the intervention will be reported in terms of specific activity, which appear below (see Included Costs, below), as well as for the intervention as a whole (cost to implement the intervention per CCL site). For the purpose of determining the ICER, we will employ outcomes related to those in:

Aim 1: cost to achieve a 10% improvement in PDC. This threshold was determined as "clinically relevant" by the practicing cardiologists participating in this proposal.

Aim 2: cost per CVE prevented. While CVEs represent an exploratory outcome, the considerable expense of CVEs justifies their inclusion in constructing the business case for the intervention.

Details of the intervention: The intervention is depicted in Figure 2.

Figure 2: Intervention Flow



* Step that incorporates WHO Dimension-based actions (Table 3, below, page 16).
Numbers in brackets refer to the days elapsed since the most recent refill gap began.
IVR = Interactive Voice Response telephone technology; SMS = Short Messaging Service (texts); PCP = Primary Care Provider; PACT = Patient Aligned Care Team (inter-disciplinary accessible, coordinated, comprehensive, patient-centered care teams, managed by primary care providers); DMARDs = Disease Modifying Anti-Rheumatic Drugs

Tailoring of the intervention: This study adopts a holistic approach to the problem of non-adherence that recognizes non-adherence as a complex, multifaceted phenomenon best addressed by tailoring both the content (i.e. the underlying reasons for non-adherence unique to each patient) and the intervention modality (i.e. each patient's preferred means of interacting with the health care system). While IVR and SMS provide simple, rapid, efficient,[40] and novel

methods for addressing veterans' most common reason for medication non-adherence,[41] the intervention also recognizes the complicated nature of adherence barriers, and incorporates an appropriately multifaceted research interventionalist-led component.

Trigger to activate intervention: We will obtain daily updates of pharmacy fulfillment data with computerized monitoring of this data to identify patients with refill gaps of 4 (dual anti-platelet therapies) to 7 (all other medication classes) or more days within 18 months following the hospital discharge of their index PCI or a randomly selected qualifying DMARD prescription. Specifically, for all eligible subjects starting on the evening following the index PCI or DMARD prescription, pharmacy data will be securely downloaded from local VistA pharmacy files into the IVR scripts and medication adherence software that we developed in prior studies. Since its deployment in December 2006, we have adapted this software to monitor med adherence using pharmacy data (including medication name, dose, dosing frequency, date dispensed and number of days supplied). In order to activate the intervention in real time, we will not measure adherence using medication possession ratio, as this is insensitive in the real-time environment. All subjects with a 4 or 7 day gap beyond the "date dispensed + number of days supplied" for any of the eligible medication classes—as detected by the software program that runs nightly—will receive the intervention, escalating from SMS (if a preference for SMS was indicated in the initial IVR call), to IVR after 48 hours, to the research interventionalist, if there is no response from subjects after another 48 hours, and finally to the patient's Primary Care Provider (PCP) or Patient Aligned Care Team (PACT; inter-disciplinary accessible, coordinated, comprehensive, patient-centered care teams, managed by primary care providers) if there is no response from subjects after another 48 hours.

Intervention components:

1. **IVR telephone calls** will notify patients of the refill gap, provide patients with the opportunity to indicate the reason for this gap (side effects, cost of medication, confusion about how to take the medication),allow them to efficiently refill the medication ("If you simply forgot to request a medication refill and would like a new refill mailed to you, press 4"), and provide veterans the opportunity to receive texts in the event of subsequent refill gaps. If necessary, the IVR will facilitate contact with a research interventionalist to address adherence barriers. We have successfully employed IVR to address med adherence for patients following ACS.[42]

2. **Short Messaging Service** texts will similarly notify patients of refill gaps. During an initial IVR call, those patients electing to incorporate SMS into their intervention will provide a mobile telephone number. For all subsequent refill gaps, patients will initially receive a text (rather than an IVR call) notifying them of the gap with instructions that simplify the refill process. Specifically, the text would provide the patients with the number to call into the IVR system and potentially connect them to a research interventionalist who would provide further assistance.

3. **Research interventionalist** engagement: For subjects who do not refill medications in response to the IVR call and/or SMS text, a research interventionalist located at each intervention site will call the patient and pursue a tailored strategy based on the WHO

dimensions of adherence barriers using actions supported by scientific evidence[43] (see Table 3). This theoretically-driven and comprehensive framework acknowledges that intervention strategies for individual patients must address the challenges and circumstances specific to each unique occurrence of a refill gap. Research interventionalists will follow an algorithm that determines which WHO dimension and adherence barriers are operative, and then pursue a course of action consistent with prior scripts we have developed for our prior adherence interventions, as indicated:

Table 3: World Health Organization (WHO) framework for barriers to adherence

WHO Dimension	Adherence Barrier	Research Interventionalist Action
Health system	Health system access	Facilitate refills/scheduling of appointments for patient
Condition	Mental health disorder	Engagement with PCP/mental health provider
Patient	Forgetful	Initiate weekly SMS or IVR prompts/medication diaries/corrective feedback
	Motivational deficits	Barrier Assessment
	Educational deficits	Counseling on appropriate usage & self-care Patient repeating back information
Therapy	Regimen complexity	Conversion to extended release formulation/fix dose combinations Pill organizer/calendars
	Adverse drug reaction	Communication with provider/Convert to alternate drug product
Socio-economics	Low literacy	Encourage social support/distribute low literacy instructional materials
	Cost	Referral to VA social worker

Detailed description of research interventionalist actions. The interventionalist/ pharmacist will invoke specific strategies to circumvent the adherence barriers responsible for each instance of a medication refill gap. For example, patients with motivational deficits will be targeted for barrier assessment (assessment and response to individual patient barriers) with a focus on changing non-adherent behavior. These sessions allow the patient to identify, verbalize, and reinforce their own positive attitudes and perceived normative support contributing to medication adherence. The interventionalist employs techniques such as open-ended questioning, positive messaging, reflective listening, constructive feedback, and goal negotiation. As an additional example, patients who tend to forget to take medications would be encouraged to use a medication diary, involve a caretaker, or if necessary receive weekly SMS prompts. Based on data from out prior studies, most interactions with the interventionalist are 10-15 minutes in duration. Pharmacists may provide brief telephone consultation with a VA social worker or written remote consultation with the subject's primary care provider (per the C3P study, conducted by our center). Of note, pharmacists can generate CPRS notes and related orders, such as simplifying dosing regimen, which providers can sign if in agreement. Local resources and practices will dictate the specific interaction but in all cases interventionalists will have comprehensive contact lists for resources that the research team will assist in assembling. The interventionalist will mediate the activation of resources directly and follow-up within 1 week to ensure the barrier is addressed, rather than passively referring the patient.

Veteran Advisory Board (VAB) input: the recently established DiSCoVVR COIN board of 12 veterans receiving care within the Department of Veterans Affairs will review all materials (including text/IVR messages and interventionalist scripts) before they are adopted to ensure they are not intrusive/coercive.

Period of observation for each patient: 18 months (primary outcome), from the date of discharge following the index PCI or randomly selected qualifying DMARD prescription. Note that as an exploratory outcome, we will assess the persistence of the intervention by reporting subjects' PDC after the 18 month active intervention period for a period up to 3 years post-PCI, until the termination of the last observation period for that sub-group of subjects enrolled in the first 3 phases.

Escalation Time**:** 48 hours. This "fail time" is defined as the allowable elapse time between each intervention modality without a successful refill before escalation to the subsequent modality (e.g. patients with a 7 day gap are contacted via SMS; if no refill occurs within 48 hours, the IVR component is triggered on day 9).

Quality Assurance Procedures: Multiple controls will ensure fidelity with the intended protocol, including:

1. Detailed written manual of operation (essentially, this study protocol) for all components of the intervention, available via the VA intranet.

2. Standardized in-person initial training session for the project coordinator and research interventionalists, with annual teleconferenced refresher training session. Interventionalist training will use the approach and schedule of our prior studies, which budget 80 hours over 6 months prior to intervention initiation and 20 hours subsequent to initiation of the intervention. The co-PIs and interventionalists previously involved in med adherence RCTs have developed a curriculum covering adherence theory, medical knowledge of cardiovascular disease/PCI therapy and rheumatic disease/DMARD therapy, barrier assessment, and provides them with local contacts for ancillary services (social work, Patient Aligned Care Team), among other topics. Training is performed through a variety of forms including interactive small group instruction, mock patient sessions, and written reference materials.

3. Rigorous validation procedures for CVEs' (see Determination of outcome for Aim 2).

Details of usual care: Control CCLs and rheumatology clinics will perform post-PCI follow-up according to the practice standards currently being delivered at each hospital and their CCLs. In general, this consists of a scheduled appointment with the patient's primary care provider or cardiologist 2-4 weeks post-PCI. Similarly, control rheumatology clinics will perform follow-up based on routine care for any patients precribed DMARDs—generally routine visits every 3-4 months. Any monitoring for medication adherence is left to the discretion of the managing provider. For most providers, the identification of adherence gaps is passive and occurs after-the-fact. Patients resolve barriers to medication adherence by 1) discussing issues with administrative or clinical staff (providers, pharmacists, nurses) during previously scheduled appointments [or occasionally on a drop-in basis]; 2) contacting clinics and pharmacy staff on the telephone either directly or through a call center; and 3) sending electronic messages to providers and staff using the My Health**e**Vet online patient portal. CCLs and rheumatology clinics in the control arm will refrain from participating in any other study or intervention focusing

on IHD or DMARD medication adherence during the period of planning or observation for this proposal.

Details of Aim 3 (cost analysis):

This is a prospective observational study to establish the cost to implement and maintain the IHD intervention, above the cost of usual care. This aim intends to encourage broad adoption of the intervention by demonstrating the costs required to achieve a 10% or greater improvement in adherence (Aim 1), and potentially demonstrate a positive return on investment from a net savings associated with reduced CVE rates (Aim 2) with the intervention. All costs will be estimated in 2019 dollars based on salary and drug costs at the end of the study. National cost data and Medicare price adjustors will be used to reduce the influence of regional variation in salaries and prices. Data for this study will be assembled concurrently from the multi-site cluster stepped-wedge RCT in Aims 1&2.

Setting, Perspective, Time Horizon: Costs and effort expended will be recorded at the 4 intervention sites randomly selected for Aims 1&2. All cost comparisons will include data from the full study sample at these four sites. Costs will be reported from the perspective of individual medical center intervention sites, since medical centers maintain budgetary and administrative authority over programs enacted at their affiliate CCLs and bear the long-term economic burden for non-adherent patients. We will employ a 5 year time horizon. Costs and effects will not be discounted because discounting is anticipated to have minimal effect over the relatively short follow-up period

Included Costs:

1. **Implementation & training costs (fixed costs)**: Using methods previously developed in Seattle for implementation studies,[44] we will quantify the direct costs required to implement and maintain the proposed intervention. Specifically, we will obtain thorough and precise activity logs all effort and investment necessary to initiate the intervention, construct timelines that describe the implementation, account for evolving implementation efforts over time, assign costs to discreet implementation activities, and characterize the variation between sites for each of these items. These expenses will include primarily personnel costs for the planning purposes, interactions with technical consultants/staff responsible for SMS and IVR development, conference calls, training activities, and e-mail communications related to start-up. Data sources for estimates of costs and/or hours will also include e-mail, which will be collected and archived from projects sites, as well as the study listserve, according to established procedures that transform these emails into time commitments.[44] Hours for all technical and staff member will be recorded and national GS-level and salary rates will be applied.[45] Non-personnel costs will include initial software licenses fees and hardware for the IVR and SMS systems and travel. For our primary analysis, we will average these fixed costs across intervention subjects. Projections of fixed costs for scaling the intervention will be based on estimates of projected patient volume in each CCL over a 5-year time horizon.

2. **Per-patient intervention costs.** Intervention activities provided by research interventionalist will be tracked for each non-adherent 7-day gap event after the

intervention is implemented at each CCL. Interventionalists will be provided with remote access to a centralized secure shared folder containing a customized database that includes an up-to-date listing of each non-adherent event. Interventionalists will catalogue all intervention activities from a pull down list of possible procedures for the duration of the study. For 2-week periods at the start of the intervention and at 6 month intervals, research interventionalists will also record the time (in minutes) required for each activity on the pull down list. Using the sample data for these 2-week periods, the average time per interventionalist per activity will be applied across all non-adherent gaps to estimate the time required for the intervention. Monitoring of completeness and quality of data collection will be performed centrally by study personnel through bi-weekly checks of the database.

3. **Drug costs.** Med adherence for statins, beta-blockers, and thienopyridines will be tracked for all subjects as part of Aim 1. Using national drug price data from the VA's pharmacy benefits management database (PBM), we will estimate the total drug costs for both control and intervention subjects for the 18 month study period from the discharge date for the index PCI.

Excluded activities / costs: Research-related costs and PCP time devoted to direct patient contact would not be included. For example, effort expended for acquisition of data, analysis of outcomes, and preparation of IRB materials would be excluded. Patient time and out-of-pocket expenses will not be included because of the organizational-oriented perspective of this study, in accordance with the parameters outlined by our operational partners.

5.6 Data Analysis

Power Analysis: (Primary outcome): Due to the modification to the traditional stepped wedge design, a simulation was designed in R to estimate power. Simulation studies were conducted by Analyst T. Glorioso, working in concert with A. Baron and A. Zhou (founding President, VA Statisticians' Association). We conservatively estimate 16 sites (4 intervention and 12 control), each enrolling 30 subjects per 6 month step, would assemble a cohort of 2400 patients (300 intervention and 2100 control), after accounting for a 15% withdrawal rate. These numbers would achieve 92% power to detect a difference in PDC of 5% and 99% power for a difference of 10% (75% increasing to 85%). These findings assume a within-site standard deviation (SD) of 1.30 and between-site SD of 0.16 on the transformed scale, based on existing 2011 CART data. Because of the multiple outcomes, we set the target two-sided significance test at a level of 0.01. Note that the number of eligible PCI subjects from these 16 sites should actually exceed 6000 (figures for 2012), providing a substantial recruitment "cushion", in terms of potential study volumes.

Analysis plan for Aim 1 & 2: Analysis of data will follow the approach outlined by Hussey and Hughes using patient level data.[46] To account for correlated observations within sites, unequal cluster sizes, and non-normal responses, the primary analysis will employ generalized linear mixed models to establish the treatment effect, after modeling time effects. Models will include terms for site (random, to account for correlation of patients within sites and to identify site-level variables), categorical time (fixed, to avoid confounding of intervention with time

trends), randomization stratum (fixed, to account for confounding caused by the PDC x PCI or DMARD volume strata), intervention variable (fixed, usual care vs. intervention, the effect of interest), and patient-level covariates. Due to left skew in the distribution of the continuous variable (PDC) caused by the upper bound of 1, a logistic transformation will be performed on this variable. Back transformation inference will be made on the difference in median PDC between intervention and control groups. No interim analyses are planned.

Analysis plan for Aim 3: We will assess the total intervention costs and drug costs for the ~300 intervention study subjects. Our primary analysis will sum the net costs for the intervention in numerator and compare those costs to adherence rates estimated in Aim 1. Confidence intervals for costs will be estimated using bootstrapping.[47] Our cost approach--which focuses on applying prices to intervention activities--minimizes the potential effect of imbalances in patient characteristics across intervention and control groups. To further safeguard against bias, multivariate linear regression models will be used to impute missing direct cost values; costs will be adjusted for any baseline socio-demographic differences between veterans during control and intervention periods.

We roughly estimate that costs of training/implementation are expected to be $31,780 per site, increased costs of drugs among intervention subjects will be $3,260 per site for each 18 month observation period, and costs incurred by research interventionalists to execute the intervention are estimated to be $11,650 per site for each 18 month observation period. Thus, we estimate a total cost of $46,690 per site to achieve a 10% improvement in adherence among 300 intervention subjects. The majority of the costs are due to initial implementation and will likely be considerably lower when scaled across multiple years and sites:

$$(Cost_{Training/implementation} + Cost_{Interv\text{-}per\text{-}patient} + Cost_{Interv\text{-}drug} - Cost_{Cntrl\text{-}drug}) / (\Delta \text{ Adherence rates})$$

Exploratory Return-on-Investment: We will assess CVE (Aim 2) based on the 18 month study period. This analysis will allow us to estimate the potential cost-savings of the intervention and return-on-investment to VHA. For example, based on the average cost of CVEs (see Table 2), the intervention would be cost neutral if rates of CVE costing an average of $28,300 were decreased from a rate of 10 per 1000/pt-yr to 8 per 1000/pt-yr through improved medication adherence from our intervention. Greater reduction in CVE rates would lead to a positive return on investment.

Characterization of Uncertainty: Statistical uncertainty in the cost and effect estimates will be modeled using nonparametric bootstrapping with 1000 replications, since this approach relaxes assumptions of the sampling distributions of the estimated cost or outcome.[47]

Characterization of Heterogeneity: A table will convey differences in costs and cost-effectiveness resulting from socio-demographic differences between veterans, presence or absence of volume discounting, variations in medication and personnel costs, and variations in the effectiveness of the intervention.

5.7 Withdrawal of Subjects

For patients who decline participation, the patients' name, state, and the current date will be recorded by the project coordinator in a centralized password-protected list that is accessible only from a computer terminal behind the VA firewall. *Reporting*

Authority for monitoring data and safety will reside with the VA-mandated National Data Safety Monitoring Board (DSMB) for multi-site interventional health services studies/randomized trials. The National DSMB will hold the PIs and other investigators responsible for data quality and completeness, safeguard the safety of all study participants, and ensure all ethical principles are respected. The PI will classify all suspected adverse events (mild / severe) and forward them immediately to the DSMB and CIRB. The principal investigator, Dr. Liron Caplan, will monitor for unanticipated, serious and related problems, and report them to CIRB, VA Research and the DSMB immediately. All other adverse events will be reported in summary format at continuing review. If CIRB or DSMB deems it necessary to disseminate information on unanticipated problems involving risk to participants, this information will be communicated to all participating sites PIs via email within 48 hours. This information will also be reinforced during bi-weekly teleconferences.

The completeness and accuracy of variables in CART are reviewed regularly by Program personnel. The biostatistician co-Investigator affiliated with this project will also conduct regular annual queries to ensure the integrity of the data, including evaluations of missing data and monitoring for outliers. The PIs will review recruitment and enrollment on a monthly basis to appraise the study progress and, if necessary, replace underperforming study sites.

6.0 Privacy and Confidentiality

Potential risks:

The proposed intervention is expected to pose minimal research risks for patients. There have been no reported adverse events with use of IVR or adherence interventions conducted by the assembled group of investigator in the past (rather, the increased surveillance may be a patient safety measure). A risk for all participants is the potential loss of confidentiality, a risk that is possible with all non-anonymous research and no greater than risks encountered in every day outpatient practice. However, based upon the mechanisms in place, this concern is very minimal.

No experimental devices or drugs will be used, minimizing the therapeutic risks of the present study. Because the decision to institute treatment (statins, beta-blockers, clopidogrel, or DMARDs) occurs prior to the proposed intervention (and is, in fact, an eligibility criteria), the physical, psychological, social, and legal risks are low. Nevertheless, this is a randomized trial and we will monitor patients closely to detect any problems posed by the intervention, and will follow all standards of the IRB and privacy (HIPAA) review and monitoring.

Measures to protect from risk:

Measures around patient tracking: To protect confidentiality, wherever possible, study records will identify patients only by unique study number. The only exception will be the tracking database that will include the patient's name, SSN, and telephone number which will be

used to obtain pharmacy data from the CDW following PCI and to validate CV events in the medical record. Access to the database and study records will be limited to research staff. All paper records will be maintained in locked file cabinets within locked offices. Electronic data files will be encrypted/password-protected and user-restricted on computers maintained in a secure environment behind the VA firewall per VA security regulations. All data will be maintained in accordance with the Records Control schedule and not indefinitely.

Measures for SMS/IVR: Our prior experience with IVR-based interventions has allowed us to develop systems that strictly protect patient privacy. No PHI is transmitted on outbound IVR calls, and we will continue to enforce this policy for SMS messaging. Rather, out-bound calls only employ generic terms and access to any PHI requires that the respondent confirm their identity using a patient-specific security code.

Measures related to Recruitment and Informed Consent: The approach to recruitment and consent is described in detail above (see Recruitment/Consent). Because our study 1) focuses on ensuring that patients are following the standard of care [i.e., filling and taking CV or DMARD medications as prescribed]; 2) involves no experimental medical procedures or medications; 3) relies on existing clinical data; and 4) does not pose a substantial burden beyond that encountered in patients' current health care setting, the risk to subjects has been classified as "minimal". In accord with this characterization and following the approach we established previously for similar trials, we are pursuing a waiver of consent and waiver of authorization for individual subjects through the IRB. In addition, we anticipate submitting this proposal for expedited review. The protocol will be reviewed annually by the CIRB and at the R&D committees at each participating VA site.

Based on our preliminary data indicating low PDC for the target medication classes, adherence to medications is likely to be poor and may place patients at higher risk of CV events.

As a workflow incorporated into existing clinical care, all patients at the Intervention sites will be provided an Patient Information form following PCI (IHD intervention) or when they leave the rheumatology clinic (rheumatology intervention). The Patient Informationform will include a telephone number for the project coordinator at the coordinating site that will allow them to ask questions and consider their involvement. A quiet room to consider the decision will be made available at each site. Each day, the central coordinating site will remotely screen the discharged patient from intervention and control sites for eligibility, based on their discharge medications listed in the electronic medical record. If the patient is ineligible (expected to be less than 5% of patients undergoing PCI and fewer than 10% of rheumatic disease patients, based on clinical guidelines and typical practice patterns in the VA) nothing regarding the screening will be recorded. If the patient is eligible, the project coordinator will tag the patient in the IVR tracking software. For patients who decline participation, the patients' name, state, and the current date will be recorded by the project coordinator in a centralized password-protected list that is accessible only from a computer terminal behind the VA firewall. If the patient indicates during the call with a member of the study staff that they wish to participate, the patient will be considered enrolled after verbal consent is obtained.

Measures related to staff training: All key personnel for this project who are responsible for the design and/or conduct of the proposed research have completed the appropriate training and continuation training for the protection of human research participants. In particular, all study staff will have completed Collaborative IRB Training Initiative (CITI) Course in the Protection of Human Subjects prior to initiation of this study. This includes a special VA module for investigators/staff working at VA sites. This initial CITI course includes HIPAA training and satisfies all IRB, VA, NIH and HIPAA requirements for research involving human subjects. Refresher training certificates will be updated as necessary throughout the study (per CITI and IRB requirements). Initial and refresher certificates of completion are kept in the IRB offices at all participating sites, with duplicate certificates documenting completion of initial and refresher courses kept by the project coordinator at the coordinating site (Denver VAMC). Reminders will be distributed to staff when refresher course completion is warranted. Written assurances will be obtained from all members of the research team mandating that the PHI will not be reused or disclosed to any other person or entity, except as required by law. Study staff will be required to certify that they have read the manual of operations yearly.

In addition to having the approval of the VA IRB and Research & Development (R&D) committees at participating sites, this research will require approval from the CART Research & Publications Committee. Participating site R&D approvals will be kept by the project coordinator at the coordinating site (Denver VAMC).

7.0 Communication Plan

We will notify all engaged participating sites of any changes in the study documents. As soon as we receive the approved documents, we will distribute them to all the participating sites. We will send an e-mail notification to the Facility Directors of all facilities involved to notify them that they are part of the study and we will evaluate their PCI data. Documents will be obtained to ensure that all participating sites are following VA information security policies. We will communicate study events to all participating sites during regularly scheduled conference calls. All non-compliance events will be reviewed and reported accordingly to the VA.

8.0 Relevance to Veterans

Execution of the intervention will have important ramifications for veterans' wellness. First, the intervention may directly improve veterans' quality of care, leading to better outcomes. Second, it will reinforce the importance of managing their IHD—a condition of widespread relevance to veterans. Third, the intervention will be responsive to veterans by assisting them in a proactive manner. Our system has the potential to make Veterans feel heard by proactively addressing adherence barriers, rather than placing the responsibility and burden entirely upon the patient to overcome obstacles and navigate the health care system. Fourth, the intervention provides a template for effective management of numerous similar clinical situations in which a procedure identifies high-risk individuals and requires med adherence to prevent recurrence or exacerbation of a serious condition. For example, in patients with an endoscopy that reveals a peptic ulcer; monitoring proton pump inhibitors adherence might avert recurrent bleeding ulcers. Thus, this proposal will hone our understanding of the risks for long-term untoward outcomes

following procedures, using some of the most common procedures for some of the most common diseases within the VA.

9.0 References

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