MEDFOCUS

MEDication Focused Outpatient Care for Underutilization of Secondary Prevention

Manual of Operations

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MOP VERSION AND AMENDMENT TRACKING

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

Version Number/Amendment	Approval Date
Original MOP Version 1.0	December 7, 2014
Version 1.1	

PROTOCOL SYNOPSIS

Study 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 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 medical record abstraction at 24 months
Intervention	A CVRS clinical pharmacist will communicate with subjects regularly to: assess knowledge, medication adherence and side effects; develop an action plan; communicate with the clinic pharmacist and provider as needed to optimize medication and non-pharmacological self-care regimens.
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 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

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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 System
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
UP	Unanticipated problem

University of Iowa Study Organization

Three teams of investigators at the University of Iowa are jointly leading this study.

The **Clinical Coordinating Center (CCC)** within the College of Pharmacy at the University of Iowa is responsible for: selection and recruitment of participating sites; assisting sites in obtaining approval to conduct the study from their local Institutional Review Board (IRB); negotiating with sites the work that is to be completed and the compensation that sites will receive; training of site staff.

Clinical Coordinating Center Team		
Barry L. Carter, co-Principal Investigator	barry-carter@uiowa.edu	319-335-8456
Christopher Parker, Clinical Pharmacist	christopher-parker@uiowa.edu	319-333-9722
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Gail Ardery, Research Manager	gail-ardery@uiowa.edu	319-384-4128
CCC Fax Number		319-384-1728

The **Data Coordinating Center (DCC)** within the Clinical Trials Statistical and Data Management Center in the College of Public Health at the University of Iowa is responsible for: oversight of data submission, monitoring procedures at research sites, and data analyses.

Data Coordinating Center Team		
Dixie Ecklund, Assoc. Director, DCC	dixie-ecklund@uiowa.edu	319-335-8446
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Trevis Huff, Research Specialist	trevis-huff@uiowa.edu	319-384-3482
Rick Peters, IT Manager	richard-peters@uiowa.edu	319-335-6872
DCC Fax Number		319-335-6535

The **Iowa Personal Health & Research Management (IowaPHRM)** system is a web-based tool that gives subjects an opportunity to increase involvement in managing their health and enhances contact between intervention site subjects and the CVRS pharmacists. IowaPHRM will be managed by the following team within the College of Public Health and the Institute for Clinical and Translational Science at the University of Iowa.

IowaPHRM Team		
Brian Gryzlak, Research Specialist	brian-gryzlak@uiowa.edu	319-335-8218
Nick Rudzianski, Research Associate	nicholas-rudzianski@uiowa.edu	319-335-9783
Michael Mueller, Lead IowaPHRM Administrator	michael-mueller@uiowa.edu	319-384-1547
Ryan Lorentzen, Application Analyst	ryan-lorentzen@uiowa.edu	319-353-8015

PROTOCOL COMMUNICATION PLAN

Contact the CCC for all questions and concerns related to:

- Subject Recruitment: Study timeline, screening process, eligibility, informed consent, and enrollment
- Visit Procedures: Visit timeline, visit windows, survey administration, lab work, BP measurement, medical record abstraction, SAE screening, SAE reporting, participant concerns, subject termination
- Study Documents: Protocol, manual of operations, completion of individual CRF items, drug lists/codes
- Regulatory Documentation: IRB approvals, delegation log, expiring documents, documentation requirements.
- Financial Documentation: Site subawards, invoicing.

Contact information for the CCC:

Gail Ardery
Phone: 319-384-4128
Fax: 319-384-1728
Email: gail-ardery@uiowa.edu

Contact the DCC for all questions and concerns related to:

Topic/Issue	DCC Contact Person
▪ Access to the study database, data entry, data submission, data queries	Trevis Huff, 319-384-3482 trevis-huff@uiowa.edu
▪ Study monitoring, data correction	Tina Neill-Hudson, 319-384-2750 tina-neill-hudson@uiowa.edu ***OR*** Julie Qidwai, 319-384-4165 julie-qidwai@uiowa.edu

Contact the IowaPHRM team for all questions and concerns related to:

- Subject access to and use of the IowaPHRM patient portal

Contact information for the IowaPHRM team:

Brian Gryzlak
Phone: 319-353-3857
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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] 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 that adding pharmacists to the primary care team improves risk factor control and guideline-support treatment.[52-54] The Institute of Medicine (IOM) and Centers for Disease Control, have called for more research to evaluate the use of pharmacists for CVD management.[54-57] Over 100 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] have included pharmacists. A 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 few 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 Rationale

Adherence to guidelines for CVD is low, and regional and age variations in guideline concordant therapy have been found.[63-68] The primary barrier is suboptimal medication use leading to poor disease control, often because busy providers must address acute non-CVD complaints.[69-71] Managed care organizations and other settings are increasingly hiring clinical pharmacists to improve management of CVD.

The 5 year **MEDFOCUS** study, funded in April 2014 by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), will evaluate a centralized, web-based CVRS designed to support primary care providers to improve the management of CVD and achieve key performance measures.[72] 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 ultimate goal of the Iowa research program is to reduce CVD events when the CVRS intervention is implemented more broadly.[12] The study provides a model for addressing 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 and adoption of the intervention by all medical offices that currently utilize clinical pharmacists could result in 20-30% fewer coronary deaths and 25-40% fewer stroke deaths in the U.S.

2. OBJECTIVE AND AIMS

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. Twenty primary care offices (see Appendix I) have been randomized 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

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.

In 2011, the American Cancer Society, American Diabetes Association and American Heart Association joined forces to create The Guideline Advantage, a program that uses data collection, analysis and feedback to translate prevention and treatment guidelines into practice within the outpatient setting. The program is particularly relevant in light of the current healthcare environment, aligning with key national initiatives and supporting Meaningful Use and Patient Centered Medical Home (PCMH) initiatives.

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.

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

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

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

MEDFOCUS is a multi-center, cluster-randomized study that will 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, and the proposed study timeline is in Appendix II. 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, HgA1c, select chemistries and liver tests (intervention subjects only), and surveys. Site study coordinators will also abstract select medical record data 24 months following enrollment.

Each subject enrolled at CVRS intervention arm clinics will receive the CVRS intervention for 12 months. A CVRS clinical pharmacist at the University of Iowa will work telephonically with each intervention arm subject and communicate with their providers to optimize subjects' pharmacological regimens and lifestyle patterns.

Subjects enrolled at usual care 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 usual care arm subjects, adheres to the Guideline Advantage measurement set criteria. If successful, the CVRS intervention model could become an important strategy to markedly reduced cardiovascular events in the United States.

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, but these research data will not be visible to intervention subjects. 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.

Key roles on the study are described below:

Roles of CVRS and Site Personnel	
Site Study Coordinator	Staff member employed within each participating institution/clinic 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 Leader	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) has stratified the 20 participating offices based on lower (<40%) versus higher (≥40%) numbers of minority population and then randomized the offices in a cluster-randomized design to avoid contamination within offices. Each office has been 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 sugars 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 CVRS intervention arm clinics will receive the study intervention. A CVRS clinical pharmacist at the University of Iowa will work telephonically with each intervention arm subject and communicate with the site clinical pharmacist to optimize subjects' pharmacological regimens and lifestyle patterns. Each subject at intervention arm clinics will receive the 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 study intervention.

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

5. OUTCOMES

5.1 Primary Outcomes

5.1.1 Adherence to Guideline Advantage criteria in All Subjects

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 baseline, at 12 months, and at 24 months. This algorithm will be applied to all subjects, with CVRS intervention subjects compared to usual care subjects. The Guideline Advantage Reporting Measure Set is presented in Appendix III. Accurate measurement of study outcomes will critically depend on capturing all CRF elements. Diligence to capture all elements is a priority.

5.1.2 Adherence to Guideline Advantage Criteria in Minority Subjects

The same algorithm will also be used to compare adherence to Guideline Advantage criteria between CVRS intervention subjects and usual care subjects who represent minority populations.

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 to Guideline Advantage criteria between CVRS intervention subjects and usual care subjects who are African-American.

5.2.2 BP Control, Mean BP, LDL Cholesterol, HgbA1c

Direct measurement (at baseline and 12 months) and medical record abstraction (at 24 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.

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 Site Physician Leader 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 in year 4 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

Site Clinical Pharmacists and Primary Care Providers will be asked to complete two validated questionnaires at the beginning of the project and again in Year 4: an instrument measuring physician-pharmacist collaboration and an instrument evaluating physician adoption of the study intervention, with scores compared between CVRS intervention clinic providers and usual care clinic providers.

6. REGULATORY AND BILLING REQUIREMENTS

Each site will be required to complete the following study-related tasks and to store and transmit to the University of Iowa CCC the relevant documents listed for each task.

6.1 IRB Oversight

Each site must obtain approval for the study from its local Institutional Review Board, including approval of study procedures, approval of informed consent documents and approval letters for modifications and continuing reviews. Required documents include:

- The Institutional Review Board's letter of approval for the study
- All stamped documents approved and dated by the local IRB, including:
  - Recruitment letter
  - Informed consent document
  - HIPPA authorization, if used.

Local IRB approval should be obtained by December 22, 2014. The University of Iowa CCC will assist clinics in responding to inquiries from their local IRB.

Each IRB-related document should be stored both in hard copy form in an organized binder and electronically. See section 9.b for details.

6.2 Subaward Agreement with the University of Iowa

Administrative personnel at each site must negotiate and sign a subaward document created by the University of Iowa's Department of Sponsored Programs. The agreement describes the terms and conditions for reimbursing sites for study-related costs. The agreement should be signed by an authorized individual at the clinic and returned to the University of Iowa within one month of receipt. The subaward budget will be negotiated on an annual basis, with an authorized signature required each year on the amended award.

Please note that payments are based upon work that is completed. A clinic that does not complete expected tasks for a given year would not be able to receive all the funds designated in the budget for that year. Questions regarding the subaward agreement should be directed to Gail Ardery at **gail-ardery@uiowa.edu**

6.3 Invoicing the University of Iowa

The Grant Accounting Department at the University of Iowa requests quarterly invoicing for project expenses. The following procedures will be maintained for submitting invoices:

a. Dr. Ardery at the CCC will email a quarterly draft invoice to the clinic staff member who is designated as responsible for invoicing. Dr. Ardery should be notified immediately of any change in person responsible for invoicing.

b. Each draft quarterly invoice will detail all costs that are reimbursable during that quarter; only tasks completed during the quarter will be included on the invoice.

c. Inquiries regarding the itemized items on the draft invoice should be directed to Gail Ardery at gail-ardery@uiowa.edu.

d. A completed invoice should be pasted onto your billing stationery and signed by an authorized individual in your clinic.
e. The signed invoice should be scanned and emailed to gail-ardery@uiowa.edu.
f. Dr. Ardery will approve the invoice and forward it to Grant Accounting for payment.
g. Payment typically occurs within 30 days of invoice receipt.

6.4 Delegation of Responsibilities Log

Each site must submit a Delegation of Responsibilities (DOR) Log to the DCC. The website will include a template for the log which each site can download. All persons working with subjects or subject data, excepting the PI, must complete a row on the log, including printing his/her name and credentials and initials, indicating all of the responsibility codes that describe their role(s) on the study, their signature and the dates of their involvement.

The site PI should sign and date at the bottom of the DOR document after all personnel have completed their respective lines.

Should a site have a change in personnel, the date on which an individual stops working on the study should be written in the Involved To column on that person's line of the DOR log. Any new personnel should add a new line to the log. Changes should be scanned and emailed to the DCC as quickly as possible.

The completed Delegation of Responsibilities Log should be scanned and sent via email to gail-ardery@uiowa.edu.

7. SITE ACTIVATION

Before each site can be fully activated and begin enrolling subjects, the following tasks must be completed:

a. The letter of approval from the site's local IRB must be emailed to the CCC.
b. The IRB-approved consent documents for each site must be reviewed and approved by the CCC.
c. Each site must submit the Delegation of Responsibilities Log to the CCC.
d. Each site must submit a signed protocol site signature page to the CCC.
e. Each site must submit a valid and current Clinical Laboratory Improvement Amendments (CLIA) certificate to the DCC.
f. The Site Study Coordinator must complete protocol training, data entry training, and BP measurement training.
g. The Site Study Coordinator must complete a phone review of training with the CCC.

Once the CCC informs the DCC that all documentation has been submitted, the DCC will activate the site in the database.

8. TELECONFERENCE CALLS

Iowa investigators will schedule periodic conference calls with the site clinical pharmacist, physician leader and study coordinator on an as needed basis during the first year of the study, and then at least once a year thereafter. These calls will be used to: 1) discuss barriers to enrollment and strategies for overcoming them; 2) solicit site input on optimizing communication, improving the intervention, ensuring fidelity to the intervention.

9. ORGANIZING AND MAINTAINING STUDY FILES

a. Patient Files

- Each patient should have a study file containing a signed informed consent document, completed case report forms and other source documentation. Arrange patient files in order of study visits.
- Complete paper copy case report forms (CRFs) before entering data on the website.
- If corrections to paper copies are needed, draw a single line through the incorrect response, write the correct response, and initial and date the correction. White-Out or other similar products that obscure the original response may not be used on source documents.

b. Keep all Regulatory documents together in hard copy form in a binder.

- MEDFOCUS Study Documents
  - Protocol: Includes copy of signed protocol signature page
  - Delegation of Responsibilities log
  - Training/Certification: Includes BP Measurement Certification and CLIA Certificates
  - Monitoring reports
- IRB of Record Documents
  - IRB approvals: All approval letters including initial approval, modification/amendment approvals and continuing review approvals.
  - IRB Correspondence/Submissions: All pertinent communications with the IRB relating to the study (e.g. recruitment materials and any correspondence) also including notification of Serious Adverse Events (SAEs), notification of any protocol deviations and notification of removal of subject.
  - Informed Consents: All copies of IRB approved informed consents.
  - Critical Study Correspondence: Copies of all relevant correspondence pertaining to protocol interpretation/clarification/modifications, study-wide notice regarding change in risk, AE/SAE Reporting and DSMB annual memo to IRBs.
  - Protocol Deviations: Some IRBs have separate templates for sites to report protocol deviations. If you have your own IRB and it requires such reporting, please include these reports under this tab.

Each IRB document should also be stored electronically on a secure computer and emailed to gail-ardery@uiowa.edu.

Site Study Coordinators will be certified in proper blood pressure measurement procedures at a Study Coordinator training session in Iowa City. Approximately one year following the initial certification, remote re-certification will be conducted using Skype.

10. SUBJECT RECORDS AND DATA DOCUMENTATION

All study data will first be completed on hard copy CRFs and stored in a folder for each individual subject. 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.

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 and user ID will be collected to denote 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.

11. STUDY MONITORING

Periodic site monitoring will be conducted by a member of the DCC team to: a) ensure that that the protocol is being followed; b) assess whether subject's rights and safety are being protected; and c) to confirm data integrity and quality and d) to ensure that serious adverse events are accurately reported.

All centers will be monitored at an interval specified in the monitoring plan. Clinical Study Sites will have an initial monitoring visit scheduled within three months of the first subject being enrolled or sooner if a site enrolls more than 5 qualified subjects. The initial monitoring visit can be delayed up to six months after the first subject's enrollment if central review of that subject's eligibility and informed consent documentation is acceptable (see below).

An initial on-site monitoring will occur within three months after the first subject is enrolled and sooner should a site's enrollments exceed 5 qualifying subjects. Whenever possible, subsequent monitoring while the study is ongoing will be done centrally (at the University of Iowa, using remote techniques). However, an additional on-site visit might occur should a site exhibit signs of inaccuracy or weakness. All sites will have an on-site close-out visit after all subject visits are completed, all medical record data have been submitted, and all outstanding data issues have been resolved.

11.1 On-Site Monitoring

11.1.1 Preliminary Activities

The monitor will email the Study Coordinator with possible dates for the on-site monitoring visit approximately 4-6 weeks ahead of these dates. Plan on at least two days for the visit. The Site Study Coordinator and local PI should be available to meet with the monitor during the visit. The visiting monitor will need full access to subjects' medical records but will have NO contact with those subjects.

The monitor will send a letter to the center approximately 2 weeks ahead of the scheduled monitoring visit date explaining objectives of the visit and necessary materials. The monitor will need a reserved space in which to work and access to a photocopy machine and electronic records, if applicable. The following items should be available for review:

- Screening Log
- Access to subjects' medical records

- Paper copy CRFs and any other study-related source documents and records
- Regulatory Documents
  - Delegation of Responsibilities Log
  - A copy of the signed protocol site signature page
  - IRB approvals
  - Approved informed consent documents
  - Approved recruitment materials
  - IRB correspondence
  - Prior monitoring reports
  - Blood pressure certifications

11.1.2 On-site Visit Activities

An initial meeting (approximately 30 minutes) will occur between the Study Coordinator and the monitor to orient the monitor to clinic/medical records, answer study questions, and review protocol procedures. The Study Coordinator should be available periodically throughout the visit to answer questions or to make data corrections, if necessary.

At the end of the monitoring visit, the monitor will meet briefly with the Study Coordinator and PI to discuss findings and a plan of action.

11.1.3 Post-Monitoring Communication

The monitor will send the Study Center a formal report containing feedback and a detailed listing of all findings within 4 weeks of concluding the monitoring visit.

The monitor will contact the Study Coordinator to discuss pending items until all items are resolved. The Study Coordinator will respond to pending items in a timely manner and inform the monitor of any issues delaying resolution of the item.

11.2 Centralized Monitoring

11.2.1 Data Entry System – The data entry system includes several mechanisms for checking the integrity of submitted data:

- Intra-form queries
- Range checks
- Overrideable fields
- Drop-down menus
- Logic checks
- Mandatory fields,
- Skip-outs
- Limited open text boxes

11.2.2 Reports – Can be used to monitor:

- Enrollment
- Subject terminations
- Data Queries
- Out of window/overdue visits
- Protocol deviations
- Missing forms/visits
- Adverse Events

11.2.4 Central review of submitted data

11.2.5 Query system

- Performs inter-form data logic checks
- Identified problems are submitted to sites for resolution

11.2.6 Serious adverse event reporting system –

- Safety reports are reviewed periodically by the Medical Monitor

11.2.7 Regulatory document tracking system –

- Enables online uploading and storage of documents
- Reports track missing documents and pending renewals

12. STUDY PROCEDURES

12.1 Recruitment Procedures

12.1.1 Identification of Potential Subjects

Sites may, with approval by the local IRB, use the following techniques to identify potential subjects:

- Run a list of patients who have the ICD9 codes listed in the ICD9 Codes for Inclusion and Exclusion Criteria (Appendix IV) to compile a pool of potential subjects (see section 11.1.2 below).
- 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 patient fully meets the inclusion criteria, including age, language, and qualifying medical conditions, and does not have any of the exclusion criteria.

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 respond by either returning an enclosed response card or calling the Study Coordinator. The letter will include a statement that the clinic Study Coordinator will call the patient if the card is not returned within 10-14 days. 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.

12.1.2 Verification of Inclusion and Exclusion Criteria

A complete list of the study's inclusion/exclusion criteria is provided on the ICD9 Codes for Inclusion and Exclusion Criteria (Appendix IV). The list is critical for determining a patient's eligibility for the study. When screening a clinic patient's medical record to assess qualification for the study, it is imperative to determine that the patient fully meets all of the inclusion criteria for the study and that s/he does not meet any of the exclusion criteria.

Section A: Demographic Criteria includes age and language criteria, as well as a criterion for having been seen in the clinic within the preceding 24 months.

For Section B: Inclusion 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 24 months).

Section C: Exclusion criteria include: current signs of acute angina, stroke, heart failure or renal failure; systolic BP > 200 mm Hg or diastolic BP > 114 mm Hg at the most recent clinic visit or at the baseline visit; 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; no access or ability use a telephone; those who refuse to at least consider attempting to obtain internet access at home, library, community center or the clinic office; and an arm circumference that measures > 50 cm at the baseline visit or per medical record review. The hard copy Eligibility CRF should be completed based on medical record review prior to a patient's baseline study visit.

Patients who are found upon initial screening not to be eligible for the study should not be invited to join the study and should not be added to the study database.

12.1.2.1 Selection Bias

No qualifying patient should be excluded from the study due to gender, ethnicity, race, or economic status. Subjects younger than 55 years of age at the time of screening must be excluded from the study. There is no upper age limit for patients who have full cognitive functioning and can travel to the clinic.

12.1.3 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 Coordinator should also verify the following criteria:

1. The patient cannot be pregnant. Pregnant women cannot be enrolled in the study, and anyone who becomes pregnant must be terminated. No test will be required to confirm the absence of pregnancy.

2. The patient has some access to the internet or will 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 be required to actually access the internet to remain in the study.

12.2 Screening Log

Each patient that is screened for the study should be entered into your site's Excel **Screening Log**. A template for the screening log is provided in APPENDIX V. Before you begin screening patients, the CCC will send each site an electronic screening log to facilitate log completion.

Each patient who is screened for the study should be tracked on this log to record their qualification, willingness to participate and consent outcome.

RETAIN THE ELECTRONIC SCREENING LOG FOR THE DURATION OF THE STUDY. You will be asked to fax or securely email a *de-identified* copy of the log, i.e., one with the patient's name and MRN eliminated, to the CCC monthly.

Screening involves the following steps:

1) Identifying Patients Who Might Qualify for the Study

   - Review the patient's medical record and confirm that s/he is $\geq$ 55 years old, has been seen in the clinic within the previous 24 months, and is able to speak English. (Section A of APPENDIX IV: ICD9 codes for Inclusion and Exclusion Criteria)
   - Verify that the patient meets **at least** one inclusion criterion from Section B of APPENDIX IV: ICD9 codes for Inclusion and Exclusion Criteria. Documentation 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.
   - Review the patient's medical record over the preceding 24 months to determine whether s/he has a history of any of the exclusion criteria in Section C of APPENDIX IV: ICD9 codes for Inclusion and Exclusion Criteria.
   - If a patient has one or more of the inclusion criteria and none of the exclusion criteria, the patient is eligible for further screening; if not, the patient is not eligible.

2) Fill in one line of the electronic screening log for each patient whose medical record is reviewed:

   Column A. Write in the patient's name for easy reference.

   Column B. Write in the patient's medical record number, if desired, for easy reference.

   Column C. N/A

   Column D. Write in the date on which the patient's record was screened.

Column E: Write in the patients age (not birthdate) at the time of screening

Column F. Type in a 1 either after M (if male) or after F (if female).

Column G. Type in a 1 after Cau (Caucasian) or after Min (Minority) to designate the patient's racial/ethnic category. Persons with a mixed heritage should always be consider Minority.

Column H. Type in a 1 afterYes or after No to designate whether the patient has been seen in the clinic in the previous 24 months. If No, then STOP. This patient cannot be in the study.

Column I. Type in a 1 afterYes or after No to designate whether the patient speaks English. If No, then STOP. If No, then STOP. This patient cannot be in the study.

Column J. Type in a 1 afterYes or after to designate whether the patient has at least one of the inclusion from Section B of APPENDIX IV: ICD9 codes for Inclusion and Exclusion Criteria. If No, then STOP. This patient cannot be in the study.

Column K. Type in a 1 after YES if the patient does NOT meet any exclusion criteria. (Careful, this is a double negative.) If the patient does meet one or more of the exclusion criteria, Type in a 1 after NO and STOP. This patient cannot be in the study.

Column L. If you typed in a 1 after YES for ALL of Columns G-J, type in a 1 after YES in Column K and continue with Column L.

If you checked NO for ONE OR MORE of Columns G-J, then check NO in Column K. The patient cannot participate in the study. The remainder of the line should not be completed.

Column M. Fill in the date on which you mailed the patient an invitation letter OR contacted the patient by phone or in the clinic.

Columns N-P. Fill in the dates of any follow-up phone calls to the patient.

Column Q. Type in a 1 after Yes if you were not able to contact the patient and STOP; do not complete the remainder of the line. Otherwise, type in a 1 after No and continue to Column Q

Column R. Type in a 1 after Yes if you identified an exclusion contact either over the phone or at the initial visit and STOP; do not complete the remainder of the line.
Otherwise, type in a 1 after No and continue to Column R

Column S. Type in a 1 after No, if the patient declined to sign consent and STOP; do not complete the remainder of the line. Otherwise, type in a 1 after Yes if the patient did sign consent and continue to Column S.

Column T. Check Yes if the patient signed consent.

Column T. Check Yes if the patient was fully enrolled into the study.

12.3 Baseline Visit Procedures

12.3.1 Eligibility Verification

At the baseline visit, the Study Coordinator should again verify with female patients that they aren't pregnant and with all patients that they are willing to consider accessing the internet to use IowaPHRM. Pregnant patients and patients who will not even consider using IowaPHRM should not sign consent.

12.3.2 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 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 should only sign consent on the day that baseline visit procedures are conducted. Patient should NOT sign consent and then com e in at a later date for completion of baseline activities.

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 on the same date that the subject signs 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. The original signed consent will be placed in the subject's study folder.

12.3.3 eCRF #2 Eligibility

Following consent, the Study Coordinator should take the hard copy eCRF #2 Eligibility and verify both inclusion criteria and exclusion criteria with the subject.

12.3.4 Subject Surveys

The study coordinator will ask the questions on the following baseline forms:

- eCRF #3 Patient Contact Information (intervention subjects only)
- eCRF #4 Demographics
- eCRF #5 Diagnosed Conditions-Care Management Patient Report
- eCRF 7# Medication Reconciliation
- eCRF #8 Medication Adherence
- eCRF #9 Behavioral History
- eCRF #10 Health Behavior Inventory
- eCRF #12 Cancer Screening
- eCRF #15 Stages of Change

Next continue with measuring research blood pressures. (See Section 11.3.5 below.)

12.3.5 eCRF #11 Blood Pressure

Study Coordinators will measure research pulse and blood pressures using the following procedures (at the baseline visit and again at the 12 month visit) with the Omron HEM907XL automated blood pressure device.

- Document all required measurements on eCRF #11 Blood

Pressure Prepare the Subject

The subject ideally should refrain from smoking or ingesting caffeine for 20 minutes prior to the blood pressure measurement. BP measurement should be delayed until 20 minutes after the most recent cigarette, if at all possible.

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
- the palm of the hand facing upward

Have the subject sit quietly 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 Recommended cuff sizes are:

- Arm circumference 17-22 cm: use "small adult" cuff
- Arm circumference 22-32 cm: use "adult" cuff
- Arm circumference 32-42 cm: use "large adult" cuff
- Arm circumference 42-50 cm: use "extra large adult" cuff

Subjects whose arm circumference exceeds 50 cm at the baseline study visit would require use of a thigh cuff and cannot continue in the study. However, should a subject gain weight between the baseline and 12 month visits and measure > 50 cm at the 12 month visit, a thigh cuff should be used for the 12 month readings.

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 eCRF #11 Blood Pressure and the Omron monitor beside you on the desk.

Tell the patient that you will be taking at least 3 blood pressure readings and that neither the patient nor the study coordinator should talk during the measurements.

Push the ON/OFF button on the monitor to turn on the power.

Take a single BP reading

- Set the MODE selector to "SINGLE."
- Set the P-Set knob to "AUTO."
- Push the START button.
- Record the displayed pulse reading on line 7 of eCRF #11 Blood Pressure.
- Record the displayed blood pressure on line 8 of eCRF #11 Blood Pressure.

Wait 60 seconds before taking the next blood pressure.

Second and third readings

- Set the MODE selector to AVG.
- Push the START button.
- The machine take TWO sequential BP readings, automatically counting down from 60 seconds between the two readings. The value obtained for each measurement will be displayed immediately after each measurement. Be especially careful to observe the monitor while waiting for the second reading. It is displayed for a very short period of time and is quickly followed by a display for the average of these two readings.
- Record the first of these double readings on line 9 and the second of these double readings on line 10 of eCRF #11 Blood Pressure.

If either the systolic or diastolic readings of the second and third (double) BPs differ by > 4 mm:

- Set the MODE selector to "SINGLE." Wait 60 seconds.
- Push the START button.
- Record the displayed fourth reading on line 11 of eCRF #11 Blood Pressure.

Take one standing pulse and BP reading

Have the patient **stand for one minute** and then repeat the Omron measurement procedure using the single setting.:

- Take another pulse, recording it on line 12 of eCRF #11 Blood Pressure.
- Take another **single BP reading** according to the instructions, above, and record on line 13 of eCRF #11 Blood Pressure.

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

12.3.6 eCRF#13 Laboratory or eCRF #14 Laboratory for Baseline Intervention

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

- Lipid panel
- HgA1c
- 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.

If a subject has a history of triglyceride levels that exceed 400, precluding calculation of an LDL, a direct LDL test should be requested.

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.

Lab results should be documented on eCRF#13 Laboratory (control subjects only at the baseline visit) or eCRF #14 Laboratory for Baseline Intervention (intervention subjects only at the baseline visit).

12.3.7 Instruction on IowaPHRM

The study coordinator will orient consented subjects to 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 such as wallet-sized cards to facilitate communication with health professionals and provides information for medications patients enter. IowaPHRM will allow the subject to enter home blood pressure and blood sugar test results. Each subject will be given a brochure about the online system and a sheet with initial login information for the system. Subjects will not be required to access IowaPHRM at any point during the study. However, it is important to ensure that subjects fully understand how to access the system.

12.3.8 Medical Record Abstraction and Verification

After completing the baseline study visit, the study coordinator should abstract the following data from the subject's medical record to complete the forms listed below. Data created as part of the baseline visit (blood pressure measurements, laboratory values) should be included.

- eCRF #6 Diagnosed Conditions and Care Management (Medical Record)
- eCRF #7 Medication Reconciliation
- eCRF #12 Cancer Screening
- eCRF #8 Medication Adherence
- eCRF #9 Behavioral History

12.3.9 Data Entry

Data should be entered into the MEDFOCUS database as soon as possible after the visit is completed. The preliminary step is to complete a hard copy for eCRF #1 Eligibility:

Initiate an electronic record for each new, qualifying subject. Log into the database and click on the link for "Enter New Subject." The link will take you to the Eligibility form.

- Enter the information from the hard copy Eligibility CRF and submit the electronic form
- The database will give you a subject ID for the subject. Place the Subject ID on every page of all the hard copy CRFs
- The database will also give you access to a link for each of the electronic case report forms (eCRFs). Click on each eCRF in order to enter data into that form

12.4 eCRF #16 4 & 8 Month Data Collection (CVRS intervention sites only)

At 4 months after the baseline visit and again at 8 months after the baseline visit, the Study Coordinator will abstract medical record data to complete eCRF #16 4 & 8 Month Data Collection. However, if the clinic gives the CVRS pharmacists access to an intervention clinic EMR, then eCRF #16 4 & 8 Month Data Collection will not need to be completed. Each intervention site Study Coordinator will be informed by the CCC about the status of EMR access and the need to complete this form.

The purpose of the CRF is to give the CVRS pharmacists updated patient status information. Timely abstraction and uploading of the CRF, therefore, is important for the clinical decision making of the CVRS pharmacists'.

12.4.1 4 months following the enrollment visit

- Abstraction and uploading of data to the study database may occur as soon as 4 months after the enrollment date and as late as 4 months and 2 weeks after the enrollment date.
- Data should be reviewed beginning with the date of the baseline visit and extending through the date that is exactly 4 calendar months following the enrollment date. Data for each element of the form should be taken from the most recent occurrence of the field in the medical record.

12.4.2 8 months following the enrollment visit

- Abstraction and uploading of data to the study database may occur as soon as 8 months after the enrollment date and as late as 8 months and 2 weeks after the enrollment date.
- Data should be reviewed beginning with the date of the 4 month data abstraction time point and the date that is exactly 8 calendar months following the enrollment date. Data for each element of the form should be taken from the most recent occurrence of the field in the medical record.

12.4.3 Specific data to be abstracted for the 4 and 8 month time points:

12.4.3.1 Laboratory tests when warranted based on diagnosed conditions

- Diabetes: HgA1c
- Atrial Fibrillation: INR
- Hyperlipidemia: Total Cholesterol, LDL Cholesterol, HDL Cholesterol and Triglycerides

12.4.3.2 Clinic blood pressure

- Use the most recent clinical blood pressure that is documented during the abstraction period
- If more than one BP is documented at a visit, select the lowest reading

12.4.3.3 Events

Record by date every hospitalization and/or emergency room visit and the reason for each of these events; record whether a new diagnosis was associated with each event and, if so, the name of the new diagnosis that was identified.

12.4.3.4 Other New Diagnoses

Other new diagnoses not linked directly to a hospitalization or emergency room visit that were documented during the abstraction window

12.5 12 Month Visit Procedures

12.5.1 Visit scheduling

Call the subject 6-8 weeks in advance of the 12 month anniversary date to schedule the 12 month follow-up visit.

The visit should be scheduled no earlier than one month before 11 calendar months after the baseline visit and no later than 13 calendar months after the baseline visit.

Phone the subject 1-2 days before the visit to remind him/her of the scheduled date and time.

If a subject fails to make the 12 month study visit, medical record abstraction should still be conducted for the forms listed under 12.5.5.

12.5.2 Surveys

The study coordinator will ask the questions on the following forms:

- eCRF #5 Diagnosed Conditions and Care Management Patient Report
- eCRF #7 Medication Reconciliation
- eCRF #8 Medication Adherence
- eCRF #12 Cancer Screening
- eCRF #15 Stages of Change

12.5.3 eCRF #11 Blood Pressure

The study coordinator will measure pulse and blood pressures as specified for the baseline visit, with the exceptions bulleted below. Arm circumference MUST be re-measured at the 12 month visit to ensure use of the best-fitting cuff.

- The Study Coordinator should use the same arm that was used at baseline unless there is a medical reason for not using the same arm (e.g., mastectomy since the baseline visit)
- If a subject had an arm circumference $\leq$ 50 cm at baseline but has gained weight such that his/her arm circumference now exceeds 50 cm, the Study Coordinator may use a thigh cuff and a regular clinic sphygmomanometer to obtain the required BP measurements.

12.5.4 eCRF #13 Laboratory

The study coordinator will draw or arrange for usual laboratory draw of ***fasting*** bloodwork for the following tests, with billing handled as previously designated:

- Lipid panel
- HgA1c

If a subject has a history of triglyceride levels that exceed 400, precluding calculation of an LDL, a direct LDL test should also be requested.

12.5.5 Medical Record Abstraction and Verification at 12 months

After the 12 month visit, the study coordinator should obtain data for the forms listed below from the subject's medical record. Data should span the period that begins the day after the baseline visit and runs through the day of the 12 month visit. Data created as part of the 12 month visit (blood pressure measurements, laboratory values) should be included.

If a subject fails to make the 12 month study visit, collect data from the day after the baseline visit through the day *anticipated for* the 12 month visit.

- eCRF #6 Diagnosed Conditions and Care Management (Medical Record)
- eCRF #7 Medication Reconciliation
- eCRF #8 Medication Adherence
- eCRF #12 Cancer Screening
- eCRF #17 Clinic Visit Tracking
- eCRF #18 SAE Screening
    - eCRF #19 Serious Adverse Event (only if an event is identified)

12.6 24 Month Medical Record Abstraction

No visit or contact will be make with subjects at this final time point.

Data should be collected for all case report forms listed below using one of the following schedules:

- If a subject completes the 12 month study visit, data should be collected from the period that begins the day after the 12 month study visit and spans through 13 months after that date
    - Record the most recent data documented after the subject's 12 month visit and prior to this date
- If a subject fails to complete the 12 month study visit, data should be collected at 25 months after the baseline study visit
    - Record the most recent data documented after the medical record review that was conducted at the 12 month time point and prior to this date

The following forms will require completion:

- eCRF #6 Diagnosed Conditions and Care Management (Medical Record)
- eCRF #17 Clinic Visit Tracking
- eCRF #20 24 Month BP, Lab and Medication form
- eCRF #18 SAE Screening
    - eCRF #19 Serious Adverse Event (only if an event is identified)

Abstracted data must be uploaded to the study database by 25 months + 2 weeks following the enrollment date.

12.7 CVRS Intervention

The CVRS clinical pharmacist will undertake the following activities with subjects and participating site clinical pharmacists in the 10 intervention offices. The CVRS intervention will last 12 months with each enrolled intervention site subject.

A schematic of the CVRS pharmacist intervention is presented in Appendix VI and summarized below:

- Communicate with subjects using email, telephone, text messages or IowaPHRM every two weeks x 2 months then at least monthly 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 on-site clinical pharmacist every 3 months or more frequently if urgent issues are identified

The on-site clinical pharmacist will communicate with the subject's primary care provider as needed to share relayed information and/or obtain approval for proposed changes to the medical regimen.

12.8 Safety Monitoring

12.8.1 Site Monitoring Roes

Sites will screen for and report all serious adverse events (SAEs). Scheduled 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 study visit.
- 24 month medical record review: The Study Coordinator will review the medical record for SAEs that occurred since the 12 month study visit

At both time points, the Study Coordinator will screen for evidence of adverse events and report screening outcomes on the **Serious Adverse Event Screening** form. The first step is to search for events that had one or more of the following attributes:

Event Attributes

- Subject death
- Hospitalization
- Life-threatening
- 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

If such an event is identified, determine if the event involved one or more of the following medical conditions:

Medical Conditions

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

If an event does not exhibit at least one of the listed attributes and one of the listed medical conditions, the event does not constitute a reportable event for the purposes of study data collection and monitoring. (However, the event might be reportable per your local IRB regulations; see 12.8.1.1 below.) The Study Coordinator should submit the **Serious Adverse Event Screening** eCRF through the MEDFOCUS database and file the hard copy CRF in the subject's study file.

If an event is identified that does meet the listed attributes and conditions, the Study Coordinator should submit the **Serious Adverse Event Screening** form through the

MEDFOCUS database AND also complete and submit a **Serious Adverse Event** form for each unique event. File all screening and reporting documents in the subject's study file.

Should a Study Coordinator or other member of the local research team become aware of a reportable SAE at any time not related to a routine screening, the Study Coordinator should also complete a hard copy **Serious Adverse Event** CRF and upload the **Serious Adverse Event** eCRF through the study database in a timely fashion. All hard copy Serious Adverse Event forms should be stored in the subject's study file.

12.8.1.1 Reporting Events to the Local IRB

The Study Coordinator of Site Physician Investigator should notify the local IRB of any events that meet the local IRB's reporting threshold, whether or not it meets the threshold for reporting to the MEDFOCUS study database. Local IRBs will review all UPs and 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. The Study Coordinator should provide the CCC with the notification they receive from a local IRB regarding its decision related to a reported event.

12.8.2 Data Coordinating Center Roles

The DCC receives submitted **Serious Adverse Event** eCRFs from the Site Study Coordinator and forwards them to the Physician Monitors for review.

The DCC also provides safety reports to the Data and Safety Monitoring Board (DSMB), and transmits any safety concerns to the DSMB that have been identified by the Physician Monitors. (See 11.7.4)

The DCC performs on-site monitoring visits to each participating site after the first 5 subjects have been enrolled and once all data have been collected and queries have been resolvedThe purpose of the visits is to evaluate the accuracy of data and will include a check for unreported SAEs.

12.8.3 Physician Monitor Roles

The Physician Monitor for the study 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 reviews of cumulative 12 month and 24 month SAE data to assess for concerning trends in the occurrence of events, and the possible relationship of those trends to the trial.
- Review any reports of SAEs that meet the NHLBI criteria for reporting to that agency (i.e. suggests greater risk of harm to study participants than was previously known or recognized).

12.8.4 Data and Safety Monitoring Board (DSMB) Monitoring Roles

12.8.4.1 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. Dr.
- 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.

12.8.4.2 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 safety data provided by the CCC:

- Quarterly reports on progress with subject enrollment
- Bi-annual reports for DSMB meetings
- Individual concerns identified by the Physician Monitors.

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 DCC chair 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 site IRBs, and to the University of Iowa IRB for the annual continuing review.

12.8.5 Clinical Coordinating Center Monitoring Roles

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

Should the Physician Monitor request additional information about a reported event, the CCC will forward the request to the Study Coordinator and facilitate transmission of de-identified information back to the Physician Monitor.

12.9 eCRF #22 Study Termination

12.9.1 Early Termination

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

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

A subject's failure to complete the 12 month study visit is not sufficient reason to terminte the subject early. As long as the subject does not withdraw consent, medical record abstraction should still be completed at 12 and 24 months

If a subject is terminated early, the site Study Coordinator should complete eCRF #22 Study Termination and upload it to the study database. Early termination indicates that the site will no longer need to follow the subject.

12.9.2 End of Study Termination

Study Coordinators will also complete a Study Termination form for each subject following completion of the 24 month medical record abstraction.

Please note that a subject who does not complete the 12 month visit and who does not withdraw consent should still have medical record data abstracted at both 12 and 24 months. Survey questions that cannot be administered at 12 months will be treated as missing data.

13 PROCEDURES FOR SITE PROVIDERS

13.1 Provider Surveys

The provider survey portion of the MEDFOCUS study has been approved and will be overseen by the University of Iowa IRB. Sites should not request permission from their local IRBs to distribute these surveys.

Staff members from the Iowa research team will create sets of surveys and invite clinic providers to complete those surveys. A survey packet will be created by Iowa researchers for each individual provider. Personalized survey packets will include a letter detailing the elements of consent that has been approved by the University of Iowa IRB and coded surveys. The survey packets will be mailed to the site Study Coordinator, who should distribute them either in mailboxes or at a staff meeting. Surveys will be distributed prior to the start of enrollment.

Signed consent will not be required; return of the surveys will constitute consent. Providers who choose to participate should return the completed surveys to the Study Coordinator sealed in the envelope provided within two weeks. Those who choose not to participate should write "Declined" on the front page of each survey and return them to the Study Coordinator.

The Study Coordinator will return the surveys to Iowa. Members of the Iowa research team will email providers who do not respond up to two times to re-request their participation.

The following surveys will be distributed to providers.

<u>Site Physician Leader only</u>:

- Medical Home Index

All Site Primary Care Providers, including the Site Physician Leader and Site Clinical Pharmacist(s):

- Managing Cardiovascular Disease States (provider version or pharmacist version)
- Collaboration Survey (provider version or pharmacist version)

Site Clinical Pharmacists and Primary Care Providers will be invited to take the same survey at the end of the study. Providers will not be compensated for completing the study surveys.

13.2 Referring Patients to the Study

All clinic providers are encouraged to refer patients who might qualify for the study to the clinic's Study Coordinator. The Study Coordinator will review records for each patient a provider refers to make sure that the patient meets the study's eligibility criteria.

13.3 Provider Interaction with the CVRS Pharmacist (Intervention sites only)

The PHCVRS pharmacist will develop an action plan that addresses gaps in guideline-recommend therapy to decrease risk of CVD and also preventive health screening. The pharmacist will communicate recommended treatment changes to the site clinical pharmacist via fax on a standardized form. The site clinical pharmacist should collaborate as needed with the subject's primary care provider, decide whether to implement the recommendation, modify the recommendation or decline the recommendation. The site clinical pharmacist should indicate the selected course of action on the faxed form and then return it via fax as soon as possible to the CVRS pharmacist. The site clinical pharmacist should then follow through with implementation whenever that course is chosen.

14. HUMAN SUBJECTS PROTECTIONS

14.1 Subject confidentiality

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 will not be visible to members of the DCC staff.

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.

Paper and 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.

14.2 Participant Education

Before starting the study, the Local Site Investigator will review the study protocol with providers in participating clinics. Provider 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.

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

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

14.4 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 thee quarterly invoicing process.

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APPENDICES

APPENDIX I: PARTICIPATING SITES

Clinic Name	City/State
Northeast Iowa Family Practice	Waterloo, IA
Siouxland Family Medicine Center	Sioux City, IA
Pocatello Family Medicine (Idaho State)	Pocatello, ID
Center for Community and Family Medicine (Texas Tech)	Amarillo, TX
Genesis Family Medical Center	Davenport, IA
Sugar House Health Center (University of Utah)	Salt Lake City, UT
Wingra Family Medical Center	Madison, WI
Northeast Family Medical Center (University of Wisconsin)	Madison, WI
Scripps Ranch Family Medicine (UCSD)	San Diego, CA
4th and Lewis Family Medicine (UCSD)	San Diego, CA
General Internal Medicine Clinic (UNC)	Chapel Hill, NC
Family Medicine Clinic (USF)	Tampa, FL
Wheaton Franciscan Medical Group Wisconsin Ave	Racine, WI
Physicians at Sugar Creek (Memorial Hermann)	Sugar Land, TX
Family Health Center (UTHSCA)	San Antonio, TX
Family Medicine at Main (University of Florida)	Gainesville, FL
Jefferson Family Medicine Center (SUNY Buffalo)	Buffalo, NY
Advocate Medical Group (Midwestern University)	Chicago, IL
Medicine Group Practice (Temple University)	Philadelphia, PA
Milwaukee Health Services, Inc. (MHSI)	Milwaukee, WI

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						
Medical record audits – passive observation group					**400 enrolled**	
Cost effectiveness analysis						
Study close out						
Manuscripts, reports and Dissemination of the findings						

APPENDIX III

GUIDELINE ADVANTAGE REPORTING MEASURE SET

THE GUIDELINE ADVANTAGE REPORTING MEASURE SET

The Guideline Advantage Reporting Measure Set consists of measures included in Universal Data System (UDS) from the Health Resources and Services Administration's (HRSA) Health Center Program and the Million Hearts™ initiative created by the Department of Health and Human Services. Both of these programs utilize measures from the Physician Quality Reporting System (PQRS) and will be calculated with strict adherence to those definitions.

HYPERTENSION

Hypertension: Controlling High Blood Pressure: Percentage of patients aged 18 through 85 years of age who had a diagnosis of hypertension and whose blood pressure was adequately controlled (<140/90 mmHG). (NQF 0018/PQRS #236, Million Hearts & UDS)

ISCHEMIC VASCULAR DISEASE

Ischemic Vascular Disease (IVD): Use of Aspirin or Another Antithrombotic: Percentage of patients aged 18 years and older with ischemic vascular disease with documented use of aspirin or other antithrombotic. (NQF 0068/PQRS #204, Million Hearts & UDS)

Ischemic Vascular Disease (IVD): Complete Lipid Panel and Low Density Lipoprotein (LDL-C) Control: Percentage of patients aged 18 years and older with ischemic vascular disease who received at least one lipid profile within 12 months and whose most recent LDL-C level in control (less than 100 mg/dL). (NQF 0075/PQRS #241, Million Hearts)

CORONARY ARTERY DISEASE

Coronary Artery Disease (CAD): Drug Therapy for Lowering LDL-Cholesterol: Percentage of patients aged 18 years and older with a diagnosis of CAD who were prescribed a lipid-lowering therapy (based on current ACC/AHA guidelines). (NQF 0074/PQRS #197, UDS)

CANCER

Screening Mammography: Percentage of women aged 40 through 69 years who had a mammogram to screen for breast cancer within 24 months. (NQF 0031/PQRS #112)

Colorectal Cancer Screening: Percentage of patients aged 50 through 75 years who received the appropriate colorectal cancer screening. (NQF 0034/PQRS #113, UDS)

Cervical Cancer Screening: Percentage of women aged 21 through 63 years who received one or more Pap tests to screen for cervical cancer. (NQF 0032/PQRS #309, UDS)

DIABETES MELLITUS

Hemoglobin A1c Poor Control in Diabetes Mellitus: Percentage of patients aged 18 through 75 years with diabetes mellitus who had most recent hemoglobin A1c greater than 9.0%. (NQF 0059/PQRS #1, UDS)

Diabetes Mellitus: Hemoglobin A1c Control (<8%): The percentage of patients 18 through 75 years of age with a diagnosis of diabetes (type 1 or type 2) who had HbA1c < 8%. (NQF 0575/PQRS #313, UDS)

Low-Density Lipoprotein (LDL-C) Control in Diabetes Mellitus: Percentage of patients aged 18 through 75 years with diabetes mellitus who had most recent LDL-C level in control (less than 100 mg/dL). (NQF 0064/PQRS #2, Million Hearts)

ASTHMA

Asthma: Pharmacological Therapy: Percentage of patients aged 5 through 50 years with a diagnosis of mild, moderate or severe persistent asthma who were prescribed either the preferred long-term control medication (inhaled corticosteroid) or an acceptable alternative treatment. **The Guideline Advantage only reports on patients 18 years and older.* (NQF 0047/PQRS #53, UDS)

PREVENTIVE CARE AND SCREENING FOR CHRONIC DISEASES AND STROKE

Body Mass Index (BMI) Screening and Follow-Up: Percentage of patients aged 18 years and older with a calculated BMI in the past six months or during the current visit documented in the medical record AND if the most recent BMI is outside of normal parameters, a follow-up plan is documented. (NQF 0421/PQRS #128, UDS)

Tobacco Use: Screening and Cessation Intervention: Percentage of patients aged 18 years or older who were screened for tobacco use one or more times within 24 months AND who received cessation counseling intervention if identified as a tobacco user. (NQF 0028/PQRS #226, Million Hearts & UDS)

Cholesterol – Fasting Low Density Lipoprotein (LDL) Test Performed AND Risk-Stratified Fasting LDL: Percentage of patients aged 20 through 79 years whose risk factors have been assessed and a fasting LDL test performed and whose risk-stratified fasting LDL is at or below the recommended LDL goal. (PQRS #316, Million Hearts)

Screening for High Blood Pressure: Percentage of patients aged 18 and older who are screened for high blood pressure. (PQRS #317, Million Hearts)

APPENDIX IV: ICD9 CODES FOR INCLUSION AND EXCLUSION CRITERIA

Section A: Demographic Criteria	**ICD9 Codes**	**Has Inclusion Criterion***	
English speaking males or females	N/A	Yes	No
≥55 years of age	N/A	Yes	No
Has been seen in the clinic within the previous 24 months	N/A	Yes	No
If the answer to all demographic questions is Yes, then proceed to Section A. If not, STOP. The patient cannot participate.			
Section B: Has a history of:	**ICD9 Codes**	**Has Inclusion Criterion***	
Coronary artery disease (CAD)	414	Yes	No
Previous MI (heart attack)	410, 411, 412	Yes	No
Stroke	430, 431, 432, 433, and 434	Yes	No
TIA	435	Yes	No
Atrial fibrillation	427.31,427.3	Yes	No
Systolic heart failure	428.20. 428.21, 428.22, 428.23, 428.40, 428.41, 428.42, 428.43	Yes	No
Peripheral vascular disease/claudication	440.2, 440.3, and 440.4	Yes	No
Carotid artery disease	433.1	Yes	No
Diabetes *with either:* • Hyperlipidemia (ICD9 272) with most recent LDL >110mg/dl Most recent LDL value from chart _____mg/dl Date: _ _ / _ _ / _ _ _ _ ***AND/OR*** • Hypertension (ICD 401, 402, 403, 404, 405) with the most recent systolic blood pressure ≥ 140 mm Hg OR the most recent diastolic blood pressure ≥ 90mmHg Most recent BP from the chart: ____ / ____ (SBP/DBP) Date: _ _ / _ _ / _ _ _ _	250	Yes	No
******Must have at least one risk factor from Section B. If so, proceed to Section C and check for Exclusion Criteria ****** ***If not, STOP. The patient cannot participate.***			

Section C: Exclusion Criteria	**Source or ICD9 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 > 114 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	V22, V23, V24 or self-report	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
If the answer to one or more questions in Section B is YES, STOP. The patient cannot participate in the study.			
****** 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 V: SAMPLE SCREENING LOG

Screening Log
[SITE NAME]

CID: [##]

DELETE THESE COLUMNS & SAVE FILE UNDER A DIFFERENT NAME BEFORE EMAILING FILE TO THE CCC!																															
Column A Patient Name	Column B Medical Record Number	Patient Screen #	Column D Screen Date	Column E Age	Column F Gender								Column G Race/Ethnicity								Column H Seen in Clinic Last 24 Mos, Current Patient								Column I Speaks English								Column J Meets At Least One Inclusion Criterion							
		1			M		F						Cau		Min						Yes		No						Yes		No					
		2			M		F						Cau		Min						Yes		No						Yes		No					
		3			M		F						Cau		Min						Yes		No						Yes		No					
		4			M		F						Cau		Min						Yes		No						Yes		No					
		5			M		F						Cau		Min						Yes		No						Yes		No					
		6			M		F						Cau		Min						Yes		No						Yes		No					
		7			M		F						Cau		Min						Yes		No						Yes		No					
		8			M		F						Cau		Min						Yes		No						Yes		No					
		9			M		F						Cau		Min						Yes		No						Yes		No					
		10			M		F						Cau		Min						Yes		No						Yes		No					

Screening Log
[SITE NAME]

CID: [##]

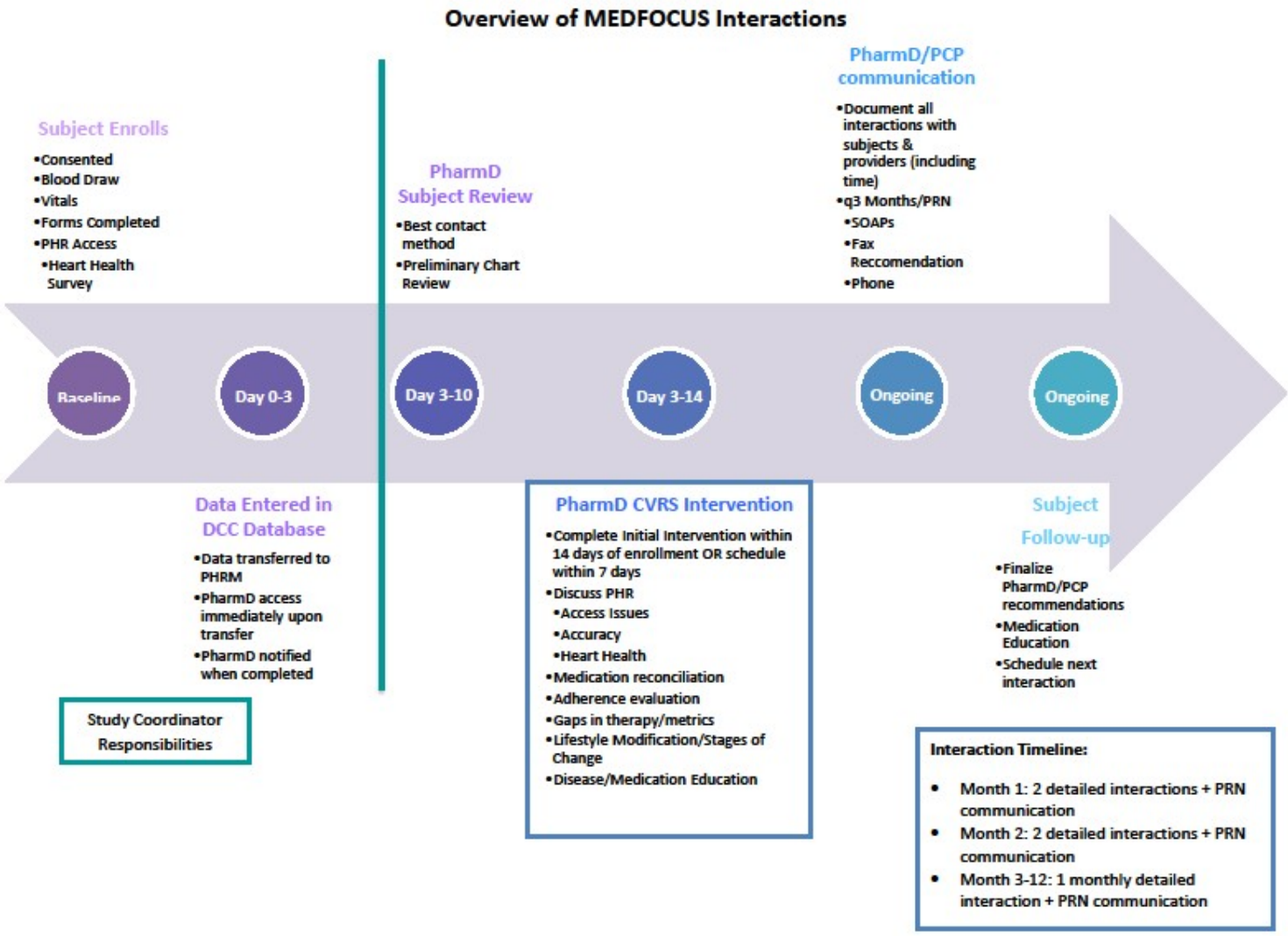
Patient Screen #	Column K Does NOT Meet ANY Exclusion Criteria				Column L QUALIFIES for Study				Communication Attempts via Mail, Phone or Clinic Visit								Outcomes							
									Column M Date Letter Mailed or Contacted in Clinic	Column N Date Phone 1	Column O Date Phone 2	Column P Date Phone 3	Column Q Unable to Contact or Schedule Visit				Column R Exclusion Criterion Identified on Contact				Column S Signed Informed Consent			
1	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
2	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
3	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
4	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
5	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
6	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
7	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
8	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
9	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	
10	Yes		No		Yes		No						Yes		No		Yes		No		Yes		No	

Screening Log
[SITE NAME]

CID: [##]

Patient Screen #	Column T Fully Enrolled into Study				HOLD for Possible Passive Arm
1	Yes		No		
2	Yes		No		
3	Yes		No		
4	Yes		No		
5	Yes		No		
6	Yes		No		
7	Yes		No		
8	Yes		No		
9	Yes		No		
10	Yes		No		

APPENDIX VI: INTERVENTION SUMMARY



APPENDIX VII: CASE REPORT FORMS

Each current hard copy case report form will be posted on the website with a detailed set of instructions for how to complete each item on the individual form. The posted form instructions should always be referenced when completing a given form.

The website will also include a link to a specific visit packet that includes all forms for each time period:

- For intervention sites only: At 4 months and 8 months after a subject's enrollment, click on the link to the packet for that data abstraction time point and print off the form.
- Prior to a subject's arrival for the baseline and 12 month study visit, click on the link to the visit packet for that visit and print off the forms.
- When you are ready complete medical record abstraction at the 24 month time point, click on the link for that time point and print off the forms.

APPENDIX VII

DRUG CODE LIST

Code	Generic Name	Brand Names
2101	acarbose	Precose
201	acebutolol	Sectral
1101	aliskiren	Tekturna
1102	aliskiren-hydrochlorothiazide	Tekturna HCT
1103	aliskiren-valsartan	Valturna
101	amiloride	Midamor
102	amiloride/hydrochlorothiazide	Moduretic
401	amlodipine	Norvasc
410	amlodipine/benazepril	Lotrel
422	amlodipine/olmesartan	AZOR
423	amlodipine/olmesartan/hydrochlorothiazide	Tribenzor
420	amlodipine/valsartan	Exforge
421	amlodipine / valsartan / hydrochlorothiazide	Exforge HCT
5202	apixaban	Eliquis
2001	aspart	Novolog
2002	aspart protamine	Novolog Mix
5401	aspirin	Ecotrin, Bufferin, Aspergum
202	atenolol	Tenormin
213	atenolol-chlorthalidone	Tenoretic
4001	atorvastatin	Lipitor
4301	atorvastatin/amlodipine	Caduet
615	azilsartan medoxomil	Edarbi
301	benazepril	Lotensin
311	benazepril-hydrochlorothiazide	Lotensin HCT
203	betaxolol	Kerlone
204	bisoprolol	Zebeta
214	bisoprolol-hydrochlorothiazide	Ziac
103	bumetanide	Bumex
3401	canagliflozin	Invokana
601	candesartan	Atacand
608	candesartan-hydrochlorothiazide	Atacand HCT
302	captopril	Capoten
312	captopril-hydrochlorothiazide	Capozide
220	carvedilol	Coreg
222	carvedilol extended release	Coreg CR
104	chlorothiazide	Diuril
3101	chlorpropamide	Diabinese
105	chlorthalidone	Hygroton and others
4802	cholesteramine light	Questran Light, Prevalite
4801	cholestyramine	Questran

Code	Generic Name	Brand Names
701	clonidine	Catapres
702	clonidine topical patch	Catapres TTS
707	clonidine-chlorthalidone	Clorpres
5101	clopidogrel	Plavix
4804	colesevelam	WelChol
4803	colestipol	Colestid
5301	dabigatran	Pradaxa
5003	daltaperin	Fragmin
3402	dapagliflozin	Farxiga
2003	detemir	Levemir
402	diltiazem	Cardizem, Dilacor, Tiazac
501	doxazosin	Cardura
303	enalapril	Vasotec
411	enalapril/felodipine	Lexxel
313	enalapril-hydrochlorothiazide	Vaseretic
5002	enoxaparin	Lovenox
1001	eplerenone	Inspra
602	eprosartan	Teveten
609	eprosartan-hydrochlorothiazide	Teveten-HCT
115	ethacrynic acid	Edecrin
3001	exanatide	Byetta
4601	exetimibe	Zetia
403	felodipine	Plendil
4902	fenofibrate	Lipofen, Lofibra, Tricor, Triglide
4903	fenofibrate - micronized	Lofibra, Antara
4003	fluvastatin, fluvastatin XL	Lescol, Lescol XL
304	fosinopril	Monopril
314	fosinopril-hydrochlorothiazide	Monopril-HCT
106	furosemide	Lasix
4901	gemfibrozil	Lopid
2004	glargine	Lantus
3102	glimeperide	Amaryl
3301	glimepiride/pioglitazone	Duetact
3302	glimepiride/rosiglitazone	Avandaryl
3103	glipizide	Glucotrol
3104	glipizide XR	Glucotrol XR
3201	glipizide/metformin	Metaglip
2005	glulisine	Apidra
3105	glyburide	Diabeta, Micronase
3106	glyburide – micronized	Glynase

Code	Generic Name	Brand Names
3202	glyburide/metformin	Glucovance
703	guanabenz	Wytensin
704	guanfacine	Tenex
901	hydralazine	Apresoline
905	hydralazine-hydrochlorothiazide	Apresazide and Hydra-Zide
107	hydrochlorothiazide	Hydrodiuril & others
109	indapamide	Lozol
603	irbesartan	Avapro
610	irbesartan-hydrochlorothiazide	Avalide
2008	isophane	Humulin N, Novolin N
902	isosorbide dinitrate	Isordil
906	isosorbide dinitrate-hydralazine	BiDil
903	isosorbide mononitrate	Imdur
404	isradipine	DynaCirc
221	labetalol	Normodyne, Trandate
2404	linagliptin	Tradjenta
2503	linagliptin-metformin	Jentadueto
3002	liraglutide	Victoza
305	lisinopril	Zestril, Prinivil
315	lisinopril-hydrochlorothiazide	Prinzide, Zestoretic
2006	lispro	Humalog
2007	lispro protamine	Humalog Mix
604	losartan	Cozaar
611	losartan-hydrochlorothiazide	Hyzaar
4004	lovastatin, lovastatin XR	Mevacor, Altoprev
4101	lovastatin/niacin	Advicor
2301	metformin	Glucophage, Fortamet, Appformin, Glumetza
2701	metformin/repaglinide	Prandimet
705	methyldopa	Aldomet
706	methyldopa-hydrochlorothiazide	Aldoril
110	metolazone	Mykrox, Zaroxolyn
206	metoprolol succinate (extended release)	Toprol XL
205	metoprolol tartrate	Lopressor
215	metoprolol-hydrochlorothiazide	Lopressor HCT
2102	miglitol	Glyset
904	minoxidil	Loniten
306	moexipril	Univasc
316	moexipril-hydrochlorothiazide	Uniretic
207	nadolol	Corgard
216	nadolol-bendroflumethiazide	Corzide

Code	Generic Name	Brand Names
2601	nateglinide	Starlix
219	nebivolol	Bystolic
4501	niacin	Niaspan
405	nicardipine	Cardene
406	nifedipine	Adalat, Procardia
407	nisoldipine	Sular
1703	nitroglycerine transdermal ointment	Nitro-Bid
1702	nitroglycerine transdermal patch	Minitran
605	olmesartan	Benicar
612	olmesartan medoxomil-hydrochlorothiazide	Benicar HCT
4701	omega – 3 fatty acids	Lovaza
208	penbutolol	Levatol
307	perindopril	Aceon
209	pindolol	Visken
2801	pioglitazone	Actos
2901	pioglitazone/metformin	ActoPlus
4007	pitavastatin	Livalo
111	polythiazide	Renese
2201	pramlintide	Symlin
5103	prasugrel	Effient
4005	pravastatin	Pravachol
502	prazosin	Minipress
504	prazosin/polythiazide	Minizide
210	propranolol	Inderal
217	propranolol la-hydrochlorothiazide	Inderide LA
211	propranolol long-acting	Inderal LA
308	quinapril	Accupril
317	quinapril-hydrochlorothiazide	Accuretic
309	ramipril	Altace
1701	ranolazine	Ranexa
2009	regular	Humulin R, Novolin R
2010	regular:isophane	NPH
2602	repaglinide	Prandin
801	reserpine	Serpalan, Serpasil
804	reserpine-hydrochlorothiazide	Hydropres
5201	rivaroxaban	Xarelto
2802	rosiglitazone	Avandia
2902	rosiglitazone/metformin	Avandamet
4002	rosuvastatin	Crestor
2403	saxagliptin	Onglyza

Code	Generic Name	Brand Names
2504	sexagliptin/metformin XR	Kombiglyze
4006	simvastatin	Zocor
4201	simvastatin/exetimibe	Vytorin
4102	simvastatin/niacin	Simcor
4401	simvastatin/sitagliptan	Juvisync
2401	sitagliptin	Januvia
2502	sitagliptin/metformin XR	Janumet XR
2501	sitagliptin/metformin	Janumet
2402	sitagliptin/simvastatin (off-market)	Juvasync
1002	spironolactone	Aldactone
112	spironolactone/hydrochlorthiazide	Aldactazide
606	telmisartan	Micardis
613	telmisartan-hydrochlorothiazide	Micardis-HCT
503	terazosin	Hytrin
5102	ticagrelor	Brilinta
5104	ticlopidine	Ticlid
212	timolol	Blocadren
218	timolol-hydrochlorothiazide	Timolide
3107	tolazamide	Tolinase
3108	tolbutaminde	Orinase
113	torsemide	Demadex
310	trandolapril	Mavik
412	trandolapril/verapamil	Tarka
114	triamterene	Dyrenium
108	triamterene/hydrochlorothiazide	Dyazide, Maxide
607	valsartan	Diovan
614	valsartan-hydrochlorothiazide	Diovan-HCT
408	verapamil	Calan, Isoptin, Verelan, Coer, Covera HS
5001	warfarin	Coumadin, Jantoven