MEDFOCUS
MEDication Focused Outpatient Care
for Underutilization of Secondary Prevention

STATISTICAL ANALYSIS PLAN

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PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses for the Medication Focused Outpatient Care for Underutilization of Secondary Prevention (MEDFOCUS) study [National Heart, Lung, and Blood Institute (NHLBI) grant # R18HL116259]. The planned analyses identified in this SAP are intended to support the completion of the Final Study Report (FSR) and will be included in regulatory submissions and/or future manuscripts. An interim analysis will involve only the first primary study hypothesis (based on the entire study population), and will be performed once the specified number of enrolled study participants have completed the 12 month study period. All final, planned analyses identified in this SAP will be performed only after the last randomized subject has completed the full 24 month study period. After study data have been cleaned and verified per the study monitoring plan, a "locked" data set will be used for reporting the final study results. Key statistics and study results will be made available to the Protocol Principal Investigator following database lock and prior to completion of the FSR.

1. STUDY DESIGN

Adherence to guidelines for cardiovascular disease (CVD) is low, and regional and age variations in guideline-concordant therapy following myocardial infarction (MI) have been found (Cabana et al, 1999; Qureshi et al, 2001; Higashi et al, 2004; Rodondi et al, 2006; Milchak et al, 2007). The primary barrier to medication adherence is suboptimal medication use leading to poor disease control, often because busy providers must address acute non-CVD complaints (Garg et al, 2005; Rose et al, 2007). Managed care organizations and other healthcare settings are increasingly hiring clinical pharmacists to improve management of CVD. The present study will evaluate an efficient, centralized, web-based CVRS to support primary care providers in improving the management of CVD and achieving key performance measures (Chan et al, 2010).

The MEDFOCUS study is a multi-center, cluster-randomized, two-arm study that aims to examine the use of a centralized cardiovascular risk service (CVRS) for medical offices with large geographic, racial, and ethnic diversity. The AHA Guideline Advantage standards of care apply for secondary prevention of CVD, and with other prevention strategies. The criteria reflect drug therapies, meeting guideline goals for specific disease conditions, and screening and prevention measures (see appendices). The main objective of the MEDFOCUS study is to determine the extent to which this CVRS model will be implemented, and to what extent the implementation of this model leads to improved guideline adherence metrics. The study will randomize 20 primary care offices to either the CVRS arm or a usual care arm. Each office will enroll approximately 20-25 patients, for a total of approximately 400 study participants (200 per group). Furthermore, the project aims to enroll approximately 240 study participants (120 per group) from minority populations who face unique challenges related to cardiovascular disease. Study participants in both groups are scheduled to be actively followed in person for 12 months, with an additional medical record abstraction scheduled for 24 months after enrollment.

All study participants will have an initial visit with the site study coordinator and a second visit 12 months later. Each visit will include a research blood pressure measurement, surveys, phlebotomy for a lipid panel, and HgbA1c. For intervention site study participants, site study coordinators will abstract select medical record data at 4 and 8 months following enrollment. Site study coordinators will abstract select medical record data at 24 months following enrollment for all study participants.

Each subject at intervention arm clinics will receive the CVRS intervention for 12 months. A CVRS clinical pharmacist at the University of Iowa will work with each intervention arm subject, and will communicate with his/her providers to optimize the subject's pharmacological regimens and lifestyle patterns. The CVRS pharmacists will communicate with study participants, site pharmacists, and participating site medical providers in the 10 intervention offices using email, telephone, text messages, or the Iowa Personal Health and Research Management (IowaPHRM) online system.

These communications will allow the CVRS pharmacist to counsel the study participants for medication adherence, side effects, exercise, CHD knowledge, weight, diet, tobacco use, and alcohol use. The CVRS pharmacist will also work with the research study participants to develop an action plan that addresses gaps in guideline-concordant therapy, update medication list, and FAX recommendations for mediation changes to the primary medical provider and on-site clinical pharmacist every 3 months or more frequently if urgent issues are identified. The CVRS pharmacists will document all patient and provider encounters and time (minutes) for each activity in the IowaPHRM database. Study participants enrolled at control site clinics will receive usual care, and will not have any exposure to the study intervention. The Guideline Advantage Scoring standards of care will be used to create a score for each subject at baseline, 12 months, and 24 months. The intervention will be evaluated based on the degree to which the care provided to intervention arm study participants adheres to the Guideline Advantage measurement set criteria, compared to adherence for control arm study participants.

1.1. Primary Objectives

Primary Objective #1: Determine if adherence to guidelines for secondary prevention of CVD will be significantly greater at 12 months in patients from clinics randomized to the centralized CVRS group compared to the control group.

Primary Objective #2: Determine if adherence to guidelines for prevention of CVD will be significantly greater at 12 months in under-represented minorities from intervention clinics compared to under-represented minorities in the control group.

1.2. Major Adherence Secondary Objectives

Major Adherence Secondary Objective #1: Determine if adherence to guidelines for prevention of CVD will be significantly greater at 12 months in African-American/Black study participants from intervention clinics compared to African-American/Black study participants in the control group.

Major Adherence Secondary Objective #2: Determine if adherence to guidelines will deteriorate after the intervention is discontinued (i.e., comparing adherence at 12 and 24 months), but still remain higher in the intervention group compared to the control group.

Major Adherence Secondary Objective #3: Determine if implementation of the CVRS model is associated with positive provider-level attitudes and beliefs about this intervention.

Major Adherence Secondary Objective #4: Determine if the CVRS model has a favorable cost-effectiveness profile for the CVRS model group when compared to the control group.

1.3. Major Risk Factor Secondary Objectives

Major Risk Factor Secondary Objective: Determine if the CVRS model group differs from the control group with respect to a number of key risk factors:

(a) BP Control

(b) Mean BP (Systolic and Diastolic)

(c) Mean LDL Cholesterol

(d) Mean HgbA1c

2. PRIMARY STUDY ENDPOINT

The primary study endpoint will measure the degree to which each individual subject's care adheres with the Guideline Advantage standards of care. The Guideline Advantage measures combine the expertise of the American Cancer Society, American Diabetes Association, and American Heart Association (AHA) to advance prevention and disease management in the outpatient setting. The measures provide the basis for evaluating and improving outpatient treatment (see appendices).

During the process of operationalizing the 2011 version of the Guideline Advantage criteria, the 2013 version was released by the AHA. This new version included several changes, some of which were omissions from the 2011 version (i.e., atrial fibrillation and congestive heart failure) and some were additions [high blood pressure control for patients with coronary artery disease CAD)]. A decision was made to use the 2011 version, along with the component for high blood pressure control for patients with CAD that was added with the 2013 version.

At the baseline and 12 month visits, the Study Coordinator will ask each subject a number of questions in order to obtain the needed information. After the visit, the Study Coordinator will verify the subject responses or obtain additional data from the subject's medical record. All information from the subject responses or medical record abstraction will be recorded on the following forms:

- Diagnosed Conditions and Care Management (Patient Report)
- Diagnosed Conditions and Care Management (Medical Record)
- Medication Reconciliation
- Medication Adherence
- Health Behavior Inventory
- Stages of Change
- Cancer Screening
- Clinic Visit Tracking

No clinic visit will occur at the 24 month time point. At 24 months following enrollment, the Study Coordinator will collect the following medical record data for the time period extending from the 12 month study visit until 24 months following enrollment:

- Diagnosed Conditions and Care Management (Medical Record)
- 24 Month Blood Pressure, Laboratory, and Medication
- Cancer Screening
- Clinic Visit Tracking

For the purposes of this study, we will create a Guideline Advantage score for each subject at baseline, 12 months, and 24 months based on the number of applicable Guideline Advantage criteria that are met. For all study participants, each eligible criterion will be scored based on whether or not it was met at each of the index dates (baseline, 12 months, or 24 months). An algorithm will use the number of Guideline Advantage criteria that apply to each subject to calculate the percentage of those applicable criteria that are met at each time point. This resulting single numeric percentage value will be used as an indicator for quality of care (with higher values indicating higher quality of care).

3. MAJOR SECONDARY ENDPOINTS

3.1. Provider Level Attitudes toward Delivering the Intervention, and Barriers and Facilitators to Implementation

To evaluate barriers and facilitators to implementing the intervention, the relationship between provider-level attitudes and beliefs with adherence scores will be assessed. All clinic providers will be asked to complete two questionnaires at the beginning of the project, and again following implementation of the study intervention. The first validated instrument measures physician-pharmacist collaboration, and will be used to evaluate the level and type of communication and any increases in the level of communication in the intervention group. The second validated questionnaire, based on the Theory of Planned Behavior (TPB), will be used to evaluate physician adoption of the study intervention.

3.2. Cost Effectiveness

A cost-effectiveness analysis will assign a cost to CVRS pharmacist time (including record review, patient assessment, email time, telephone follow-up), clinic visits, emergency room visits, hospitalizations, and laboratory procedures. The perspective of the cost analysis is society in general. For each subject- pharmacist encounter, the beginning and end time of the encounter will be recorded. Subject-specific pharmacist costs will be estimated by multiplying pharmacist time by the average compensation rate. Each subject visit with a physician in the office will be documented, but not the specific length of the visit. Physician costs will be estimated by multiplying the average amount of time spent in physical consultation with study participants by the average compensation rate for family practice physicians. Compensation rates will be obtained from the Occupational Employment Statistics survey, Bureau of Labor Statistics. For drug costs, cost per prescription (specific to each drug, dose, and strength) for each subject will be calculated by multiplying the average wholesale price (AWP) or average AWP price from Lexicomp Online (https://online.lexi.com) with frequency and dose. Generic prices will be used when available.

3.3. Blood Pressure

At baseline and 12 months, the main secondary outcome for mean BP will come from the research nurse-measured BP. Study coordinators will measure the subject's height, weight, and research blood pressures. Resulting measures will be documented on the Blood Pressure case report form. All BP measurements should be obtained using the OMRON HEM907XL automated blood pressure device. 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. Study participants who require use of a thigh cuff at the baseline visit cannot continue in the study. However, should a subject whose BP was successfully measured at baseline using the Omron monitor gain sufficient weight between the baseline and 12 month visits to require a thigh cuff at 12 months, the Study Coordinator should take the 12 month BP measurements using a thigh cuff and manual sphygmomanometer. Sitting blood pressure will be measured at least three times at each study visit. If the 2nd and 3rd measurements differ by more than 4 mm Hg, a fourth measure will be taken. If three measures are taken, the endpoint is defined as the average of the 2nd and 3rd measures. If four measures are taken, the endpoint is defined as the average of the two closest readings, excluding the first measurement. If four measures are taken, and the last three readings are equidistant apart, the endpoint is defined as the average of the two highest readings.

At the 24 month time point, or if only medical record abstraction was possible at the 12 month visit, only a single chart-audited BP value will be obtained. This value should correspond to the last BP value recorded in the chart prior to the corresponding visit date.

After determining either the mean BP (for baseline and in-person month 12 visits) or the single BP value recorded from the chart abstraction (month 24 visits and chart-abstracted month 12 visits), BP control will be defined using the JNC-8 guidelines (James et al, 2014):

- For study participants < 60 years of age, systolic BP must be < 140 mm Hg AND diastolic BP must be < 90 mm Hg
- For study participants ≥ 60 years of age, diastolic BP must be < 150 mm Hg AND diastolic BP must be < 90 mm Hg

3.4. LDL Cholesterol & HgbA1c

Direct measurement (at baseline and 12 months) and medical record abstraction (at 24 months) will also yield values for LDL cholesterol and HgbA1c. The Study Coordinator will draw or arrange for usual laboratory draw of blood for these tests. Study lab results will be documented on the Laboratory Case Report Form, excepting intervention study participants at the baseline visit only whose values will be reported on the Laboratory for Baseline Intervention Case Report Form.

4. ENROLLMENT & RANDOMIZATION OF CLINICAL SITES

4.1. Enrollment of Study Participants

Sites may use several techniques to identify potential study participants: generating a list of all of their clinic patients who have the ICD9 codes listed in the inclusion/exclusion criteria, recommendations from clinic providers, or looking at the daily clinic schedule to identify potential study participants. For each potential subject that is identified, the site coordinator will review the medical record over the preceding 24 months to see whether the medical record supports eligibility criteria for age, language, and qualifying medical conditions and does not include documentation of any exclusion criteria. Documentation of a medical condition in the patient's problem list is preferred, but explicit mention of a diagnosis in a provider note can be used if the problem list has not been regularly updated. Qualifying conditions include coronary artery disease, previous myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, systolic heart failure, peripheral vascular disease/claudication, carotid artery disease, and diabetes with either uncontrolled hyperlipidemia or uncontrolled hypertension (as evidenced from the most recent lab values taken within the preceding 12 months).

4.2. Randomization

Initially, each site was classified as either a high minority (estimated ≥40% minority patient population) or low minority (estimated <40% minority patient population) site. Randomization was stratified by site minority status and each site was randomized using a pseudo-random number generator via SAS software in a 1:1 manner to one of two arms: a) CVRS, or b) usual care. Each site is expected to consent 20-25 patients. All study participants enrolled at a given site will participate in the study arm to which the site was randomized.

Due to the nature of the CVRS intervention, it is not possible to blind pharmacists, physicians, or study participants to their intervention assignment. As a result, no attempt to blind intervention assignments will be made.

5. PRELIMINARY TABULATIONS

All study participants who provide informed consent will be accounted for in this study. Regularly generated reports will describe:

- Number of study participants consented, eligible, and enrolled by site
- Ongoing study status of all enrolled study participants
- Reasons for ineligibility
- Protocol deviations
- Early study terminations

Subject data will also be summarized be treatment group (intervention vs. control) with respect to important demographic characteristics. Distribution of categorical variables will be tabulated by intervention group and overall. Comparisons of categorical variables between the two groups will be made using models based on Generalized Estimating Equations (GEE) with a logit link function and an exchangeable working correlation matrix. Continuous variables will be summarized as mean, median, standard deviation, minimum, and maximum by intervention group and overall. Comparisons of continuous variables between the two groups will be made using models based on GEE with an identity link function and an exchangeable working correlation matrix. Variables to be collected will include:

- Gender
- Race/Ethnicity
- Education

- Marital Status
- Insurance Coverage
- Annual Household Income
- Smoking Status
- Current Alcohol Intake
- Age
- Guideline Advantage Metric Score

All analyses will be performed using SAS® Software version 9.2 or later. Unless stated otherwise, all statistical tests will be performed using a 0.05 significance level. In order to account for the relatively small number of clusters, we will utilize the Kenward and Roger adjustment (1997) when reporting the results of all analyses (Johnson et al, 2013).

6. PRIMARY EFFICACY ANALYSES

6.1. Main Analysis

6.1. ***Primary Objective #1:*** *Determine if adherence to guidelines for secondary prevention of CVD will be significantly greater in patients from clinics randomized to the centralized CVRS group compared to the control group.*

6.2. ***Primary Objective #2:*** *Determine if adherence to guidelines for secondary prevention of CVD will be significantly greater in under-represented minorities from intervention clinics compared to under-represented minorities in the control group.*

The primary outcome will be adherence to the AHA Guideline Advantage criteria that apply for secondary prevention of CVD at the end of the intervention. For each subject, the primary outcome will involve a determination of the percentage of applicable criteria met at the end of the twelve month period. Both primary analyses will follow the intention-to-treat (ITT) principle. As such, it will be critically important to minimize the occurrence of missing data. Obviously, the optimal strategy for dealing with missing data is to make every effort to obtain complete data during the conduct of the study. Our team will use a variety of methods in order to minimize the percentage of missing data in this trial. Nevertheless, there is likely to be a small percentage of missing data. For study participants who drop out of the study before their 12 month data can be obtained, we propose to use a multiple imputation method to impute their outcome. This multiple imputation model will be implemented, separately for each intervention group, using a model based on minority strata, guideline adherence at baseline, and 12 month guideline adherence values for all study participants with observed data. We will use five separate imputations, and will average the parameters across all five imputations for the final analysis.

Both hypotheses will be assessed using a mixed model, adjusted for adherence at baseline and the minority status strata grouping. The only difference for the two primary hypotheses is that the first analysis will apply the model to all enrolled study participants, while the second analysis will be restricted only to minority study participants (whether they were enrolled at a high or low minority site). This model will also use an exchangeable correlation structure to adjust for the correlation among study participants treated in the same clinic. This corresponds to the ‘compound symmetry’ assumption that implies that all members of a cluster are equally correlated with each other – and that members in different clusters are independent of each other, a reasonable assumption since physicians and pharmacists only practice in one study location. We will also assess the normality assumption involved in the model. If this assumption is violated, an appropriate transformation will be employed, or a nonparametric model will be fit.

To assess this objective, the following model will be fit to these data:

$$Y_{ij} = \beta_0 + \beta_1 X_{min,j} + \beta_2 X_{Int,j} + \beta_3 X_{GAM,ij} + \gamma_j + \varepsilon_{ij}$$

where:

- Y_{ij} is the Guideline Adherence score at twelve months for the i^{th} subject from the j^{th} clinic
- $X_{min,j}$ is an indicator for the minority status of the j^{th} clinic [0 if < 40% (low), 1 if ≥ 40% (high)]
- $X_{Int,j}$ is an indicator for whether the j^{th} clinic was randomized to the CVRS or usual care arm (0 = usual care, 1 = CVRS group)
- $X_{GAM,i,j}$ is the baseline Guideline Adherence score for the i^{th} subject from the j^{th} clinic
- γ_i is the random effect for the j^{th} clinic
- ε_{ij} is random error for i^{th} subject from j^{th} clinic

The desired test of interest can be obtained by testing the null hypothesis of the following contrast:

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

Because there are two primary hypotheses of interest, we will apply a Bonferonni correction and test each hypothesis at the 0.05/2 = 0.025 significance level. If β_2 is significantly larger than zero, we will conclude that the CVRS group achieves higher mean Guideline Adherence scores than the control group at 12 months. If β_2 is significantly less than zero, we will conclude that the CVRS group achieves lower mean Guideline Adherence scores than the control group at 12 months. If we fail to reject the null hypothesis, then we will conclude that there is no difference in mean Guideline Adherence scores at 12 months between the CVRS and usual care groups.

6.2. Sensitivity Analyses

6.2.1. Missing Data

We will perform two simple sensitivity analyses to determine the potential dependence of the results of the primary analysis on the missing 12 month values. The analyses will include:

- Baseline observation carried forward
- Using all observed data (no imputation)

6.2.2. Potential Baseline Confounders

Because randomization is performed at the site level, it is possible that some other important subject-level covariates (age, gender, smoking status, education level, insurance status, economic status, or marital status) may be imbalanced in this study. Thus, we will carefully monitor the ongoing study for any important imbalances among important covariates. Should important imbalances occur, we will conduct additional sensitivity analyses to determine if the primary study results change after adjustment for any of these relevant baseline characteristics.

6.2.3. Prematurely Terminated Sites

On 04/11/2016, the study PI notified the site PIs that two sites were being dropped, one in each of the study arms. These sites had notable enrollment problems, and the Data Coordinating Center (DCC) monitor discovered many concerns with data quality and completeness during routine monitoring visits to these sites. Because the primary analysis is based on the ITT principle, the study participants from this site will be included in all final analyses – though in most cases, their endpoints will be imputed. Thus, the DSMB requested an additional sensitivity analysis to examine the primary efficacy hypotheses stated above excluding all study participants from the prematurely terminated sites.

7. PRE-SPECIFIED SECONDARY ANALYSES

Unless major differences are observed across sensitivity analyses for the primary hypotheses, all secondary analyses will be based on the population of study participants with observed endpoint data. All statistical tests for secondary analyses will use a 0.05 significance level.

7.1. Guideline Adherence in African American/Black Study participants

One of the secondary objectives of the MEDFOCUS study is to determine if African-American/Black study participants have better mean Guideline Adherence scores in the CVRS intervention clinics as compared to the control clinics. This hypothesis will be assessed in the same manner as the primary hypothesis, except the analysis will be restricted only to the population of African-American/Black study participants.

7.2. Guideline Adherence at 24 months – after intervention is discontinued

Another objective is to determine if the intervention effect is sustained even after the intervention is discontinued. This hypothesis will be assessed in the same manner as the primary hypothesis, except the adherence at 24 months will be used in place of the 12 month adherence outcome variable.

7.3. Provider Level Attitudes to Deliver Intervention

Because this is an effectiveness trial, provider characteristics may vary among the participating clinics. The Theory of Planned Behavior (TPB), which has been used previously to explain provider intentions to perform an activity, (e.g., implementation of therapy guidelines) is used in the MEDFOCUS study to assess physician and pharmacist attitudes towards the CVRS. A validated survey instrument to measure attitudes toward CVRS will be sent to physicians and pharmacists at all sites participating in the MEDFOCUS study at the beginning of the study and again following implementation of the study intervention. Attitudes will be measured in four domain areas, Behavioral Intentions, Social Norms, Perceived Behavioral Control, and Attitudes toward CVRS. A subscale score for each domain will be calculated as the mean of the survey item responses related to a particular domain. The overall TPB score will be calculated as the mean of the subscale scores. Details regarding the survey instrument may be found in DeMik et al (2013). To summarize TPB at the site level, the mean of the TPB scores within a site will be calculated. These site level scores are then used to determine if attitude towards intent to implement a CVRS is related to guideline adherence.

An analysis of 12 month outcomes will be performed for provider TPB scores. This analysis will be based on the models described in the sections above for comparing guideline adherence between the intervention and control groups – with the exception that terms will be added to address the two-way interaction between the intervention group and the provider level characteristics.

To assess the effect of pharmacist TPB score on guideline adherence, we will use the linear mixed effects model specified in section 6 but with the addition of the site level TPB score and a corresponding interaction term between site level TPB score and intervention arm assignment:

$$Y_{ij} = \beta_0 + \beta_1 X_{min,j} + \beta_2 X_{Int,j} + \beta_3 X_{GAM,ij} + \beta_4 X_{TPB,j} + \beta_5 X_{TPB,j} * X_{Int,ij} + \gamma_j + \varepsilon_{ij}$$

where:

- Y_{ij} is the adherence at twelve months for the i^{th} subject in the j^{th} cluster
- $X_{min,j}$ is the minority status of the j^{th} cluster (0 if < 40%, 1 if ≥ 40%)
- $X_{Int,j}$ is an indicator variable for whether the j^{th} cluster was randomized to the CVRS or usual care group
- $X_{GAM,i,j}$ is the baseline adherence score for the i^{th} subject in the j^{th} cluster

- $X_{TPB,j}$ is the baseline Theory of Planned Behavior score based on pharmacist responses for the j^{th} clinic
- γ_j is the random effect for the j^{th} center
- ε_{ijk} is random error for i^{th} subject from j^{th} clinic at the 9 month visit

The 2-way interaction between intervention group and pharmacist TPB score will first be tested with the following contrast:

$$H_0: \beta_5 = 0 \text{ vs. } H_A: \beta_5 \neq 0$$

If the 2-way interaction is significant, then the mean difference in guideline adherence for a five unit increase in TPB score will be estimated separately within each group as:

- Intervention Group: $(\beta_4 + \beta_5)*5$
- Control Group: $(\beta_4)*5$

If the 2-way interaction is not significant, then the model terms for the 2-way interaction (β_5) will be removed and the model will be refit. Under this scenario, the mean difference in guideline adherence for a five unit increase in TPB score will be estimated as: $B_4 * 5$.

7.4. Cost Effectiveness

Costs will be assigned to each activity and CVD and diabetes medication. All CVRS pharmacist time, including record review, patient assessment, email time, telephone follow-up, clinic visits, emergency room visits, hospitalizations, and laboratory procedures will have costs assigned and analyzed using methodologies previously used. We will determine the cost of the intervention by subtracting the average costs for the intervention groups from the average costs for the control group. The incremental cost-effectiveness ratio will be calculated as the additional costs of the intervention divided by the change in outcomes related to the intervention.

In addition, we will conduct sensitivity analyses. For example, costs and incremental cost-effectiveness ratios will be estimated for only those who finished the intervention. Also, the average wholesale price often overstates the cost of drugs. As a sensitivity analysis, we will deflate our drug costs and recalculate the incremental cost-effectiveness ratios.

We note that the cost effectiveness analysis will be performed separately by Dr. Linnea Polgreen, and will not be part of the final study report prepared by the DCC.

7.5. BP Control

To determine if study participants in clinics randomized to the CVRS intervention groups achieve better BP control than study participants in the control group, the following non-linear random effects model will be estimated using likelihood methods:

$$logit(P_{ij}) = \beta_0 + \beta_1 X_{min,j} + \beta_2 X_{int,j} + \beta_3 X_{BP,ij} + \gamma_j + e_{ij}$$

where:

- P_{ij} is an indicator of whether the i^{th} subject in the j^{th} clinic has their BP controlled at the 12 month visit
- $X_{min,j}$ is the minority status of the j^{th} cluster (0 if < 40%, 1 if ≥ 40%)
- $X_{Int,j}$ is an indicator variable for whether the j^{th} cluster was randomized to the CVRS or usual care group
- $X_{BP,ij}$ is an indicator of whether the i^{th} subject in the j^{th} clinic hade their BP controlled at baseline
- γ_j is the random effect for the j^{th} center
- ε_{ij} is random error for i^{th} subject from j^{th} clinic

The desired test of interest can be obtained by testing the null hypothesis of the following contrast:

$$H_0: \beta_2 = 0 \text{ vs } H_1: \beta_2 \neq 0.$$

7.6. Mean SBP and DBP

An additional secondary objective of the MEDFOCUS study is to determine whether mean BP is improved in the CVRS intervention clinics as compared to the control clinics. Separate hypothesis for mean SBP and mean DBP will be assessed in the same manner as described in section 6.1 (for 12 month BP measurements) and section 7.2 (for 24 month BP measurements), except the mean BP values will be used in place of the AHA Guideline Adherence outcome measure for both the outcome and baseline covariate.

7.7. Mean LDL Cholesterol

Another secondary objective is to determine if the intervention leads to a difference between intervention groups in LDL cholesterol after 12 months. This hypothesis will be assessed in the same manner as the primary hypothesis, except LDL cholesterol will be used in place of the AHA Guideline Adherence outcome variable and baseline covariate.

7.8. Mean HgbA1c

Another secondary objective is to determine if the intervention leads to a difference between intervention groups in HgbA1c after 12 months. This hypothesis will be assessed in the same manner as the primary hypothesis, except HgbA1c will be used in place of the AHA Guideline Adherence outcome variable and baseline covariate.

7.9. Additional Secondary Analyses

A number of additional secondary, tertiary, and exploratory analyses are also planned, but will not be included as part of the FSR. These additional analyses include, but are not limited to:

- Measurement of Stages of Change
- Intensity of Medication Management
- Medical Home Index
- Adherence comparison in passive observation study participants

8. SAMPLE SIZE JUSTIFICATION

8.1. Primary Analyses & Major Adherence Secondary Objective #1

For the purposes of justifying the sample size for the primary outcomes in this trial, preliminary estimates were obtained from guideline adherence measures collected in a previous study by the investigators (Carter et al, 2009). In that study, only 40% of applicable criteria were adhered to for hypertension. Based on this and other information (Taveira et al, 2006; Bove et al, 2011), we expect baseline adherence scores to be 30-35% ± 20% - but have conservatively assumed baseline values of 40% ± 20% for sample size calculations. We expect these scores to increase to 50% ± 20% in the control group and to 60% ± 20% in the intervention group at 12 months. We also expect the intervention to be as effective in racial and ethnic minorities, so the same assumptions apply to that sample size calculation as well. Finally, further examination of the previous study suggested that the observed intra-class correlation coefficient was 0.004. Of the 402 study participants enrolled into the adherence study, 60 (15%) dropped out and completed only the baseline and/or 3 month visits (Carter et al, 2009). The CAPTION trial enrolled a total of 625 study participants into the BP component of the study, with 125 early study terminations not due to early study closure (20%) – and 85 (14%) due to drop-out or loss to follow-up (Carter et al, 2015). For these reasons, we believe that a 15% lost-to-follow-up rate is a good estimate for this trial. Thus, based on this information, the following assumptions were made:

- We expect a conservative absolute average of approximately 10% increase in the guideline adherence at twelve months for study participants enrolled at centralized CVRS sites versus study participants at usual care sites
- Standard deviation for baseline and 12 month adherence scores is expected to be 20% for both groups
- The intra-class correlation coefficient is conservatively assumed to be less than or equal to 0.005.
- Each participating site will be expected to enroll approximately 20-25 study participants
- Both primary hypotheses will be tested at the 0.025 significance level.
- The secondary hypothesis for the African-American subset will be tested at the 0.05 level
- The dropout rate is expected to be 15%

The approach used for determining the sample size here is to first compute the number of study participants (not clinics) required in each group in a usual clinical trial setting (denoted by m – assuming independence of observations). This sample size will then need to be inflated in order to account for: 1) the correlation between study participants at the same clinic (Donner et al, 1992), and 2) dropouts. The required final sample size is:

$$n^* = m^*[1/(1-d)]^*[1 + (n-1)^*\kappa] ,$$

where n is the number of study participants in each cluster (assumed to be 25), κ is the estimated intra-class correlation coefficient (assumed to be 0.005), d is the assumed dropout rate (assumed to be 15%), and n^* is the sample size adjusted to take into account the dropout rate and correlation among subjects in the same clinic.

Based on the assumptions above, the study would only require 300 study participants to have 93% power to assess the primary hypothesis in the overall population. However, the choice of sample size is complicated for this trial due to the fact that we are also interested in ensuring adequate power for the secondary primary hypothesis, which involves only under-represented minority study participants (a subset of the population used to assess the first primary hypothesis). Hence, the sample size should be chosen in such a way to ensure adequate power for both primary hypotheses. In the CAPTION study, about 55% of the enrolled study participants were from under-represented minorities – with 45% of the enrolled study participants being African-American/Black (Carter et al, 2015). Based on these assumptions, Table 1 provides power levels for a variety of adjusted sample sizes for the overall population, the minority population, and the African-American/Black (AA) population:

Table 1. Observed Power for Different Adjusted Overall and Minority Sample Size Values

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

The table shows that a sample size of 400 study participants provides reasonable power to detect both primary hypotheses of interest, as well as the first secondary hypothesis. This proposed sample size would provide greater than 99% power to detect the effect of interest in the overall population,

while providing 83% power to detect these same effects in both the under-represented minority population and the African-American population (although one is a subset of the other, the fact that we plan to use a significance level of 0.05 for the secondary hypothesis and a significance level of 0.025 for the second primary hypothesis leads to similar power). With each site expected to enroll a total of 20-25 study participants, this corresponds to a total requirement of 16-20 sites.

Finally, it is important to note that we have not adjusted these sample size calculations to account for the fact that the final model will include baseline adherence and site minority status as covariates. The inclusion of these covariates should increase the power of the proposed tests. Hence, these sample size estimates are somewhat conservative. Although not optimal, we were not comfortable making any a priori assumptions about the impact of these covariates due to lack of preliminary data. Hence, we chose this conservative approach to ensure that the trial is adequately powered.

8.2. Major Adherence Secondary Objective #2

We expect that guideline adherence scores will deteriorate after the intervention is discontinued. However, it is generally expected that guideline adherence scores at 24 months will remain higher in the intervention group (50% ± 20%) versus the control group (40% ± 20%). Hence, although the actual adherence scores will be lower, we expect the same difference across groups. As a result, Table 1 also suggests that the study has adequate power to detect whether a difference in adherence remains at 24 months after the intervention is discontinued.

9. SAFETY MONITORING

9.1. Serious Adverse Event Screening and Reporting

Sites will screen for and report all serious adverse events (SAEs) that meet BOTH:

- Criterion A – The SAE resulted in at least one of the following outcomes:
    - Death
    - Life-Threatening Condition
    - Hospitalization
    - Disability
    - Congenital Abnormality
    - Intervention was required to prevent permanent impairment or damage
    - The lead provider or pharmacist for the study judged the event to be an important medical event
- Criterion B: The SAE involved at least one of the following health situations:
    - Loss of Consciousness
    - Hypoglycemia
    - Hypertensive Urgency/Emergency
    - Rhabdomyolysis
    - Stroke
    - Excessive Bleeding
    - Myocardial Infarction
    - Thromboembolism
    - Diabetic Ketoacidosis

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

- 12 Month Study Visit – The Study Coordinator will review each subject's medical record for additional SAEs that have occurred since the baseline visit.
- 24 Month Study Visit – The Study Coordinator will review each subject's medical record for SAEs that occurred since the 12 month visit.

All SAEs that are identified by the site coordinators, and that meet the qualifying criteria for reporting, must be reported as quickly as possible through the study database. To help with this process, all SAEs are collected, analyzed, and monitored using an Online Adverse Event Reporting system. This system allows the site to enter data electronically for all SAEs. If a site initiates, but does not submit, an SAE form within 24 hours of notification, an automatic email notifies the DCC staff so that follow-up may occur.

9.2. Medical Safety Monitor

Dr. Paul James will serve as the independent Medical Safety Monitor (MSM) for this trial. Dr. James will work closely with the DCC, and will use the online AE reporting system to review all reported SAEs in near real time. For any reported SAEs, an automatic email will be sent to Dr. James to prompt a review of the event for determination of whether the event is related to the study intervention. With the assistance of the coordinators at the DCC, Dr. James has the option of requesting additional information about any SAE. He will complete a form for each review, and this information will be entered into the data entry system. If the MSM determines that an SAE should be shared on an emergency basis with the DSMB, he will contact the DCC.

9.3. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed and charged with the task of providing regular oversight of data and safety monitoring issues in alignment with NHLBI policy (*NHLBI Policy for Data and Safety Monitoring of Extramural Clinical Studies*, December 2014). These scientific experts will periodically review and evaluate the accumulated data for participant safety, adverse events, study conduct, and study progress. The DSMB will make recommendations to NHLBI concerning continuation, modification, or termination of the study.

The DCC will prepare regular reports for the DSMB to review at each meeting. These reports will include overall summaries, as well as AE & SAE summaries by treatment group in a blinded fashion. These reports will include a summary of the following topics:

- Performance Monitoring: Subject recruitment, comparison with targeted recruitment, retention, protocol adherence, and quality of data collection procedures
- Intervention Monitoring: Data on intervention integrity and adherence
- Safety Monitoring: Data related to the safety of the study participants, including confidentiality, any serious adverse events
- Futility Monitoring: One interim futility analysis is to be performed when half (approximately 200) of the enrolled study participants have completed their 12 month visit

At the time of each DSMB meeting, a DSMB closed session report will include all available safety-related data to allow the DSMB to monitor for trends. These unblinded reports will also include a memo from the Medical Safety Monitor to allow the communication of any concerns or findings that may be of interest to the DSMB in their study deliberations. In general, interim safety monitoring will rely on these interim reviews to identify any potential trends of interest.

After each scheduled DSMB meeting, the DSMB chair or his designee sends a summary report of the meeting to the CCC that summarizes the DSMB deliberations and recommendations. The CCC

forwards the summary report to the study sites for reporting to their local IRBs and to the University of Iowa IRB for reporting during the annual continuing review.

10. INTERIM ANALYSES

One formal futility analysis will be conducted when half of the planned active participants have completed their twelve month follow-up. The futility assessment will be based on a determination of the predictive power for the overall comparison (Spiegelhalter et al, 1986). If this predictive power is below 5% at the time the analysis is conducted, then we propose that the trial should stop for futility.

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APPENDICES

Appendix 1. Guideline Advantage Fact Sheet, 2011 Version

Appendix 2. Guideline Advantage Fact Sheet, 2013 Version

Appendix 3. Guideline Advantage Metric Scoring, Version 2.0

THE GUIDELINE ADVANTAGE™

FACT SHEET

OVERVIEW

The Guideline Advantage™ (formerly known as Get With The Guidelines®-Outpatient) combines the expertise of the American Cancer Society, American Diabetes Association and American Heart Association (ACS, ADA, AHA) to advance prevention and disease management in the outpatient setting. Available at no charge to practices, the program promotes the use of evidence-based treatment guidelines, performance measurement tools and quality improvement strategies with the goal of helping you offer your patients every advantage for a healthy life.

PROGRAM DESCRIPTION

The Guideline Advantage works with outpatient electronic health record (EHR) or health technology systems, using data already entered into the EHR, to track measures for wellness, primary prevention and longitudinal care. We welcome submission of all data elements currently collected through your practice's EHR.

THERE ARE THREE WAYS TO PARTICIPATE IN THE PROGRAM:

01 EHR or health information technology platforms may match and submit data collected in your practice's existing platform.

02 Practices with technical staff may independently match and submit data to the program without the involvement of the EHR vendor.

03 Your practice may export a standard data file from your EHR system and submit directly to the program.

Participating outpatient practices receive quarterly reports providing performance feedback and comparative benchmarking information. Reports are intended to help you identify and focus on specific areas for improvement based on better practices, tools and resources to drive quality improvement. The program includes a recognition component to publicly acknowledge early program adopters and performance achievements by participating practices.

Data from The Guideline Advantage feedback reports can also be used to complete American Board of Internal Medicine's Self-Directed Practice Improvement Module (PIM) and to earn credit for ABIM Maintenance of Certification (MOC). Additionally, The Guideline Advantage is working to align the program with those meaningful use (MU) measures that will be most directly related to conditions and risk factors of interest to the ACS/ADA/AHA. Currently, the core clinical quality measures are captured in our ideal data set.

MEASURES OVERVIEW

Measures provide the basis for evaluating and improving outpatient treatment. Initial selection of measures used in The Guideline Advantage program was based on review of nationally accepted ambulatory care measures. The ideal measures that the program seeks to collect include, but are not limited to, those measures developed by the American Heart Association and American Cancer Society, individually or with co-developers such as the American College of Cardiology, American Medical Association Physician Consortium for Performance Improvement (AMA PCPI) and the National Committee for Quality Assurance (NCQA). The measures used in this program will undergo regular review and will change periodically to reflect maintenance of measures and changes in EHR reporting conventions. Corresponding changes may be made in data elements requested for collection.

This list is intended to represent an ideal measure set. Individual practices are unlikely to collect and report on all of the listed measures, but even limited data sets can be instructive in improving quality. We encourage you to give us what you have, and we will work from your current data elements to begin the quality improvement process.

THE GUIDELINE ADVANTAGE™

American Cancer Society® | American Diabetes Association® | American Heart Association® | American Stroke Association®

IDEAL MEASURES

ATRIAL FIBRILLATION

- **Assessment of thromboembolic risk factors:** Patients with an assessment of all of the specified thromboembolic risk factors documented during the 12-month reporting period. (AMA PCPI/AHA/ACCF 2007)
- **Chronic anticoagulation therapy:** Patients who were prescribed warfarin during the 12-month reporting period. (AMA PCPI/AHA/ACCF 2007)
- **Monthly INR:** Number of calendar months in which at least one INR measurement was made. (AMA PCPI/AHA/ACCF 2007)

CANCER

- **Screening mammography:** Percentage of women aged 40 through 69 years who had a mammogram to screen for breast cancer within 24 months. (PQRS-comparable)
- **Colorectal cancer screening:** Percentage of patients aged 50 through 75 years who received the appropriate colorectal cancer screening. (PQRS-comparable)

CORONARY ARTERY DISEASE

- **Oral antiplatelet therapy prescribed for patients with CAD:** Percentage of patients aged 18 years and older with a diagnosis of CAD who were prescribed oral antiplatelet therapy. (PQRS-comparable)
- **Beta-blocker therapy for CAD patients with prior myocardial infarction (MI):** Percentage of patients aged 18 years and older with a diagnosis of CAD and prior MI who were prescribed beta-blocker therapy. (PQRS-comparable)
- **Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy for patients with CAD, diabetes and left ventricular systolic dysfunction (LVSD):** Percentage of patients aged 18 years and older with a diagnosis of CAD who also have diabetes mellitus and/or LVSD (LVEF < 40%) who were prescribed ACE inhibitor or ARB therapy. (PQRS-comparable)
- **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 ACCF/AHA guidelines). (PQRS-comparable)
- **Symptom and activity assessment:** Percentage of patients aged 18 years and older with a diagnosis of CAD who were evaluated for both level of activity and anginal symptoms during one or more visits. (AMA PCPI/AHA/ACCF 2005)
- **Symptom control:** Percentage of visits for patients aged 18 years and older with a diagnosis of CAD who are angina-free OR are prescribed at least two anti-anginal medications. (AMA PCPI/AHA/ACCF 2005)
- **Cardiac rehabilitation patient referral from an outpatient setting:** All patients evaluated in an outpatient setting who within the past 12 months have experienced an acute myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, a percutaneous coronary intervention (PCI), cardiac valve surgery, or cardiac transplantation, or who have chronic stable angina (CSA) and have not already participated in an early outpatient cardiac rehabilitation/secondary prevention (CR) program for the qualifying event/diagnosis are to be referred to such a program. (AACVPR/AHA/ACCF 2010)

DIABETES

- **Hemoglobin A1c poor control:** Percentage of patients aged 18 through 75 years with diabetes who had most recent hemoglobin A1c greater than 9.0%. (PQRS-comparable)
- **HbA1c good control:** Comprehensive diabetes care-percentage of members 18 through 64 years of age with diabetes (type 1 and type 2) whose most recent hemoglobin A1c (HbA1c) level is less than 7.0% (controlled). (NCQA)
- **Low-density lipoprotein (LDL-C) control:** Percentage of patients aged 18 through 75 years with diabetes who had most recent LDL-C level in control (less than 100 mg/dl). (PQRS-comparable)
- **High blood pressure control:** Percentage of patients aged 18 through 75 years with diabetes who had most recent blood pressure in control (less than 140/80 mmHg). (PQRS-comparable)
- **Dilated eye exam:** Percentage of patients aged 18 through 75 years with diabetes who had a dilated eye exam. (PQRS-comparable)
- **Urine screening for microalbumin or medical attention for nephropathy:** Percentage of patients aged 18 through 75 years with diabetes who received urine protein screening or medical attention for nephropathy during at least one office visit within 12 months. (PQRS-comparable)
- **Foot exam:** The percentage of patients aged 18 through 75 years with diabetes who had a foot examination. (PQRS-comparable)

HEART FAILURE

- **Left ventricular function (LVF) assessment:** Percentage of patients aged 18 years and older with a diagnosis of heart failure who have quantitative or qualitative results of LVF assessment recorded. (AMA PCPI/AHA/ACCF 2005)
- **Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy for left ventricular systolic dysfunction (LVSD):** Percentage of patients aged 18 years and older with a diagnosis of HF and LVSD (LVEF < 40%) who were prescribed ACE inhibitor or ARB therapy. (PQRS-comparable)
- **Beta-blocker therapy for left ventricular systolic dysfunction (LVSD):** Percentage of patients aged 18 years and older with a diagnosis of heart failure who also have LVSD (LVEF < 40%) and who were prescribed beta-blocker therapy. (PQRS-comparable)

HYPERTENSION

- **Blood pressure control:** Percentage of patients with BP≤140/90 or who are taking or were prescribed two or more antihypertensive agents at most recent visit during the previous 12 months. (ACCF/AHA 2009)

PERIPHERAL ARTERY DISEASE

- **Cholesterol-lowering medications (statin):** Drug therapy for lowering low-density lipoprotein cholesterol in patients with PAD. (AHA/ACCF/ACR/SCAI/SIR/SVM/SVN/SVS 2010)
- **Smoking cessation:** Smoking-cessation intervention for active smoking in patients with PAD. (AHA/ACCF/ACR/SCAI/SIR/SVM/SVN/SVS 2010)
- **Antiplatelet therapy:** Antiplatelet therapy to reduce the risk of myocardial infarction, stroke, or vascular death in patients with a history of symptomatic PAD. (AHA/ACCF/ACR/SCAI/SIR/SVM/SVN/SVS 2010)

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 parameters, a follow-up plan is documented. (PQRS-comparable)
- **Inquiry regarding tobacco use:** Percentage of patients aged 18 years and older who were queried about tobacco use one or more times within 24 months. (PQRS-comparable)
- **Advising smokers to quit:** Percentage of patients aged 18 years and older and are smokers who received advice to quit smoking. (PQRS-comparable)
- **Unhealthy alcohol use – screening:** Percentage of patients aged 18 years and older who were screened for unhealthy alcohol use using a systematic screening method within 24 months. (PQRS-comparable)
- **Influenza immunization for patients ≥ 50 years old:** Percentage of patients aged 50 years and older who received an influenza immunization during the flu season (September through February). (PQRS-comparable)
- **Pneumonia vaccination for patients 65 years and older:** Percentage of patients aged 65 years and older who have ever received a pneumococcal vaccine. (PQRS-comparable)
- **Blood lipid therapy and control:** Proportion of patients who meet current LDL-C treatment targets OR who are prescribed ≥1 lipid-lowering medications at maximum tolerated dose. (AHA/ACCF 2009)
- **Weight management:** Counseling to achieve and maintain ideal body weight at least once within the past two years. (AHA/ACCF 2009)
- **Blood pressure measurement:** Measurement of blood pressure in all patients. Patients for whom blood pressure (BP) measurement is recorded at least once in the last two years. (AHA/ACCF 2009)
- **Aspirin use in patients without clinical evidence of atherosclerotic disease who are at higher CVD risk:** Patients who were advised to use aspirin. (AHA/ACCF 2009)

METRICS DEVELOPED SPECIFICALLY FOR THE GUIDELINE ADVANTAGE

PREVENTIVE CARE AND SCREENING

- **Colorectal cancer screening:** The percentage of adults 50–75 years of age who had appropriate screening with tests and intervals (based on ACS guideline) for colorectal cancer.
- **Cervical cancer screening:** The percentage of women 21–69 years of age who received one or more Pap tests to screen for cervical cancer during the past 2 years.
- **Breast cancer screening:** The percentage of women 41-69 years of age who had a mammogram to screen for breast cancer.
- **Ongoing low-density lipoprotein (LDL-C) control:** Percentage of patients aged 18 years and older with a documented LDL-C ≥ 100 mg/dl and with a prior history of diabetes mellitus, peripheral artery disease, coronary artery disease, stroke or TIA whose most recent LDL-C level is in control (less than 100 mg/dl).
- **Calculate time to lipid control**
- **Preventive care and screening:** Percentage of patients aged 18 and older with prior history of peripheral artery disease, coronary artery disease, heart failure or prior stroke who had most recent LDL-C level in control (less than 100 mg/dl) who are on maximum dose statin or multiple lipid-lowering drugs.

The Continuity of Care Record (CCR) and Continuity of Care Document (CCD) are the standards for electronic health record interoperability. Initially, The Guideline Advantage anticipates collecting data from a number of sources, including the CCR and CCD, which capture the ICD-9/ICD-10 codes.

For purposes of this fact sheet, measures designated as "PQRS-comparable" denote those that are very similar to the PQRS measure specifications; however, they do not (at this time) rely on CPT or G-codes, as these types of codes are not collected by CCR/CCD. There may be EHR vendors and practices that do collect code sets besides ICD-9/ICD-10 codes and The Guideline Advantage will evaluate other code set data when available.

This fact sheet will be periodically updated and posted at guidelineadvantage.org to reflect changes to evidence-based guidelines and measures. Additionally, new measures will be added based on national priorities. Please check The Guideline Advantage website periodically to obtain the most current information, including updated fact sheets.

THE GUIDELINE ADVANTAGE™ FACT SHEET

OVERVIEW

The Guideline Advantage™ combines the expertise of the American Cancer Society, American Diabetes Association and American Heart Association (ACS, ADA, AHA) to advance prevention and disease management in the outpatient setting. The program promotes the use of evidence-based treatment guidelines, performance measurement tools and quality improvement strategies with the goal of helping you offer your patients every advantage for a healthy life.

The Guideline Advantage gives you a quality advantage as a health care provider and gives you the opportunity to offer your patients every advantage for a healthy life. With The Guideline Advantage you will:

- Have the benefit of state-of-the-art population health management technology
- Receive full advisory services for your data – mapping, cleansing and alignment
- Translate your patient data into action
- Create action lists for your practice
- View population snapshots by condition
- Accurately measure performance based on nationally recognized quality measures
- Compare your practice to national benchmarks
- See physician-level reporting or system-wide data aggregation
- Lay the groundwork for a value-based reimbursement model
- Be part of a national learning community

PROGRAM DESCRIPTION

The Guideline Advantage interactive platform gives you a powerful new data advantage. Now, you can not only meet your reporting requirements but also transition your practice into advanced population health management—an important new technology that offers you exciting potential to improve your patients' health. Couple this powerful solution with the robust resources of the American Cancer Society, American Diabetes Association, and the American Heart Association to support quality improvement efforts, your new data advantage provides everything your practice needs to move forward— with The Guideline Advantage.

MEASURES OVERVIEW

Measures provide the basis for evaluating and improving outpatient treatment. Initial selection of measures used in The Guideline Advantage program was based on review of nationally accepted ambulatory care measures. The program's measures will be reviewed and updated periodically to reflect measure maintenance, electronic health record (EHR) reporting changes and alignment with national programs. Beyond the measures included as part of the program, participants can add populations and measures to align with their priorities. If additional populations are added, corresponding changes may be made in data elements requested for collection.

The Guideline Advantage program includes two primary measure sets:

- Reporting Measure Set will be calculated with strict adherence to the definitions provided by the measure developer.
- The Guideline Advantage Common Measure Set is intended to provide quality improvement feedback based on a simplified version of established measures. These simplified versions of the established measures may have similar titles or measure descriptions to existing measures, but may have different measure constructs.

THE GUIDELINE ADVANTAGE COMMON MEASURE SET DEFINITIONS

CORONARY ARTERY DISEASE

LDL-C Test: Percentage of patients aged 18 years and older with an LDL test during the 12 month measurement period.

LDL-C Control: Percentage of patients aged 18 years and older with a diagnosis of CAD with most recent LDL-C <100 mg/dL.

Drug Therapy for Lowering LDL-C: Percentage of patients aged 18 years and older with a diagnosis of CAD who were prescribed a lipid-lowering therapy.

Antiplatelet Therapy: Percentage of patients aged 18 years and older with a diagnosis of CAD who were prescribed aspirin or clopidigrel.

Blood Pressure Screening: Percentage of patients aged 18 years and older with a diagnosis of CAD whose blood pressure was screened.

High Blood Pressure Control: Percentage of patients aged 18 years and older with a diagnosis of CAD whose blood pressure was adequately controlled (<140/90 mmHg).

High Blood Pressure Drug Therapy: Percentage of patients aged 18 years and older with a diagnosis of CAD whose blood pressure was greater than or equal to 140/90 mmHg and were prescribed 2 or more antihypertensives.

Tobacco Use Screening: Percentage of patients aged 18 years and older with a diagnosis of CAD screened for tobacco use within 24 months.

Tobacco Use Cessation Intervention: Percentage of patients aged 18 years and older with a diagnosis of CAD who are tobacco users that received cessation intervention within 24 months.

BMI Testing: Percentage of patients aged 18 years and older with a diagnosis of CAD with a BMI calculated within 6 months.

BMI Follow-up: Percentage of patients aged 18 years and older with a diagnosis of CAD with a BMI calculated within 6 months that is outside of the expected parameters and have a documented follow-up plan.

BMI Outside Expected Parameters: Percentage of patients aged 18 years and older with a diagnosis of CAD with a BMI within 6 months that is outside of the expected parameters.

CANCER SCREENING

Cervical Cancer Screening: Percentage of female patients aged 21 through 63 years who received one or more Pap tests within 3 years.

Colorectal Cancer Screening: Percentage of patients aged 50 through 75 years who received the appropriate colorectal cancer screening.

Mammography Screening: Percentage of female patients aged 40 through 69 years who had a mammogram to screen for breast cancer within 24 months.

DIABETES MELLITUS

Hemoglobin A1c Test: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus with hemoglobin A1c tested within 12 months.

Hemoglobin A1c Control: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus with their most recent hemoglobin A1c less than 7.0%, between 7.0% and 7.9%, between 8.0% and 9.0%, or greater than 9.0%.

LDL-C Test: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus with an LDL test within 12 months.

LDL-C Control: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus with most recent LDL less than 100 mg/dL.

Blood Pressure Screening: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus whose blood pressure was screened within 12 months.

High Blood Pressure Control: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus whose blood pressure was adequately controlled (<140/80 mmHg).

Urine Albumin Testing: Percentage of patients aged 18 through 75 years with a current diagnosis of diabetes mellitus with urine albumin tested within 12 months.

HYPERTENSION

Blood Pressure Screening: Percentage of patients aged 18 through 85 years with a diagnosis of hypertension whose blood pressure was screened within 12 months.

High Blood Pressure Control: Percentage of patients aged 18 through 85 years with a diagnosis of hypertension whose blood pressure was adequately controlled (<140/90 mmHg).

THE GUIDELINE ADVANTAGE COMMON MEASURE SET DEFINITIONS

ISCHEMIC VASCULAR DISEASE

Use of Aspirin or Other Antithrombotic: Percentage of patients aged 18 years and older with a current diagnosis of ischemic vascular disease (IVD) with documented use of aspirin or other antithrombotic.

LDL-C Test: Percentage of patients aged 18 years and older with a current diagnosis of IVD with an LDL test within 12 months.

LDL-C Controlled: Percentage of patients aged 18 years and older with a current diagnosis of IVD with most recent LDL-C less than 100 mg/dL.

PREVENTIVE CARE AND SCREENING

Blood Pressure Screening: Percentage of patients aged 18 years and older whose blood pressure was measured within 24 months.

Tobacco Users: Percentage of patients aged 18 years and older who are tobacco users.

Tobacco Use Screening: Percentage of patients aged 18 years and older screened for tobacco use within 24 months.

Tobacco Use Cessation Intervention: Percentage of patients aged 18 years and older who are tobacco users that received cessation intervention within 24 months.

Tobacco Use Pneumococcal Immunization: Percentage of patients aged 18 years and older who are tobacco users who have ever received a pneumococcal immunization.

BMI Testing: Percentage of patients aged 18 years and older with a BMI calculated within 6 months.

BMI Outside Expected Parameters: Percentage of patients aged 18 years and older with a BMI within 6 months that is outside of the expected parameters.

BMI Follow-Up: Percentage of patients aged 18 years and older with a BMI within 6 months that is outside of the expected parameters and have a documented follow-up plan.

Influenza Immunization: Percentage of patients aged 18 years and older who received or reported receipt of an influenza immunization.

LDL-C Test: Percentage of patients aged 18 years and older with an LDL test within 5 years.

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).

The Guideline Advantage Metric (GAM) score used for MedFocus was created to determine how well clinics are adhering to guidelines when treating patients. The total for this score is entirely dependent on what and how many medical conditions a subject has. For the purposes of this study a case report form was created specifically to capture the conditions that were of interest:

- Atrial fibrillation (Afib)
- Coronary artery disease (CAD)
- Diabetes
- Congestive heart failure (CHF)
- Hypertension
- Myocardial Infarctions (MI).
- Preventative Care and Screening

Blood pressure (BP) and blood pressure control is determined from an average of two BP readings. Sitting blood pressure will be measured at least three times at each study visit. If the 2nd and 3rd measurements differ by more than 4 mm Hg, a fourth measure will be taken. If three measures are taken, then the study BP is defines as the average of the 2nd and 3rd measures. If four measures are taken, the study BP is defined as the average of the two closest readings, excluding the first measurement. If four measures are taken, and the last three readings are equidistant apart, the study BP is defined as the average of the two highest readings. BP control is defined as follows:

- For subjects ≥ 60 years old, average systolic BP must be < 150 mm Hg AND average diastolic BP must be < 90 mm Hg.
- For subjects < 60 years old, average systolic BP must be < 140 mm Hg AND average diastolic BP must be < 90 mm Hg.
- For subjects with diabetes, regardless of age, the average systolic BP must be < 140 mm Hg AND average diastolic BP must be < 90 mm Hg.

The GAM score requires that a BP and an LDL be taken at least every two years. At baseline this would be the most recent clinic (chart recorded) BP documented in the medical record prior to the date of the baseline visit. At 12 months, this is the most recent clinic (chart recorded) BP that was documented in the medical record after the date of the BP measurements obtained at the Baseline visit and up to one day preceding the date of the 12 month visit. At 24 months, this is the most recent clinic (chart recorded) BP that was documented in the medical record after the date of the BP measurements obtained at the 12 month visit and up to one day preceding the date of the 24 month visit.

If a subject has not had any of the following atherosclerotic cardiovascular disease (ASCVD) events: stroke, transient ischemic attack (TIA), CAD, peripheral artery disease (PAD), or CHF, then an ASCVD risk score needs to be calculated. The Pooled Cohort Risk Reduction Equations calculator will be used to calculate the ASCVD 10yr risk score. This risk score will be used to determine the appropriate statin a patient should be taking, according to the AHA/ACC 2013 Cholesterol Guidelines. (Figure 1)Statin intensity is described in table 1. This score requires cholesterol and HDL values. At baseline these would come from the most recent clinic (chart recorded) lab values run prior to the date of the baseline visit. At 12 months these would come from the most recent clinic (chart recorded) lab values run after the test result obtained for the baseline visit and up to one day preceding the date of the 12 month visit. At 24 months these would come from the most recent clinic (chart recorded) lab values run after the test result obtained for the 12 month visit and up to one day preceding the date of the 24 month visit.

Table 1: AHA/ACC High-, Moderate-, and Low-Intensity Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C by approximately ≥50%	Daily dose lowers LDL–C by approximately 30% to <50%	Daily dose lowers LDL–C by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** (40) mg	**Atorvastatin 10** (*20*) **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** (80) **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** *Lovastatin 20 mg* *Fluvastatin 20–40 mg* Pitavastatin 1 mg

Bold = evaluated in RCTs and demonstrated a reduction in major cardiovascular events.

Italics = approved by the U.S. FDA but not tested in RCTs

Individual responses to statins might vary in clinical practice.

†Evidence from one RCT only (down-titration if unable to tolerate atorvastatin 80 mg)

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Point Distribution by Medical Condition:

Atrial Fibrillation:

- If patient is on warfarin
    - Must have a recorded INR an average of at least every 2 months: **1 point**

Coronary Artery Disease

    - Must have BP controlled**: 1 point**
    - Must have documentation that provider asked patient about dyspnea and chest pain**: 1 point**
    - Must either be free of chest pain or be on at least two anti-anginal medications**: 1 point**
- If BP is uncontrolled
    - Must be on at least 2 anti-hypertensive medications**: 1 point**
- If a patient has had a cardiac event in the last 12 months or has chronic stable angina
    - Must have participated in an early outpatient cardiac rehabilitation/secondary prevention program OR been referred to such a program**: 1 point**
- If a patient has also had an MI
    - Must be on a beta-blocker**: 1 point**
- If a patient also has diabetes
    - Must be on an ACE inhibitor or an ARB**: 1 point**

Diabetes:

- If patient is between the ages of 55-75
    - Must have a documented HbA1c within the last 12 months**: 1 point**
    - HbA1c must be < 7**: 1 point**
    - Must have had a dilated eye exam at least once in the last 12 months**: 1 point**
    - Must have had a foot exam at least once in the last 12 months**: 1 point**
    - Must have had a urine screening for microalbumin at least once in the last 12 months**: 1 point**
- If patient DOES NOT also have CAD
    - Must have BP controlled**: 1 point**
- **We will allow patient reported information for dilated eye exam and foot exam. All other information must be documented in the EMR.**

Heart Failure

    - Must have a document Ejection Fraction**: 1 point**
- If Ejection Fraction < 40
    - if patient does NOT also have CAD OR has CAD but does NOT have diabetes
        - Must be on an ACE inhibitor or an ARB**: 1 point**
    - If patient does NOT also have CAD OR has CAD but has NOT also had an MI
        - Must be on a beta-blocker**: 1 point**

Hypertension

- If patient does NOT also have CAD or diabetes
    - Must have BP controlled**: 1 point**

Preventative Care and Screening

All patients must meet the following criteria regardless of what conditions they have based on the eligibility for the MEDFOCUS study and their high risk for CV disease. **We will allow patient reported information with regard to influenza and pneumonia vaccinations.**

    - Must have a BMI < 25**: 1 point**
    - Must have had a tobacco screening in the last 12 months**: 1 point**
    - Must have documentation that provider asked patient about alcohol use in the last 24 months**: 1 point**
    - Must have had an influenza immunization during the most recent flu season**: 1 point**
    - Must have had an LDL cholesterol test in the last 2 years**: 1 point**
    - Must be on appropriate statin therapy**: 1 point**
    - Must have had a BP taken in the last 2 years**: 1 point**
    - Must be taking Aspirin or some other anticoagulant or antithrombotic**: 1 point**
- If patient is 75 years of age or younger
    - Must have had a documented colorectal cancer screening(any one of the following)**: 1 point**
        - Colonoscopy (flexible fiberoptic/optical) within the last 10 years
        - 3 Card Fecal Immunochemical Test (FIT) within the last year
        - 2 Card Fecal Immunochemical Test (FIT) within the last year
        - Flexible Sigmoidoscopy within the last 5 years
        - CT colonoscopy/CT colonography within the last 5 years
- If BMI is 25 or greater
    - Must have a documented weight plan within the last 6 months**: 1 point**
- If patient uses any form of tobacco
    - Must have had a documented smoking cessation intervention in the last 12 months**: 1 point**
    - Must have had an pneumonia immunization**: 1 point**
- If female and 63 years of age or younger
    - Must have had a documented cervical cancer screening within the last 3 years**: 1 point**
- If female and 69 years of age or younger
    - Must have had a documented mammogram within the last 2 years**: 1 point**

Figure 1. Major recommendations for statin therapy for ASCVD prevention