MEDFOCUS

MEDication Focused Outpatient Care
for Underutilization of Secondary Prevention

Study Protocol

Date: 11/17/2014 (revised 6/14/2017)

Version: 2.0

Special Note: (This version reflects the changes following the decision of the Data and Safety Monitoring Board [DSMB] at their meeting February 2017). The DSMB decision was to terminate data collection once all subjects complete their 12-month study visit. That will occur on June 30th, 2017. Reference to the data collection termination date below will be that date. Some subjects who enrolled in the trial first had a 24-month chart abstraction done prior to that date. While we do not plan to use the data from these latter subjects, the following protocol reflects the procedures for those subjects who had a 24-month abstraction prior to the data collection termination date.

Principal Investigators:

Barry L. Carter, Pharm.D., the Patrick E. Keefe Endowed Professor of Pharmacy in the College of Pharmacy, and Professor in the Department of Family Medicine, College of Medicine, University of Iowa.

Christopher Coffey, PhD., Professor in the Department of Biostatistics and Director of the Clinical Trials Statistical and Data Management Center, College of Public Health, University of Iowa.

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PROTOCOL APPROVAL PAGE

Study Title: MEDication Focused Outpatient Care for Underutilization of Secondary Prevention

Version: 2.0

Date of Issue: 6/14/2017

Study Sponsor: National Heart, Lung and Blood Institute, National Institutes of Health

The signatures below constitute the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations

We, the undersigned, have read and approve this protocol and agree on its content.

Co-Principal Investigator (printed)	Co-Principal Investigator (signature)	Date
Barry L. Carter, PharmD		6/14/17
Christopher S. Coffey, PhD		06/14/17

PROTOCOL VERSION AND AMENDMENT TRACKING

Study Title: MEDication Focused Outpatient Care for Underutilization of Secondary Prevention

Version Number/Amendment	Approval Date
Original Protocol, Version 1.0	11/17/2014
Revised Protocol, Version 2.0	6/14/2017

PROTOCOL SYNOPSIS

Protocol Title	MEDication Focused Outpatient Care for Underutilization of Secondary Prevention (MEDFOCUS)
Diagnoses and Main Criteria for Inclusion	Patients who have at least one risk factor for cardiovascular disease (CVD)
Study Objective	To determine the extent to which a care delivery model utilizing a centralized Cardiovascular Risk Service (CVRS) will be implemented in medical offices with large geographic, racial and ethnic diversity
Study Design	A 20 site, two-arm, cluster-randomized trial
Number of sites	20
Study arms	Each site will be classified as either a high minority (estimated ≥40% minority) or low minority (estimated <40% minority) site. At the outset of the trial, a stratified randomization (stratified by minority status) will be used to assign each site in a 1:1 fashion to one of two arms: a) the centralized cardiovascular risk service (CVRS) group or b) the usual care group, with all patients at a given site participating per the site's randomization. Each site will consent 20-25 patients to the site's study arm.
Total Number of Subjects	400
Duration of Study Participation	12 months active, with additional medical record abstraction at 24 months for subjects who reach that time point prior to the data collection termination date. No 24-month abstraction will be performed for the remaining subjects.
Primary Outcome	The degree to which care adheres with the Guideline Advantage standards of care that apply for secondary prevention of CVD and other prevention strategies.
Secondary Outcomes	1. Adherence to Guideline Advantage standards of care in minorities and in African Americans 2. BP control, mean BP, LDL cholesterol, HgbA1c all subjects 3. Measurement of Stages of Change 4. Intensity of medication management 5. Medical Home Index 6. Provider attitudes to deliver intervention, barriers and facilitators to implementation

Statistical Analysis Methods	Guideline Advantage Scoring: We will create a score for each subject at baseline and 12 months based on the number of applicable Guideline Advantage criteria that are met. For each subject, the primary outcome will involve a determination of the percentage of applicable Guideline Advantage criteria met at the end of the twelve month active participation period. The analysis will use a mixed model, adjusted for adherence at baseline and the minority status grouping. The same process will be used to calculate a percent score for a) the subgroup of all minority subjects and b) the subgroup of African-American subjects. To evaluate barriers and facilitators to implementing the intervention, the relationship between provider-level attitudes and beliefs and adherence scores will be calculated. A cost-effectiveness analysis will assign a cost to CVRS pharmacist time (including record review, patient assessment, email time, telephone follow-up), clinic visits, emergency room visits, hospitalizations, and laboratory procedures. Incremental costs as a function of differences in guideline adherence, LDL cholesterol, blood pressure, or HgbA1c will be calculated at baseline and 12 months. These findings will be expressed as dollars per incremental improvement in guideline adherence or individual outcomes such as LDL cholesterol, blood pressure, or HgbA1c.
Futility Analysis	One futility assessment based on a determination of predictive power will be conducted at a time when half of the planned active participants have completed their twelve month follow-up. Predictive power < 5% will be considered an indicator of futility. This analysis was conducted for the February 2017 DSMB meeting. The results met the criteria for futility so the DSMB recommended that all subjects completethe 12 month visit but that would not be collected following the data collection termination date.

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ABBREVIATIONS	
ADA	American Diabetic Association
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood pressure
CAD	Coronary artery disease
CCC	Clinical Coordinating Center
CCM	Chronic Care Model
CVD	Cardiovascular disease
CVRS	Cardiovascular risk service
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
HgbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IowaPHRM	Iowa Personal Health and Research Management
IRB	Institutional Review Board
LDL	Low density lipoprotein
MEDFOCUS	Medication Focused Outpatient Care for Underutilization of Secondary Prevention
MI	Myocardial infarction
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
PI	Principal Investigator
SAE	Serious adverse event

1. INTRODUCTION

1.1. Background

Cardiovascular disease (CVD) causes 2,200 deaths in Americans each day, with one death occurring every 39 seconds.[1] Although evidence suggests that these deaths can be prevented with better risk factor management, many risk factors remain uncontrolled. The Patient-Centered Medical Home, a system of care in which the patient has an ongoing relationship with a personal physician and medical team[2-8] and which utilizes self-management and personalized health records, has been proposed as a strategy to reduce gaps in care delivery.[9] Medical Home models often use physician/pharmacist collaboration, a process by which pharmacists work directly with patients and physicians to optimize therapy.[10,11,12, 13-36]The Chronic Care Model (CCM),[37-48] which includes pharmacists as care managers,[37, 38, 42, 44] places particular emphasis on self-management support, delivery system redesign and health care organization and community resources.[8, 40, 43, 49-51]

Several Cochrane reviews and meta-analyses have found evidence that adding pharmacists to the primary care team improves risk factor control and physician adherence to guidelines.[52-54] And the IOM, Centers for Disease Control and Cochrane center, have called for more research to evaluate the use of pharmacists for CVD management.[54-57] Over 100 studies on CVD have involved pharmacists including studies on heart failure,[28, 54,] anticoagulation,[23, 29-30] hypertension,[16, 59-61] hyperlipidemia,[12, 26, 31, 32, 34] diabetes,[33, 58] and multiple risk factors.[12, 15] A systematic review of 30 trials in patients with CVD found significant improvements in risk factor control with pharmacist management.[62] However, most studies have involved single disease states, single clinics and limited intervention pharmacists.

One managed care organization has found that a centralized cardiovascular risk service (CVRS) managed by pharmacists can reduce mortality.[12] It is not known, however, if a comprehensive CVRS model can be scaled up, implemented and disseminated within numerous, diverse primary care settings that are not within an integrated health system. This lack of evidence constitutes a major gap in knowledge.

1.2 Clinical Experience with the Study Intervention

The University of Iowa research team has extensive experience using team-based care to improve care management of patients with complex medical histories. We have pioneered strategies to evaluate team care implementation and guideline adherence using cluster-randomized trials.[63-64] Iowa investigators have conducted evaluations of physician adherence to guidelines[60, 65-70] and will use similar strategies for MEDFOCUS. The Iowa research team is a national leader in studying models of primary care delivery.[17, 19-20, 26, 36, 59, 60, 70-76] Drs. Carter, Chrischilles and James have developed and evaluated theoretical models and instruments for physician-pharmacist collaboration,[35, 77-78] physician knowledge,[36, 67, 79] and guideline adherence,[60, 65-6, 69-70, 79-82] and Dr. Carter has conducted nine health services outcome studies funded by National Heart, Lung and Blood Institute (NHLBI) and the Agency for Healthcare Research and Quality in the last six years.

The study will be conducted within our practice-based research network (PBRN), led by Barry L. Carter (PI). The CVRS model will provide services by telephone, text messages or asynchronous web discussions. The CVRS intervention pharmacist will be integrated into the on-site primary care team and frequently have two-way communication with providers.

1.3 Rationale

Adherence to guidelines for CVD is low, and regional and age variations in guideline concordant therapy following myocardial infarction (MI) have been found.[65, 83-87] The primary barrier is suboptimal medication use leading to poor disease control, often because busy providers must address acute non-CVD complaints.[88-90] Managed care organizations and other settings are increasingly hiring clinical pharmacists to improve management of CVD. The present study will evaluate an efficient, centralized, web-based CVRS to support primary care providers to improve the management of CVD and achieve key performance measures.[91] The ultimate goal of the Iowa research program is to reduce CVD events when our intervention is implemented more broadly.[12] These findings will be significant because there could be 20-30% fewer coronary deaths and 25-40% fewer stroke deaths in the U.S. if this intervention were applied across all medical offices that currently utilize clinical pharmacists. This study will meet important targets in the NHLBI strategic plan, the Million Hearts Campaign, the American Diabetes Association (ADA) and the American Heart Association (AHA) as outlined in the Guideline Advantage program.

2. OBJECTIVE, AIMS, AND HYPOTHESES

2.1 Objective

The objective of this project is to conduct a multi-center, cluster-randomized study utilizing a centralized CVRS for medical offices with large geographic, racial and ethnic diversity to determine the extent to which the CVRS model will be implemented. We will randomize 20 primary care offices to either the CVRS arm or a usual care arm and enroll 20-25 patients per office for a total of 400 subjects, of which 240 will be from racial minorities.

2.2 Aims and Hypotheses

Our central hypothesis is that a centralized CVRS managed by clinical pharmacists will be implemented and significantly improve care adherence to nationally recognized guidelines for standards of care when measured utilizing the Guideline Advantage metrics. We will test our central hypothesis with three specific aims:

2.2.1 Aim 1: To determine if a web-based CVRS managed by clinical pharmacists will be implemented within diverse primary care offices.

2.2.1.1 Primary Hypothesis 1a: Adherence to guidelines for secondary prevention of CVD will be significantly greater in patients from clinics randomized to the centralized CVRS group compared to the control group.

2.2.1.2 Primary Hypothesis 1b: Adherence to guidelines for prevention of CVD will be significantly greater in under-represented minorities from intervention clinics compared to the control group.

2.2.1.3 Secondary Hypothesis 1c: Adherence to guidelines for prevention of CVD will be significantly greater in African American/Black subjects from intervention clinics compared to the control group.

2.2.2 Aim 2: To evaluate barriers and facilitators to implementation and dissemination of the intervention.

2.2.2.1 Secondary Hypothesis 2a: Implementation of the CVRS model will be associated with positive provider-level variables attitudes and beliefs about the intervention.

2.2.3 Aim 3: To demonstrate a favorable cost for the CVRS using a robust cost-effectiveness analysis.

2.2.3.1 Hypothesis 3a: The CVRS will have a favorable cost-effectiveness when compared to the control group.

NOTE: due to the results of the futility analysis, a true cost-effectiveness analysis will not be done. However, costs to provide the service and costs-effectiveness of secondary endpoints will be assessed.

3. SUBJECT SELECTION/ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- English speaking males and females
- ≥ 55 years of age
- Has a history of at least one of the following conditions:
  - Coronary artery disease (CAD)
  - Previous MI (heart attack)
  - Stroke
  - TIA
  - Atrial fibrillation
  - Systolic heart failure
  - Peripheral vascular disease/claudication
  - Carotid artery disease
  - Diabetes *with either:*
    - Hyperlipidemia with most recent LDL >110mg/dl

    AND/OR

    - Hypertension with the most recent systolic blood pressure ≥ 140 mm Hg OR the most recent diastolic blood pressure ≥ 90mmHg

3.2 Exclusion criteria

- Signs of acute angina, stroke, heart failure or renal failure
- Systolic BP > 200 mm Hg or diastolic BP > 114 mm Hg
- Significant hepatic disease, including;
  - Cirrhosis
  - Hepatitis B or C infection
  - Serum ALT or AST > 3 times control

- Total bilirubin > 2.0 mg/dl

- Pregnancy
- Inability to give informed consent or impaired cognitive function
- Residence in a nursing home or diagnosis of dementia
- No telephone or have a hearing impairment not allowing them to use a phone
- Refusal to consider attempting to use the internet at home, community center, library, medical office or other source.
- A measured arm circumference that exceeds 50 cm

4. STUDY DESIGN

4.1 Overview

The **MEDFOCUS** study was funded in April 2014 by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The study is being headed by University of Iowa co-principal investigators Dr. Barry L. Carter, Professor of Pharmacy and Professor in Family Medicine, and Dr. Christopher P. Coffey, Professor of Biostatistics in the College of Public Health.

The goal of **MEDFOCUS** is to conduct a multi-center, cluster-randomized study to determine the extent to which medical offices with large geographic, racial and ethnic diversity will implement a care delivery model that utilizes a centralized cardiovascular risk service. The study will last five years and involve active recruitment of 400 subjects from 20 family practice offices across the United States. Participating offices are listed in Appendix I. The project hopes that at least 240 subjects will represent minority populations, who face unique challenges related to cardiovascular disease. Each participating clinic will be randomized to either the CVRS intervention arm or the usual care arm of the study.

All subjects will have an initial visit with the site study coordinator and a 2nd visit 12 months later. Each visit will include research blood pressure measurement, phlebotomy for a lipid panel, HgbA1c, select chemistries and liver tests (intervention subjects only), and surveys. Site study coordinators will also abstract select medical record data, at 4 and 8 months for intervention site subjects only, and at 24 months following enrollment for subjects. A timetable for the study is provided in Appendix II.

All subjects will have access to the Iowa Personal Health and Research Management (IowaPHRM) online personal health record. IowaPHRM will enable subjects to keep track of medications, record health-related data (e.g. BP, blood sugar), and enter allergies and health conditions. It supports printing reports, including wallet-sized cards to facilitate communication with health professionals and provides information for medications patients have entered. IowaPHRM will also include key data including medical history, problem list, laboratory values, key vaccinations, cancer screening, and medications collected by the study coordinators in intervention sites that will be used by the CVRS pharmacists to perform their interventions. IowaPHRM will facilitate implementation and measure many of the aspects of the Medical Home. This strategy will provide a more efficient approach for managing large populations of patients with multiple chronic conditions.

Each subject at intervention arm clinics will receive the CVRS intervention for 12 months. Subjects enrolled at control site clinics will receive usual care and will not have any exposure to the

study intervention. The intervention will be evaluated on the degree to which the care provided to intervention arm subjects, when compared to control arm subjects, adheres to the Guideline Advantage measurement set criteria. If successful, the CVRS intervention model could become an important strategy to markedly reduce cardiovascular events in the United States.

Key personnel roles on the study are described below:

Key Personnel	
Site Study Coordinator	Staff member employed within each institution who will recruit subjects and collect data
CVRS Pharmacists	Clinical pharmacists located centrally within the University of Iowa Clinical Coordinating Center who will provide telephonic, web-based, and email support for intervention subjects and communicate with site clinical pharmacists
Site Clinical Pharmacist	Clinical pharmacist working in the clinic who will communicate directly with the Iowa CVRS clinical pharmacists and notify primary providers about status changes and recommendations for treatment regimen changes
Site Physician Investigator	The medical provider who will lead the project at the local institution
Site Primary Care Providers	Primary care providers within the clinic

4.2 Site randomization and Treatment Arms

Dr. Coffey (biostatistician) will stratify the 20 participating offices based on lower (<40%) versus higher (≥40%) numbers of minority population and then randomize the 20 offices in a cluster-randomized design to avoid contamination within offices. Each office will be randomized to one of two arms: 1) the CVRS intervention arm or 2) the usual care arm. All subjects enrolled at a given site will participate in the study arm to which the site was randomized.

All subjects will be able to track their medications, home blood sugar and blood pressure measurements, and diagnosed conditions and also receive links to related publications and news through an Iowa Patient Health and Research Management (IowaPHRM) online portal.

Only subjects at intervention arm clinics will receive the CVRS intervention. A CVRS clinical pharmacist at the University of Iowa will work telephonically with each intervention arm subject and communicate with his/her providers to optimize subjects' pharmacological regimens and lifestyle patterns. Each subject at intervention arm clinics will receive the CVRS intervention for 12 months. Patients at intervention arm clinics can also communicate with their Iowa clinical pharmacist using IowaPHRM. Subjects enrolled at usual care clinics will receive the clinic's usual medical care and will not have any exposure to the CVRS intervention.

The intervention will be evaluated on the degree to which the care provided to intervention arm subjects, when compared to control arm subjects, adheres to the Guideline Advantage measurement set criteria.

4.3 Recruitment Procedures

4.3.1 Identification and Contact of Potential Subjects

Sites may use the following techniques to identify potential subjects, if approved by the local IRB:

- Run a list of patients who have the ICD9 codes listed in the inclusion/exclusion criteria (Appendix III) to compile a pool of potential subjects.
- Clinic providers may recommend patients to the Study Coordinator.
- Study Coordinators may look at the daily clinic schedule to identify patients who might qualify

For each potential subject that is identified, the Study Coordinator should review the medical record over the preceding 24 months to see whether the medical record supports eligibility criteria for age, language, and qualifying medical conditions and b) does not include documentation of any exclusion criteria.

Documentation of a medical condition in the patient's problem list is preferred, but explicit mention of a diagnosis in a provider note can be used if the problem list has not been regularly updated. Qualifying conditions include coronary artery disease, previous myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, systolic heart failure, peripheral vascular disease/claudication, carotid artery disease; , and diabetes with either uncontrolled hyperlipidemia or uncontrolled hypertension (as evidenced from the most recent lab values taken within the preceding 12 months).

Exclusion criteria include: signs of acute angina, stroke, heart failure or renal failure; systolic BP > 200 mm Hg or diastolic BP > 114 mm Hg; significant hepatic disease, including cirrhosis, Hepatitis B or C, serum ALT or AST > 3 times control or total bilirubin > 2.0 mg/dl; pregnancy; inability to give informed consent or impaired cognitive function; residence in a nursing home; impaired cognitive function; no telephone or have a hearing impairment not allowing them to use a phone; refusal to consider attempting to use the internet at home, community center, library, medical office or other source; a measured arm circumference that exceeds 50 cm.

Sites may use the following techniques to approach potential subjects, if approved by the local IRB:

- Mail patients who appear to qualify a letter approved by the local IRB inviting them to participate. The letter will provide a brief description of the study and request they return an enclosed response card and the date by which the card should be returned. The letter will include a statement that the clinic study coordinator will call the patient if the card is not returned by this date. The letter will include an explanation of how the patient can avoid the call by returning the card or calling the staff to decline participation.

  Patients who do not respond to the invitation letter may be called up to 3 times to assess their interest.

- The Study Coordinator may approach patients at the time of an unrelated clinic visit to ask about their participation in the study.
- Patients who are referred to the study by a provider may either be mailed an invitation letter or approached in the clinic.

Interested patients will be asked to set up a time for an initial study visit in the clinic with the study coordinator.

4.3.2 Confirmation of Eligibility

Once a patient whose medical record review supports their eligibility indicates interest in the study, the Study Coordinator should call the patient or speak with the patient in the clinic to answer any questions the patient might have. The Study Coordination should also ask the patient two additional screening questions:

1. Is the patient pregnant? Pregnant women cannot be enrolled in the study. No test will be required to confirm the absence of pregnancy.
2. Does the patient have internet access and, if not, would they consider accessing the internet either on a home computer or at a public location (e.g., library)? Patients who state that they will absolutely not consider having internet access will not be allowed to sign consent. Patients will not need to actually access the internet to continue in the study.

If a patient passes both of these screening questions, the Study Coordinator should verify with the patient that s/he meets the eligibility criteria.

4.4 Baseline Visit Procedures

4.4.1 Informed Consent Procedures

The study coordinator will describe the study, have the patient read the informed consent document and answer any questions. The study coordinator will specifically review the following areas of the consent document:

- Purpose of the research study, duration of study participation, and the number of research visits or study contacts (e.g. telephone calls) required
- That subjects will not receive any investigational procedures
- The study procedures/requirements
- The risks of the study
- The voluntary nature of the study: The subject may stop the study at any time
- Their decision to participate or not will have no effect on the patient's relationship with their physician or on the clinical care that they receive
- When a subject's participation in the study may be stopped (safety, compliance, pregnancy, sponsor stops the study)

- HIPAA section: The research team must be allowed to have access to the participant's medical information and to create medical information in order for the subject to be in the study; the investigators will obtain medical record data for the time period that spans the period from two years preceding enrollment until 2 years following enrollment in the study
- The Research Related Injury section.
- Contact information that subjects can use to reach clinic investigators and University of Iowa investigators for study-related issues

Patients may take the unsigned consent document with them if they wish to think about participation. The Study Coordinator will tell them that s/he will call the patient within a week to assess their interest should the patient not contact the Study Coordinator.

Patients may sign informed consent but schedule completion of other baseline visit activities for a later date to meet their scheduling needs.

Per policy of the local IRB, a patient who wishes to participate will sign and date the consent, and the Study Coordinator will subsequently sign and date the consent. A copy of the signed consent will be given to the patient. A scan of the consent will be placed in the medical record per the clinic and IRB policy.

4.4.2 Surveys

The study coordinator will ask the questions on the following forms and record subjects' responses:

1. Eligibility
2. Contact Information (intervention subjects only)
3. Demographic Information
4. Diagnosed Conditions and Care Management (Patient Report)
5. Medication Reconciliation
6. Medication Adherence
7. Cancer Screening
8. Health Behavior Inventory
9. Stages of Change

4.4.3 Blood Pressure Measurement

Study Coordinators will measure the subject's height, weight and research blood pressures. Resulting measurements will be documented on the Blood Pressure case report form.

All blood pressures should be obtained (at the baseline visit and again at the 12 month visit) using the Omron HEM907XL automated blood pressure device and the following procedures:

Prepare the Subject

Subjects should refrain from smoking for 20 minutes prior to the blood pressure measurement.

Have the subject remove all clothing that covers the location of cuff placement.

The subject should be comfortably seated in a chair, with the back supported, legs uncrossed and flat on the floor, the arm supported, ideally at heart level on a desk, and the palm of the hand facing upward

Have the subject sit for at least 5 minutes. Instruct the patient to relax as much as possible.

Cuff Measurement

The subject's arm circumference should be measured at **BOTH** study visits. A cuff should be selected based on the measurement ranges specified for each cuff. Should an arm measurement fall on a number that is specified for use on two cuffs, place both cuffs on the arm sequentially and choose the cuff for which the **INDEX ↑** that is marked on the edge of the cuff better falls within the range bar on the cuff.

Subjects who require use of a thigh cuff at the baseline visit cannot continue in the study. Should a subject whose BP was successfully measured at baseline using the Omron monitor gain sufficient weight between the baseline and 12 month visits to require a thigh cuff at 12 months, the Study Coordinator should take the 12 month BP measurements using a thigh cuff and manual sphygmomanometer.

Cuff Placement

Do not allow a sleeve to form a tourniquet on the arm.

Palpate the brachial artery in the antecubital fossa and place the **ART ↓** that is marked on the midline of the bladder of the cuff so that it is over the arterial pulsation of the patient's bare upper arm.

The lower end of the cuff should be ½ to 1 inch above the inner side of the elbow joint.

The middle of the cuff should be at the level of the right atrium (the mid-point of the sternum).

Pull the cuff snugly around the bare upper arm so that you can insert only one finger between the cuff and the arm.

Blood Pressure Measurement

Have the Blood Pressure form and the Omron monitor beside you on the desk.

Tell the patient that you will be taking at least 4 blood pressure readings and that neither the patient nor the study coordinator should talk during the measurements.

1. Take a **single sitting BP reading** with the MODE selector set to **"SINGLE"** and record. Wait 60 seconds before taking the next blood pressure.
2. Take a **double sitting BP reading** with the MODE selector set to **"AVG"** and record both readings.
3. If either the two systolic readings or the two diastolic readings from the double BP readings **differ by ≤ 4mm**, take **one additional sitting BP** with the MODE selector set to "SINGLE" and record the results.
4. Have the patient **stand for one minute** and then take another **single BP reading** and record.

IF YOU GET AN ERROR MESSAGE AT ANY POINT, START THE SEQUENCE OVER.

4.4.4 Laboratory Specimens

The study coordinator will draw or arrange for usual laboratory draw of blood for the following tests:

- Lipid panel
- HgbA1c
- Serum creatinine, sodium and potassium (intervention subjects only)
- ALT and AST tests (intervention subjects only).

Sites may select specific panels that are typically used in their clinic, so long as they include all the needed individual tests. Results will be documented on the Laboratory case report form, excepting intervention subjects at the baseline visit only, whose results will be reported on the Laboratory for Baseline Intervention case report form.

Laboratory costs should not be billed to the patient or the patient's insurance. The site should request reimbursement of $225.00 for each set of labs through the subaward invoicing mechanism.

4.4.5 Instruction on IowaPHRM

The study coordinator will instruct consented subjects on use of the Iowa Personal Health and Research Management (IowaPHRM) system, an online study record that enables subjects to keep track of medications, record health-related data (e.g. BP, blood sugar), and enter allergies and health conditions. IowaPHRM supports printing reports, including wallet-sized cards to facilitate communication with health professionals and provides information for medications patients have entered. IowaPHRM will allow the subject to enter data into his/her record, including home blood pressure and blood sugar test results. Each subject will be given a sheet with initial login information for the system and told that they should create new login information. They will also be given a brochure about the online system. Subjects will not be required to access IowaPHRM at any point during the study, but they should be encouraged to try it and offered help getting started. Patients who would like help will be telephoned by the PHR support team for assistance.

4.4.6 Medical Record Abstraction and Verification

After the visit, the study coordinator will verify or obtain information documented at the patient's most recent visit with his/her provider to complete the following forms:

1. Diagnosed Conditions-Care Management (Medical Record)
2. Medication Reconciliation
3. Cancer Screening

4.5 4 & 8 Month Medical Record Abstraction (CVRS intervention sites only)

At 4 months after enrollment and again at 8 months after enrollment, the Study Coordinator will abstract medical record data to complete the 4 & 8 Month Data Collection form, which includes data for pertinent laboratory values, new diagnosis, and hospital and emergency room visits since enrollment. This form is completed only at CVRS intervention sites to give the CVRS pharmacists updated patient status information.

4.6 12 Month Visit Procedures

4.6.1 Surveys

The study coordinator will ask the questions on the following forms and record subjects' responses:

1. Diagnosed Conditions and Care Management (Patient Report)
2. Medication Reconciliation
3. Medication Adherence
4. Health Behavior Inventory
5. Stages of Change
6. Serious Adverse Event Screening
7. Cancer Screening

4.6.2 Blood Pressure Measurement

The study coordinator will measure height, weight and research blood pressures as specified for the baseline visit and document results on the Blood Pressure case report form.

4.6.3 Laboratory Specimens

The study coordinator will draw or arrange for usual laboratory draw of blood for the following tests, with billing handled as previously designated. Data should be recorded on the Laboratory form.

- Lipid panel
- HgbA1c

4.6.4 Medical Record Abstraction and Verification

After the visit, the study coordinator will verify or obtain the following data from the subject's medical record to complete the forms listed below. Data should span the period from the baseline visit through the 12 month time point.

1. Diagnosed Conditions and Care Management (Medical Record)
2. Medication Reconciliation
3. Cancer Screening
4. Serious Adverse Event Screening
5. Clinic Visit Tracking

4.7 24 Month Medical Record Abstraction (only conducted on those subjects who reach the 24-month time point prior to the data collection termination date)

The study coordinator will collect the following medical record data for the time period extending from the day following the date of the 12 month study visit or medical record data abstraction through 13 months following that 12 month time point. No visit will occur at the 24 month time point.

1. Diagnosed Conditions and Care Management (Medical Record)
2. 24 Month Blood Pressure, Laboratory and Medication
3. Cancer Screening
4. Serious Adverse Event Screening
5. Clinic Visit Tracking

4.8 CVRS Intervention

The CVRS clinical pharmacist will undertake the following activities with subjects, participating site pharmacists and participating site medical providers in the 10 intervention offices. A schematic of the intervention is presented in Appendix IV.

- Communicate with subjects using email, telephone, text messages or IowaPHRM every two weeks x 2 months then at least monthly for 10 additional months to engage patient and obtain any self-monitoring data
- Use motivational interviewing to conduct monthly follow-up assessment and counseling for medication adherence, side effects, exercise, CHD knowledge, weight, diet, tobacco use and alcohol use
- Assess stages of change for key issues such as exercise, diet, weight management and tobacco use
- Provide more frequent contact with the subject if necessary to improve or resolve medication problems
- Continue to address problems with medication adherence or persistence
- Develop an action plan that addresses gaps in guideline-concordant therapy, update medication list and FAX recommendations for medication changes to the primary medical provider and on-site clinical pharmacist every 3 months or more frequently if urgent issues are identified
- Document all patient and provider encounters and time (minutes) for each activity in the IowaPHRM database

4.9 Serious Adverse Event Screening and Reporting

Sites will screen for and report all serious adverse events (SAEs) that meet *BOTH* Criterion A *AND* Criterion B:

Criterion A. The SAE resulted in an least one of the following outcomes:

- Death
- Life-threatening condition
- Hospitalization
- Disability
- Congenital abnormality
- Intervention was required to prevent *permanent* impairment or damage
- The lead provider or pharmacist for the study judged the event to be an important medical event

Criterion B. The SAE involved at least one of the following health situations:

- Loss of consciousness
- Hypertensive Urgency/Emergency
- Stroke
- Myocardial Infarction
- Diabetic Ketoacidosis
- Hypoglycemia
- Rhabdomyolysis
- Excessive Bleeding
- Thromboembolism

Screening for reportable SAEs will occur at the following two time points:

12 month study visit: The Study Coordinator will ask the patient about emergency room visits and hospitalizations and also review the medical record for SAEs that occurred since the baseline visit (submit Serious Adverse Event Screening case report form).

24 month medical record review: The Study Coordinator will review the medical record for SAEs that occurred since the 12 month visit (submit Serious Adverse Event Screening case report form) for any subjects who completed the 24 month review prior to the data collection termination date. No 24 month abstraction will be performed for subjects whose 24 month data abstraction is scheduled after the data collection termination date.

SAEs that are identified through screening and that meet the criteria for reporting must be reported to the DCC using the Serious Adverse Event Reporting case report form and uploaded to the study database. In addition Study Coordinators should report all SAEs that come to their attention between the key study time points and that meet both Criterion A and Criterion B.

4.10 Study Termination

4.10.1 Early Termination

Subjects will be terminated early should any of the following situations arise:

- The subject withdraws consent
- The subject no longer is a patient at the clinic.
- The subject dies

Early termination indicates that the site will no longer need to follow the subject, complete additional study visits or collect any additional data.

4.10.2 End of Study Termination

Study Coordinators will complete a study termination form for each subject following either:

a. Completion of the 24 month medical record abstraction
b. The data collection termination date, for subjects whose 24 month time point follows the data collection termination date.

5. STUDY OUTCOMES

5.1 Primary Outcomes:

5.1.1 Adherence to Guideline Advantage Criteria in All Subjects

The primary outcome will be adherence to the Guideline Advantage criteria that apply for secondary prevention of CVD. (See link below to the Guideline Advantage Fact Sheet.) The criteria reflect drug therapies, meeting guideline goals for specific disease conditions, and screening and prevention measures.

http://www.guidelineadvantage.org/idc/groups/tga-public/@wcm/@tga/documents/downloadable/ucm_429605.pdf

Each eligible criterion will be scored based on whether or not it was met at each of the index dates (baseline, 12 months, and 24 months). An algorithm will take the number of Guideline Advantage criteria that apply to each patient and then calculate the percent of those applicable criteria that are met at each time point. The resulting single numeric value will be used as a surrogate for quality of care. This algorithm will be applied to all subjects, with CVRS intervention subjects compared to usual care subjects.

5.1.2 Adherence to Guideline Advantage Criteria in Minority Subjects

The same algorithm will also be used to compare adherence between CVRS intervention subjects and usual care subjects who represent minority populations. This analysis will use a mixed model and an exchangeable correlation structure.

5.2 Secondary Outcomes

5.2.1 Adherence to Guideline Advantage Criteria in African-American Subjects

The same algorithm will also be used to compare adherence between CVRS intervention subjects and usual care subjects within the African-American population. This analysis will use a mixed model and an exchangeable correlation structure.

5.2.2 BP Control, Mean BP, LDL Cholesterol, HgbA1c all subjects

Direct measurement (at baseline and 12 months) will yield values for BP control, Mean BP, LDL cholesterol and HgbA1c. Values will be compared for CVRS intervention subjects and usual care subjects. However, since this analysis will include many subjects with controlled values at baseline, the effect in those with uncontrolled values will be diluted.

5.2.3 Measurement of Stages of Change

Scores on the Stages of Change instrument will be compared for CVRS intervention subjects and usual care subjects at baseline and 12 months.

5.2.4 Intensity of Medication Management

The number of recommended medication changes per subject and the percent of recommended medication changes that were accepted/implemented.

5.2.5 Medical Home Index

The lead medical provider at each site will complete the Medical Home Index, a validated, self-assessment tool for evaluating primary care practice. Providers will complete this tool at the beginning of the project and again following implementation of the study intervention to determine how each office has improved on adoption of the Medical Home and if there is greater adoption in intervention offices compared to usual care offices.

5.2.6 Provider attitudes to deliver intervention, barriers and facilitators to implementation

All clinic providers will be asked to complete two questionnaires at the beginning of the project and again following implementation of the study intervention. The first validated instrument measures physician-pharmacist collaboration and will be used to evaluate the level and type of communication and any increases in the level of communication in the intervention group. The second validated questionnaire based on the Theory of Planned Behavior (TPB) will be used to evaluate physician adoption of the study intervention, with scores compared between CVRS intervention clinic providers and usual care clinic providers.

6. Statistical Analysis Plan

6.1 Statistical Design

This study will utilize a two-arm, randomized, cluster design. A total of 400 subjects will be enrolled into the trial at 20 primary care offices across the U.S. Offices have been stratified into either a high (>40%) minority population site or a low minority population site. After stratification, offices were randomized in a 1:1 fashion into either the centralized cardiovascular risk service (CVRS) or usual care groups. Each subject will be followed for 12 months, with an additional chart abstraction performed at 24 months to assess the extent to which increased guideline adherence is sustained after the intervention is discontinued. A total of 400 subjects will be enrolled into the trial.

The trial will follow the intent-to-treat principle. The analysis model corresponds to the ‘compound symmetry’ assumption that implies that all members of a cluster are equally correlated with each other – and that members in different clusters are independent of each other, a reasonable assumption since physicians and pharmacists only practice in one study location.

6.1.1 Primary Analysis

Primary Hypotheses 1 & 2: ***Adherence to guidelines for CVRS intervention vs. control group (in all active observation subjects and restricted to under-represented minority groups)***

The primary outcome will be adherence to the AHA Guideline Advantage criteria that apply for secondary prevention of CVD at the end of the intervention. For each subject, the primary outcome will involve a determination of the percentage of applicable criteria met at the end of the twelve week period. Both primary hypotheses will be assessed using a mixed model, adjusted for adherence at baseline and the minority status grouping. The only difference for the two primary hypotheses is that the first analysis will apply the model to all active observation subjects, while the second analysis will be restricted only to minority subjects (whether they were enrolled at a high or low minority site). This model will also use an exchangeable correlation structure to adjust for the correlation among subjects treated in the same clinic. For example, the following model will be fit to these data:

$$Y_{ij} = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3ij} + \gamma_i + \varepsilon_{ij}$$

where Y_{ij} represents the adherence at twelve months for the j^{th} subject in the i^{th} cluster, X_{1i} is an indicator variable for the minority status of the i^{th} cluster (=0 if < 40%, =1 if ≥ 40%), X_{2i} is an indicator variable for whether the i^{th} cluster was randomized to the CVRS or usual care group, X_{3ij} is the baseline adherence score for the j^{th} subject in the i^{th} cluster, γ_i is the cluster i 'random effect' with variance σ_C^2, and ε_{ij} is the usual random measurement error term with variance σ^2. Hence, this model corresponds to the 'compound symmetry' assumption that implies that all members of a cluster are equally correlated with each other – and that members in different clusters are independent of each other. Correspondingly, the hypothesis of interest can be assessed by performing the following hypothesis test:

$$H_0: \beta_2 = 0 \quad vs. \quad H_A: \beta_2 \neq 0 \ .$$

This test will be implemented using an appropriate contrast statement with the model specified above. Because there are two primary hypotheses of interest, we will apply a Bonferonni correction and test each hypothesis at the 0.05/2 = 0.025 significance level.

Because randomization is performed at the site level, it is possible that some other important subject-level covariates (age, gender, family history, co-morbidities, number of CV medications at baseline, baseline medication adherence, smoking status, education level, insurance status, economic status, or marital status) may be imbalanced in this study. Thus, we will carefully monitor the ongoing study for any important imbalances among important covariates. Should important imbalances occur, we will control for these additional covariates in the linear regression model above. We will also assess the normality assumption involved in the model. If this assumption is violated, an appropriate transformation will be employed, or a nonparametric model will be fit.

6.1.2 Secondary Analyses

Secondary Hypothesis 1: ***Relationship between guideline adherence and provider-level variables (attitudes and intent to implement the CVRS model)***

This hypothesis will be assessed in the same manner as the primary hypotheses, except the appropriate provider-level variable will be used as a model covariate in place of the dichotomous group assignment.

6.1.3 Cost-Effectiveness Analysis

Costs will be assigned to each activity and CVD and diabetes medication. All CVRS pharmacist time including record review, patient assessment, email time, telephone follow-up, plus clinic visits, emergency room visits, hospitalizations, and laboratory procedures will have costs assigned and analyzed using methodologies previously used.

6.2 Covariates

Since randomization will be performed at the clinic level, we will control for subject-level covariates that might be imbalanced between study arms. These include: age, gender, family history, co-morbidities, minority status, number of CV medications at baseline, baseline medication adherence, smoking status, education level, insurance status, economic status, and marital status.

6.3 Power and Sample Size

Preliminary estimates for justifying the sample size for the primary outcomes were obtained from guideline adherence measures collected in a previous study by the investigators (Carter et al, 2009).[11] In that study, only 40% of applicable criteria were adhered to for hypertension. Additionally, in our evaluation of Medicare patients who suffered an acute MI, only 34% received all guideline concordant medications.[20] Based on this and other information,[95, 143] we expect baseline adherence scores to be 30-35% ± 20% but conservatively assumed baseline values of 40% ± 20% for sample size calculations. We expect these scores to increase to 50% ± 20% in the control group and to 60% ± 20% in the intervention group at 12 months. Further, we expect that guideline adherence scores will deteriorate after the intervention is discontinued but scores in the intervention group (50% $\pm$ 20) will remain significantly higher than the control group (40% $\pm$ 20) at 24 months. Finally, further examination of the previous study suggested that the observed intra-class correlation coefficient was 0.004. Based on earlier studies, we believe that a 15% lost-to-follow-up rate is a good estimate for the proposed trial.

Based on the assumptions above, the study would only require 300 subjects to have 93% power to assess the primary hypothesis in the overall population. However, it is also important to ensure adequate power for the second primary hypothesis, which involves all under-represented minority subjects or African Americans/Blacks (AA) (a subset of the population used to assess the first primary hypothesis). We expect the intervention to be as effective in racial and ethnic minorities compared to Caucasians and the study is powered to detect these differences. We will have sufficient Black subjects to evaluate this aim (n=180). The numbers of Hispanics (n=40) will have low power but we will use our comparisons as hypothesis generating for future research.

Table 1 provides power levels for a variety of adjusted sample sizes for the overall population, the minority population, and the African-American population. The table shows that a sample size of 400 subjects provides reasonable power to detect both primary hypotheses of interest, as well as the first secondary hypothesis. This proposed sample size would provide greater than 99% power to detect the effect of interest in the overall population, while providing 83% power to detect these same effects in both the under-represented minority population and the African-American population (although one is a subset of the other, the fact that we plan to use a significance level of 0.05 for the secondary hypothesis and a significance level of 0.025 for the second primary hypothesis leads to similar power).

Table 1. Observed Power for Different Adjusted Overall and Minority Sample Size Values					
Adjusted Overall Sample Size	Adjusted Minority Sample Size	Adjusted AA Sample Size	Power (Overall)	Power (Minority)	Power (AA)[1]
100	55	45	46%	25%	29%
200	110	90	79%	50%	53%
300	165	135	93%	60%	71%
400	220	180	>99%	83%	83%
500	275	225	>99%	91%	90%

[1]*Uses a significance level of 0.05, AA = African Americans/Blacks*

Thus, the following assumptions were made:

- We expect a conservative absolute average of approximately 10% increase in guideline adherence at twelve months for subjects enrolled at centralized CVRS sites versus subjects at usual care sites.
- Standard deviation for change from baseline is expected to be 20% for both groups.
- The intraclass correlation coefficient is conservatively assumed to be less than or equal to 0.005.
- Each participating site will be expected to enroll 20-25 subjects.
- Both primary hypotheses will be tested at the 0.025 significance level. The secondary hypothesis will be tested at the 0.05 level.
- The drop-out rate is expected to be 15%.

6.4 Futility Analysis

One formal futility analysis will be conducted when half of the planned active participants have completed their twelve month follow-up. The futility assessment will be based on a determination of the predictive power. If this predictive power is below 5% at the time the analysis is conducted, then we propose that the trial should stop for futility.

6.5 Strategies to Limit and Handle Missing Data

The primary analysis will follow the intent-to-treat principle. As such, it will be critically important to minimize the occurrence of missing data. Our team will use a variety of methods in order to minimize the percentage of missing data in this trial, including required data fields for critical variables and queries to sites regarding missing data.

For subjects who drop out of the study before their 12 month data can be obtained, we propose to use a multiple imputation method to impute their outcome. This multiple imputation will be implemented using a model based on guideline adherence at baseline and the 12 month guideline adherence values for all subjects with observed data. We will use five separate imputations, and will average the parameters across all five imputations for the final analysis.

7. Data and Safety Monitoring

7.1 Site Monitoring Roles

Each participating site will have the following monitoring responsibilities:

- At the 12 month visit, the site Study Coordinator will ask each subject if they have had any hospitalizations or emergency room visits. The Study Coordinator will also screen each subject's medical record for documentation regarding these types of events. SAEs that meet the qualifying criteria specified in Section 4.8 should be reported through the study database.
- At the 24 month time point, the Study Coordinator will review each subject's medical record for documented SAEs. Those that meet the qualifying criteria specified in Section 4.9 should be reported through the study database.
- Should a Study Coordinator or site investigator become aware of an SAE that meets the qualifying criteria specified in Section 4.9 at any other time point during a subject's 24 month period in the study, the site Study Coordinator should report that event through the study database.
- Local site personnel also submit reports of SAEs to their local Institutional Review Boards (IRBs) per their IRB's policy. The Study Coordinator should provide the CCC with the notification they receive from a local IRB regarding its decision related to a reported event.
- Local site personnel forward to their IRB the DSMB summary report from each meeting, either when received or at the next continuing review.

7.2 Local IRB Monitoring Roles

Local IRBs will review all SAEs reported to them by the site per their own procedures. The local IRB will make a decision on each case regarding what further action might be needed and communicate that decision to the site's PI.

7.3 Data Coordinating Center Roles

The DCC receives submitted reports of SAEs from local investigators, and forwards them to the Physician Monitor for review. If an SAE that meets the criteria for expedited reporting is identified, the DCC notifies the CCC of the determination.

The DCC provides a biannual safety report to the DSMB based upon the 12 and 24 month SAE screenings that are conducted by site Study Coordinators.

The DCC performs remote and on-site monitoring checks to each participating site per the monitoring plan.

7.4 Physician Monitor Roles

The Physician Monitor for the study, Dr. Paul James, will serve three major roles in the evaluation of SAEs for the trial:

- Perform ongoing, real-time reviews of all individual SAE reports to determine if events are unanticipated, related and serious, and suggestive of greater risk;
- Perform quarterly reviews of cumulative SAE data to judge whether there are concerning trends in the occurrence of events, and the possible relationship of those trends to the trial; and
- Review any reports of SAEs that meet the NHLBI criteria for reporting (i.e. suggests greater risk of harm to study participants than was previously known or recognized).

7.5 Data and Safety Monitoring Board (DSMB) Monitoring Roles

7.5.1 Board Composition

The following persons have agreed to serve on the MEDFOCUS Data and Safety Monitoring Board (DSMB):

- Barry Davis, MD, PhD, University of Texas School of Public Health, an internationally recognized researcher who was the PI for the ALLHAT trial, will chair the DSMB.
- Keith Ferdinand, MD, Tulane University, a cardiologist and member of the Association of Black Cardiologists, led the Community Outreach program for the American Society of Hypertension that conducted screening programs in underserved areas of Harlem, New Orleans and San Francisco.
- Michael Murray, PharmD, MPH, Regenstrief Institute, has conducted numerous pharmacist intervention studies in heart failure, asthma and others.
- The DSMB members will agree upon a person at one of their institutions to serve as the DSMB Executive Secretary.

7.5.2 DSMB Tasks

The DSMB is responsible for safeguarding the interests of study participants by assessing the safety and efficacy of study procedures and by periodic monitoring of safety data and the overall conduct of the study. The DSMB reviews the following types of data provided by the DCC:

- Bi-annual reports on overall study progress, including enrollment and study completions
- One futility assessment conducted when half of the enrolled subjects have completed the 12 month study visit
- Reviews of the SAE screenings and related SAE reports conducted at 12 months
- Individual concerns identified by the Physician Monitor.

After reviewing pertinent reports, the DSMB determines whether any trend that may be identified is related to the trial.

After each scheduled DSMB meeting, the DSMB chair or his designee sends a summary report of the meeting to the CCC that summarizes the DSMB deliberations and recommendations. The CCC forwards the summary report to the study sites for reporting to their local IRBs and to the University of Iowa IRB for reporting during the annual continuing review.

7.6 Clinical Coordinating Center Monitoring Roles

7.6.1 Disseminating DSMB meeting summary reports

The CCC receives the DSMB meeting summary report from the DSMB Chair and forwards the summary report to the participating sites, and to the University of Iowa IRB for the annual continuing review.

7.6.2 Reports to NHLBI

If an SAE is determined to meet the relevant criteria (specified below), it must be reported to the NHLBI, the DSMB, and Site Investigators through an expedited reporting process. The procedure for expedited reporting of SAEs is presented below:

- The CCC PI submits an expedited report to NHLBI, the DSMB, and the Site Investigators for submission to their local IRBs within seven (7) days of learning of an SAE that meets both of the following criteria for expedited reporting:
  - The event or problem was unanticipated

  AND
  - The event or problem either could probably have been related to the study intervention, or was definitely related to the study intervention.
- For unanticipated events or problems suggesting that "*the research places subjects or others at a greater risk of physical or psychological harm that was previously known or recognized*", the CCC PI is responsible for preparing a report for submission to NHLBI within 30 days, and to others as directed by institutional procedures and IRB-approved data and safety monitoring plans.
- Expedited SAE reports to NHLBI should include the following elements:
  - Study title, grant number, PI name
  - Description and date of the event or problem, including why it merits expedited reporting
  - When it becomes available, the date on which the SAE was reported to the CCC PI, the clinical site PI, NHLBI, and applicable oversight bodies (relevant IRBs, the DSMB, Office for Human Research Protections).
  - Any corrective action planned or taken in response to the SAE (e.g., study suspension, consent or protocol changes, additional training or security measures). Corrective action plans for a UP that occurs at a local site should be developed by the site, and then approved by the CCC.
  - Signature of the CCC PI (B. Carter)
  - All communications from the relevant oversight bodies regarding an expedited SAE must be reported to NHLBI.

7.7 Data Management to Maintain Blinding

The physician monitor will usually be blinded, with subjects identified only by a study ID. However, during the review of SAE reports, it is possible that content within an SAE report could indicate the subject's treatment arm.

All reports created for the DSMB by the DCC will be blinded to treatment arm by the biostatistician. However, the DSMB may request un-blinding to improve the quality of their decisions.

8. STUDY RESPONSIBILITIES

8.1 University of Iowa PI Responsibilities

By signing this protocol, the study's two PIs agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol, with accepted standards of GCP, and with all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The CCC PI will provide current copies of the study protocol to all sub-investigators and other site personnel responsible for study conduct.

The CCC PI will provide NIH with copies of all institutional review board (IRB) actions regarding the study.

8.2 Training

The CCC PI will hold a remote webinar/Skype session with site providers and research team members at the beginning of the study to review the study and the roles of key personnel. The CVRS pharmacists will participate in these sessions for sites randomized to the CVRS intervention group.

All study coordinators will attend a 1-2 day session at the University of Iowa for training on the protocol and the study database.

8.3 Communication with Sites

The CCC PI and CVRS pharmacists will hold teleconference calls with the site pharmacist and lead physician as needed during the first year of the intervention to develop strategies to optimize communication, improve implementation of the intervention, if necessary, and ensure fidelity to the intervention.

The CCC PI will hold teleconference calls on an as needed basis with research team members at any usual care sites that do not meet expectations for recruitment or data collection.

8.4 Study Documentation

Study documentation includes all electronic and paper forms, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and regulatory documents (signed protocol and amendments, IRB correspondence and approval, clinical supplies receipts and distribution records).

By signing the protocol, the Site PI acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to UI appropriate parties upon request. It will also be made available upon request for inspection, copying, review, and audit at reasonable times by representatives of UI or responsible government agencies as required by law.

8.5 Data Transmission and Record Retention

The study coordinator will enter required data into the DCC study database as soon as possible after a data collection activity (study visit or medical record abstraction time point). Data will be transmitted via the internet using encryption mechanisms to ensure security and confidentiality. Timestamps will be collected to identify the occurrence of data entries and changes. Edit checks, electronic queries, and audit trails are built into the data collection system to ensure accurate and complete data collection.

Sites will keep hard copy case report forms until both of the following criteria for destroying data are met: 1) the CCC informs the site that data may be destroyed and 2) the timeframe meets the policy of the local IRB.

8.6 Use of the Iowa Personal Health and Research Management (IowaPHRM) Online Record

Subjects will be able to enter their own health information into the separate IowaPHRM website application.

IowaPHRM has automated features that subjects may use to reset usernames and passwords, assuming that the subject has an active email address. Persons who do not have email should call the CCC and request a reset. The CCC will validate subject identity by requiring that subject responses match information in the database for (1) first and last name, (2) year of birth, (3) full address (current or previous if recently moved) and (4) at least one phone number documented for the subject.

8.7 Study Closeout

Once all study data has been entered and all queries have been resolved, the DCC will conduct closeout activities with the site, either at the site or remotely.

8.8 Publication Policies

The PI will be primarily responsible for creation, review, and submission of publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study.

The manuscript containing the overall study results will be distributed to all study investigators at the University of Iowa for review and comment before submission to a peer-

reviewed journal with a reasonable period for review, but the final content will be at the discretion of the PIs. Any other manuscripts containing these data, including abstracts, will be distributed to all relevant study investigators who are participating on such publications before submission, with a reasonable period for review. Submitted publications will conform to international standards for biomedical manuscripts, including those regarding authorship.

9. ETHICAL CONSIDERATIONS

By signing this protocol, the PI agrees to conduct the study in compliance with the protocol; the Declaration of Helsinki; and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

9.1 Role of University of Iowa

The University of Iowa has overall responsibility for the conduct of the study, including assurance that the study meets the sponsor's regulatory requirements.

9.2 Informed Consent

The local site investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Informed consent will be obtained from all subjects before any data are collected and before any study-related procedures are performed. University of Iowa investigators will oversee site submission of IRB applications and store local IRB approval letters and consent documents.

Before and after subject provision of informed consent, research team members will be available via email, IowaPHRM, or phone to answer questions or concerns regarding procedures and risks. Research team contact information will be included on all study materials and the study website.

9.3 Confidentiality of Subjects

Subject confidentiality will be maintained throughout the clinical study. A unique subject ID code will be used to identify all data reported for each subject. Full name and comprehensive contact information will be collected only for subjects in the CVRS intervention arm, so that the CVRS pharmacists can contact them upon enrollment. Names and other identifying information will not be visible to members of the DCC staff. The only identifiers collected for usual care subjects, as well as intervention subjects, will be birthdates and the dates of clinic visits.

Subject information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by HIPAA and as mandated in Title 45 CFR Parts 160 and 164. All records will be kept confidential, and the subject's name will not be released to non-authorized persons or entities at any time. Subject records will not be released to anyone other than members of the research team at each site who have a need for such information, and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is guaranteed.

Hard copy records containing subject data collected at sites (eg, case report forms, informed consent documents) will be stored in a locked cabinet in a locked office at each

respective site. Identification numbers will be used in place of names on case report forms. All electronic study data will be stored on encrypted, password-protected servers located within security firewalls, such that only members of the research team who need access will be allowed access to study files. Subject data will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which disclosure of the requested data would be permitted by the HIPAA Privacy Rule. If needed, any transport of electronic data will occur via a password-protected disk or secure transfer protocol.

9.4 Authorization for Use and Disclosure of Protected Health Information (HIPAA)

All subjects will consent, through their IRB-approved informed consent document or HIPAA release, to release of protected health information to the University of Iowa research teams as part of the consent process.

9.5 Human Subject Protections

9.5.1 Research Subject Selection

Before implementation, the investigators at each site will review the study protocol with physicians in participating clinics. The physician engagement activities will ensure that the involved clinical services approve of the study protocol.

Subjects will have multiple opportunities, both before and during the first visit, to ask questions and read information about the study. After an initial review of the informed consent document, patients will be given up to 10 days to decide whether they want to participate. No coercion or undue influence on this decision will be used.

There will be no exclusion from participation in the study on the basis of gender, ethnicity, or race. Subjects younger than 55 years of age at the time of screening will be excluded from the study.

9.5.2 Compensation to Subjects

Subjects will be compensated $75 for completion of the baseline visit and $75 for completion of the 12 month visit for their time and inconvenience related to the blood draws and surveys. No compensation will be provided for a subject who does not complete a visit. Compensation will be provided by the participating site and reimbursed through quarterly invoices to the University of Iowa.

9.5.3 Risks/Discomforts of Study Participation

Subjects might experience one or more of the risks indicated below from being in this study:

- Some of the questions that the study coordinator asks might cause a subject to feel uneasy or anxious, but subjects may choose not to answer any questions.
- Drawing blood for laboratory tests could cause mild and temporary discomfort and might also result in bruising, fainting/lightheadedness and/or infection.
- There is a risk of loss of data confidentiality. To help protect confidentiality, all patient forms completed during study visits will be kept in locked file cabinets in locked offices. The study coordinator will send data electronically to study researchers at the University of Iowa using a confidential computer system. Only

individuals working on the study will have access to these records. Data will be entered electronically using a unique study ID for each subject. All research data collected will be stored in password-protected computer files that can be seen only by the subject and the research team. The blood samples that are drawn will be analyzed in the clinic or hospital laboratory, and the results of those labs will only be visible to the research team. If study investigators write a report or article about this study or share the study data set with others, individual subjects will not be directly identified.

9.6 Institutional Review Board Review

The local IRB will approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The study investigator will be responsible for submitting any and all revisions to the appropriate IRB before implementation of any deviation from the approved protocol. The local investigator must provide the CCC with the IRB annual re-approval of the protocol and with all approved versions and revisions to the informed consent documents and recruitment letters or any amendments to the protocol.

The CCC will obtain IRB approval from the University of Iowa IRB (UI IRB) and submit modifications (when needed) and annual continuing review applications. The CCC will notify the UI IRB when an event occurs that is both unanticipated and deemed by the medical monitor to be related to participation in the study.

The CCC will also track modifications and annual renewals for each participating site.

APPENDICES

APPENDIX I: PARTICIPATING SITES

Clinic Name	City/State	% Minority in CAPTION
LOW MINORITY SITES		
Northeast Iowa Family Practice	Waterloo, IA	0%
Siouxland Family Medicine Center	Sioux City, IA	0%
Pocatello Family Medicine (Idaho State)	Pocatello, ID	4%
Center for Community and Family Medicine (Texas Tech)	Amarillo, TX	8%
Genesis Family Medical Center	Davenport, IA	13%
Sugar House Health Center (University of Utah)	Salt Lake City, UT	22%
Wingra Family Medical Center	Madison, WI	22%
Northeast Family Medical Center (University of Wisconsin)	Madison, WI	24%
Scripps Ranch Family Medicine (UCSD)	San Diego, CA	27%
4th and Lewis Family Medicine (UCSD)	San Diego, CA	39%
HIGH MINORITY SITES		
General Internal Medicine Clinic (UNC)	Chapel Hill, NC	56%
Family Medicine Clinic (USF)	Tampa, FL	57%
Milwaukee Health Services, Inc. (MHSI)	Milwaukee, WI	70%*
Wheaton Franciscan Medical Group Wisconsin Ave	Racine, WI	74%
Physicians at Sugar Creek (Memorial Hermann)	Sugar Land, TX	88%
Family Health Center (UTHSCA)	San Antonio, TX	88%
Family Medicine at Main (University of Florida)	Gainesville, FL	89%
Jefferson Family Medicine Center (SUNY Buffalo)	Buffalo, NY	93%
Advocate Medical Group (Midwestern University)	Chicago, IL	100%
Medicine Group Practice (Temple University)	Philadelphia, PA	100%

*Current minority population per Medical Director's report; did not participate in CAPTION

APPENDIX II: STUDY TIMETABLE (months)

Activity	***0- 9***	***9-18***	***19-27***	***28-39***	***40-50***	***51-60***
Stratify and randomize clinics						
Validate web-based data collection forms and procedures						
Train CVRS pharmacists						
Train study coordinators in data collection, web database						
Train physician leaders/clinical pharmacists via webinar						
Recruit active subjects		**200 enrolled**	**200 enrolled**			
CVRS intervention						
Onsite visits and monitoring						
Safety monitoring by DSMB						
Cost effectiveness analysis						
Study close out						
Manuscripts, reports and Dissemination of the findings						

VERIFICATION OF INCLUSION AND EXCLUSION CRITERIA

Demographic Criteria	Has Inclusion Criterion*	
English speaking males or females	Yes	No
≥55 years of age	Yes	No
Has been seen in the clinic in the previous 24 months	Yes	No

If the answer to both questions is Yes, then proceed to Section A. If not, then stop. The patient cannot participate in the study.

Section A: Has a history of:	ICD9 Codes*	ICD10 Codes*	Has Inclusion Criterion*	
Coronary artery disease (CAD)	414	**I25**	Yes	No
Previous MI (heart attack)	410, 411, 412	**I21, I25.2**	Yes	No
Stroke	430, 431, 432, 433, and 434	**I60, I61, I62, I63**	Yes	No
TIA	435	**G45**	Yes	No
Atrial fibrillation	427.31,427.3	**I48.0, I48.1, I48.2, I48.91**	Yes	No
Systolic heart failure	428.20. 428.21, 428.22, 428.23, 428.40, 428.41, 428.42, 428.43	**I50.2, I50.4**	Yes	No
Peripheral vascular disease/claudication	440.2, 440.3, and 440.4	**I70.2, I70.3, I70,4, I70.5, I70.6, I70.7, I70.92**	Yes	No
Carotid artery disease	433.1	**I65.2, I63.03, I63.13, I63.23**	Yes	No
Diabetes *and must also have one of both of the following conditions:*	250	**E10, E11**	Yes	No
Hyperlipidemia	272	**E78**, *PLUS* most recent chart documented LDL must be > 110 mg/dl	Yes	No
Hypertension	401, 402, 403, 404, 405	**I10, I11, I12, I13, I15** *PLUS* most recent chart documented systolic BP ≥ 140 mm Hg and/or most recent diastolic pressure ≥ 90 mm Hg	Yes	No

* If a listed code does not include any digits to the right of a decimal point, then all sub-codes included under the listed code qualify. If a listed code or set of codes includes one or more digits following a decimal point, then only those sub-codes that are listed and any codes underneath that sub-code qualify.

******Must have at least one risk factor from Section A. If so, proceed to Section B and check for Exclusion Criteria******

Section B: Exclusion Criteria Prior to Consent	**Source or ICD code**	**Has Exclusion Criterion***	
Signs of acute angina, stroke, heart failure or renal failure	Direct observation or medical record documentation	Yes	No
Systolic BP > 200 mm Hg or diastolic BP > 144 mm Hg	Direct observation or most recent value documented in medical record	Yes	No
Significant hepatic disease, including; ▪ Cirrhosis ▪ Hepatitis B or C infection ▪ Serum ALT or AST > 3 times control ▪ Total bilirubin > 2.0 mg/dl	Medical record documentation	Yes	No
Pregnancy	self-report or ICD9: V22, V23, V24 *or* ICD10: **000-008 through 094-09A**	Yes	No
Inability to give informed consent or impaired cognitive function	Direct observation or medical record documentation	Yes	No
Residence in a nursing home or diagnosis of dementia	Self-report or medical record documentation	Yes	No
No telephone or have a hearing impairment not allowing them to use a phone	Self-report or medical record documentation	Yes	No
Refusal to consider attempting to use the internet at home, community center, library, medical office or other source.	Self-report	Yes	No
A measured arm circumference that exceeds 50 cm.	Direct observation or medical record documentation	Yes	No

*** ***BEFORE THE SUBJECT SIGNS CONSENT, VERIFY THAT S/HE HAS:***

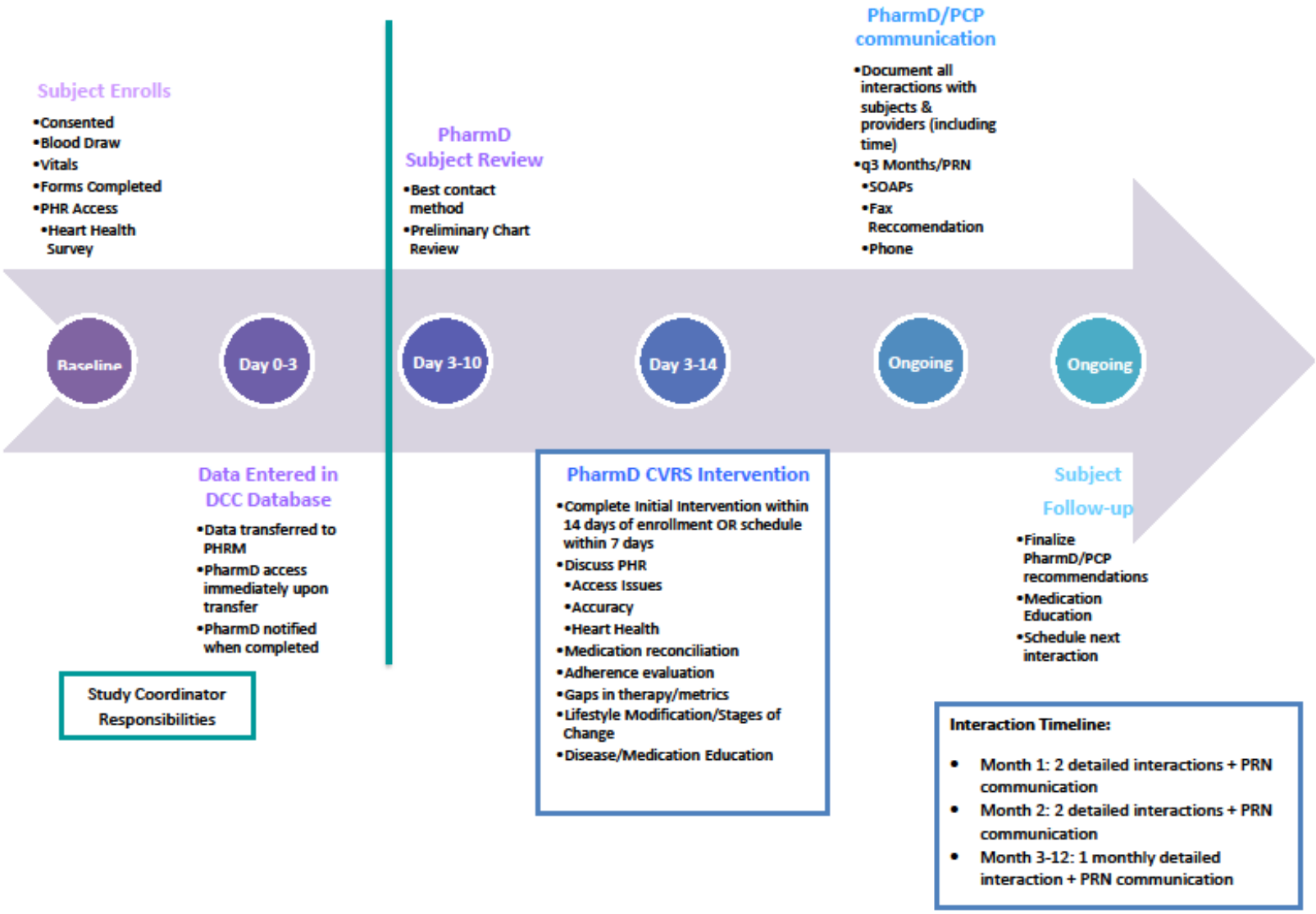
☐ **AT LEAST ONE "YES" ANSWER FROM SECTION A (RISK FACTORS)**

AND

☐ **NONE OF THE EXCLUSION CRITERIA IN SECTION B**

APPENDIX IV: INTERVENTION SUMMARY

Overview of MEDFOCUS Interactions



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