2. Candidate's Background

Commitment to a Career in Patient-Oriented Research. Dr. Safford began her focus on patient-oriented research in 1997, joining the Women's Health Initiative (WHI) as an investigator and quickly succeeding in obtaining her first extramural grant to study quality of care for persons with diabetes enrolled in managed care health plans and maintaining uninterrupted federal funding ever since. Her foundational WHI experience was strengthened by meeting the leaders in cardiovascular epidemiology at the American Heart Association Council on Epidemiology and Prevention Summer Program in Tahoe City, CA, including Drs. Beth Lewis and George Howard, both major influences in the decision to move in 2003 to the University of Alabama at Birmingham (UAB). In UAB's rich collaborative, interdisciplinary environment, she has engaged health services researchers, behavioral scientists, economists, biostatisticians and epidemiologists to build her program in observational outcomes research, quality of care and implementation science, focusing on the prevention of cardiovascular disease outcomes in chronic disease, especially in diabetes, and the elimination of racial/ethnic disparities in health care.

A consistent theme throughout Dr. Safford's work has been her commitment to mentoring junior clinical investigators as they build their own independent programs in patient-oriented research. In her career, Dr. Safford has prioritized both the conduct of patient-oriented research and mentoring others to do the same, making specific choices in favor of research over clinical and administrative activities. In fact, her unusual career path began as a clinician educator, including 4 years of private practice, prior to turning her energies to patient-oriented research 14 years ago. The committed funding of the K24 award will assure her ability to continue this highly productive career path.

Dr. Safford has demonstrated superior **ability to conduct high-quality patient-oriented research** which is rigorous and hypothesis-driven, with 159 scientific publications in the peer-reviewed literature in leading journals (22 since her initial application for this award). She has made contributions in health disparities and cardiovascular outcomes research,[1-15] as well as diabetes quality of care.[1, 16-33] She has developed conceptual frame works to guide studies of complex patients[34, 35] and of clinical inertia.[36] Her outcomes research has both an observational and an implementation trial component, briefly described next.

Her observational outcomes program is currently centered around the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national prospective cohort study including 30,239 Black and White community-dwelling adults recruited at age >45 between 2003-7. Through her NHLBI-funded R01 ancillary study, she added rigorously adjudicated acute coronary heart disease (CHD) outcomes to the rich REGARDS data. REGARDS used a highly innovative, centralized approach with a single operational center and a partnership with a national company to collect physiologic measures in participants' homes. This novel, cost-efficient approach engaged far fewer investigators than would normally be included in a study of this size, creating exciting opportunities for junior investigators. Dr. Safford has authored/coauthored 31 peer-reviewed manuscripts on REGARDS findings,[2, 13, 37-50] adding 11 since the first submission of this proposal, and has engaged a dozen junior investigators to conduct studies using this remarkable resource.

Dr. Safford's implementation trial program builds on more traditional clinical trials such as WHI and Look Ahead. In contrast to these latter *efficacy* trials, she is conducting real-world trials testing the *effectiveness* of behavioral strategies to improve cardiometabolic parameters in high-risk, vulnerable populations. Two currently funded trials make up the Encourage program, which are being conducted in the Alabama Black Belt region characterized by deep poverty, a rural setting, and large minority populations. These studies have also spawned a number of exciting projects for trainees.

In addition to her publication track record and record of grant awards, Dr. Safford's scientific abilities and judgment are recognized by leadership as Co-PI in the UAB Health Services Research Fellowship, which include a T-32 mechanism from AHRQ and additional Comparative Effectiveness trainee slots now totaling 18 fellows; her serving as Associate Director of UAB's Center for Outcomes and Effectiveness Research and Education; and her membership of various scientific review panels for NHLBI (serving on the K08 panel since 2008), American Heart Association and the VA. Her expertise has led to her being a sought-after collaborator on projects, currently splitting her effort among 16 projects, and she also has administrative duties as Assistant Dean for Continuing Medical Education (CME). These activities combine to diffuse her ability to focus on

mentoring and building her research program. This award will permit the candidate to consolidate her efforts, freeing time to devote to both continuing to build her research program and to mentoring the next generation of patient-oriented researchers.

3. Career Goals and Objectives.

Dr. Safford's short- and intermediate-term goals are to continue to build a patient-oriented research program bringing scientific rigor and innovation to the optimization of health for complex patients, with an emphasis on cardiometabolic diseases. The maximum benefit of such a program can only be achieved if it also involves training and mentoring of the next generation of investigators who combine a thorough understanding of the principles and challenges of outcomes research using both observational and interventional approaches with the ability to perform scientifically based and hypothesis-driven clinical research. More immediate goals are to build on the successful refunding of her R01 to include the expansion of the impact of the REGARDS study by supplementing it with existing data, including Medicare and Area Resource File data, both to expand the candidate's skill set and to expand the opportunities for trainees to conduct outcomes research. A parallel goal is to build on her current implementation trials of peer support and community health workers to spawn additional implementation trials in high-risk populations. Longer-term career development goals are to examine the feasibility of integrating peer support programs into primary care delivery models, including the patient-centered medical home, with the broader objective of integrating effective behavior change interventions into primary care. Dr. Safford plans to accomplish these goals while advancing to Professor of Medicine, with potential administrative responsibilities directing research and research training.

Mentoring Commitment

Dr. Safford has had a life-long dedication to furthering the career of younger professionals. Her deep commitment to teaching has in the past 15 years translated to a long record of successful mentoring of young scientists (Table 1 in Mentoring section). She is continually described by her mentees and in faculty evaluations as highly enthusiastic and encouraging of independent thinking. She seeks opportunities to influence young people to considering research careers at the earliest stages of education, incorporating honors high school students and honors university undergraduates into her research programs, including obtaining funding for summer student experiences. Her approach to mentoring includes a dedication to encouraging the mentee to develop an original hypothesis, plan a study, carry it out, and present it at a national meeting and in a peer-reviewed publication, emphasizing the skills needed to help potential investigators appreciate their strengths, and the wisdom needed to help them balance individual success with strong teamwork. Previous mentees now hold positions such as Director of Health Services Research (Dr. Kahler, Novartis), Director of a safety net hospital Diabetes Clinic (Dr. Heckemeyer), and Associate Professor with an active patient-oriented research program (Dr. Kertesz). See also letters of support from mentees in the Appendix, and the separate section on Mentoring.

Contribution of this Award to Attainment of Long-Term Career Objectives.

This award mechanism recognizes the time-intensive nature of effective mentoring, reflected in the specific steps in the Mentoring Plan. The candidate is an integral member of a busy research division that is entirely grant-funded, and her expertise has resulted in requests for multiple collaborations as well as an administrative leadership role of the UAB School of Medicine's Division of CMD, with the goal of building its research program. These activities leave less and less time for mentoring.

This Award is critically important to permit her to consolidate her efforts, ensuring that adequate time and effort can be provided to mentor trainees at all stages, but especially as they develop independence, as well as to continue to build the candidate's research programs and evolve her career. This is particularly important for her in order to support the mentored K-type awards of Drs. Brown, Halanych, Cherrington, Durant, and Levitan. The effort consolidation will also ensure focused time for Dr. Safford's own research program, permitting her to develop strategic plans and generate pilot data for her next steps to achieve her longer term goals.

Dr. Safford has worked with the PIs of several of her collaborative studies where she serves as co-investigator to find similar expertise and free up 15% effort (see shaded studies in the biosketch). She has also worked with the Senior Associate Dean for Education and the Dean of the School of Medicine to restructure the Division of

CME, resulting in the decision to hire a Director who will offload the administrative burden of the Assistant Dean of CME, freeing 10% additional effort. The position was posted in October 2011 and candidates are being interviewed at the time of the submission of this proposal. This solution reflects considerable institutional support and commitment to Dr. Safford's career development.

Evidence of Ongoing High-Quality Patient-Oriented Research and its Relationship to this Program.

The research plan in this application builds on the candidate's prior work in both the REGARDS and Encourage programs. The plan is designed to build skills for the candidate while greatly expanding the possibilities for trainees and young investigators to conduct independent research. The research plan has been adapted and extended from Dr. Safford's recently refunded R01 on acute CHD outcomes in REGARDS, as well as her implementation trials in the Encourage program. Its success is particularly relevant to the overall mentoring goals of the K24 Award. It uses a variety of data sources and analytic approaches to articulate hypothesis-driven studies of patient-oriented outcomes in both REGARDS and Encourage, taking advantage of the well-established interdisciplinary groups that are conducting these studies to carry out cutting-edge outcomes and comparative effectiveness research.

Evidence of Monetary Support for Patient-Oriented Research. The candidate's research studies, summarized below, now total $17,030,000 ($3 million more since the last submission) as Principal Investigator:

1997-2005	Coinvestigator, Women's Health Initiative RCT and observational study
1998-2003	PI, CDC U48: Translating Research Into Action for Diabetes, NJ site, observational study
2001-2003	PI, ADA Investigator Initiated Award: Case-Mix Adjustment of HbA1c observational study
2003-2015	Coinvestigator, NIDDK: Look Ahead study RCT
2005-2010	Co-PI, NIDDK R18: Rural Online Diabetes Care RCT
2006-2009	PI, VA Investigator Initiated Research: Intermediate Health Outcomes in Diabetes observational study
2006-2016	PI, NHLBI R01: REasons for Geographic And Racial Differences in Stroke-Myocardial Infarction (REGARDS-MI) observational study, refunded in May 2011 for another 5 years
2007-2010	Project PI, AHRQ U18: Osteonecrosis of the Jaws observational study
2009-2010	Project Co-PI, NIDCR U01: Screening for Diabetes in Dental Practices pilot study
2009-2011	PI, Peers for Progress Investigator Initiated Award: Community health advisors to improve diabetes outcomes RCT
2010-2013	PI, AHRQ R18: Comparative Effectiveness Reviews to improve quality of life for people with chronic pain and diabetes RCT
2011-2012	PI, Pfizer: Performance Improvement for Pain Management, education for physicians

The candidate's current R01 was competitively renewed on the first submission for a full five years, and her Encourage program, including a Peers for Progress-funded trial and an AHRQ-funded R18 trial will be used to develop new proposals beyond the funding period of this K24. Her track record of success in obtaining extramural funding is evident from the above record.

4. Career Development/Training Activities

Dr. Safford's career development will be greatly facilitated by the ability to consolidate her effort under this award, permitting her to focus more on continuing to build her own research program, integrated with mentoring activities. The new work proposed here includes the use of Medicare data; although she has previously worked as a team member in studies that included CMS data,[22, 23, 51-53] she has not previously led studies using these data. Therefore, she will continue her collaborations with the CMS Data Group at UAB, an ongoing $18 million contract with Amgen over 8 years to study both national data and 5% subsample data linked with Part D pharmacy data. The CMS Data Group is led by Drs. Elizabeth Delzell and Jeff Curtis, both close collaborators of Dr. Safford's with several joint publications already.[52-55] Dr. Safford will build her skills by focused study with this group in new areas including the use of skilled nursing facility data and Part D data, with which she has limited experience.

Dr. Safford will continue to be integral to the T32 Health Services Research Training program activities, continuing her active role as a lecturer in the Fellow Conferences on such topics as Implementation Science,

Conceptual Models, secondary data analysis and community-based trials. More detail on training activities are detailed in the Mentoring Plan.

5. Mentoring Plan – see separate enclosure

6. Research Plan

Dr. Safford's Research Plans center around the REGARDS study and the Encourage program. This section therefore first presents a brief overview of each study, followed by the proposed new research.

a. REGARDS and REGARDS-MI.

Brief Overview of REGARDS and REGARDS-MI.

The REGARDS Study's main goals are to identify associations with regional and racial variations in stroke and stroke mortality; NINDS has funded it from 2003-13 (plans for an extension through 2018 are underway). This community-dwelling cohort of 30,239 individuals age ≥45 was designed to represent all regions of the continental US, oversampling the Stroke Belt (20% from the coastal plain of NC, SC and GA, 30% from the remainder of NC, SC and GA plus TN, MS, AL, LA, AR); equal numbers of Blacks and Whites; and equal representation of women and men. Recruitment occurred from 2003-2007, resulting in a final cohort consisting of 42% Blacks and 55% women (Table 2). Participants were sampled from commercial lists of residents, using a combination of mail and telephone contact for recruitment. Of those in whom eligibility was determined, 49% agreed to participate; projecting similar eligibility onto those never reached,[56] the response rate would have been 33%, similar to response rates in other epidemiology studies.[57] After obtaining verbal informed consent, participants were screened and baseline risk factors established using a structured computer-assisted telephone interview (CATI). Written informed consent, physical characteristics (height, weight, etc.), physiological assessments (BP, pulse, 12-lead ECG, etc.), and biological specimens (blood, urine) were collected by sending health professionals to the participant's home. Self-administered questionnaires assessing dietary intake, family history, and psychosocial factors were left for return by participants to the REGARDS Operations Unit. Biosamples were shipped to the Laboratory for Clinical Biochemistry Research at the University of Vermont (M. Cushman, PI of UVM subcontract). See Appendix 2 for summary of baseline data available. To date, REGARDS has 21 funded ancillary studies.

REGARDS cohort retention and follow-up data.

Follow-up is conducted every 6 months by CATI. Stroke- or heart-related hospital and/or physician records, death certificates and information surrounding circumstances of death are collected by the Outcomes Unit, directed by Dr. Safford. We are able to retrieve 88% of records, a remarkable accomplishment in the HIPAA era.[39] Internet searches of the Social Security Death Index confirm the date of death, triggering an interview with next-of-kin focused on ascertaining cardiac symptoms and the circumstances surrounding the death.[13] To date, with a median follow-up >5 years, 89% of the cohort remains under study, higher than the projected 12% attrition rate at this point in the study (2% per year). Completion rates of expected follow-up interviews are near or above 80%. As of October 1, 2011, there have been 2783 confirmed deaths.

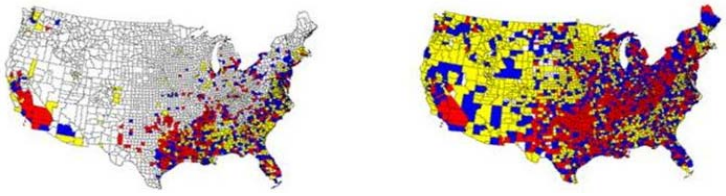


Figure 1. US Counties in low, medium and high tertiles of CHD mortality for blacks and whites age ≥45, CDC Wonder, 1999-2006. Low = Yellow. Blue = Medium. Red = High. White = too few residents for stable estimates. Agreement on high mortality tertile designation for blacks and whites is 0.56.

REGARDS-MI uses procedures to define endpoints modeled on epidemiologic studies such as the Atherosclerosis Risk In Communities (ARIC) study, the Multi-ethnic Study of Atherosclerosis (MESA) study, the Coronary Artery Risk Development In Young Adults (CARDIA) and the Cardiovascular Health Study (CHS) and national consensus statements[58] (see Appendix 3 for Adjudication Forms for MI and Death events). As of June

30, 2008, the end of the first 5 year observation period for REGARDS-MI, there are 651 primary endpoint events (definite/probable MI or acute CHD death). REGARDS-MI was competitively renewed in May, 2011 on the first submission for a full five years.

The main aims of REGARDS-MI are to define exposures that lead to racial and regional differences in incident fatal and nonfatal acute CHD events. In fact, from 1999 to 2006, Black-White mortality ratios for coronary heart disease (CHD) mortality actually grew from 1.23 to 1.27 for men and from 1.13 to 1.19 for women (CDC Wonder data). The REGARDS study includes Blacks from all over the US, not just the single community from which Blacks were drawn for the landmark ARIC study, one of the only previous sources of CHD incidence data in the US. Furthermore, county-level CHD mortality varies as much as 10 fold, a wider difference than that for stroke mortality; ARIC data cannot be used to examine causes for such regional differences due to the small number of geographic areas included. As a result, many years after the original observations were made, we still do not know why Blacks have lower MI incidence yet higher CHD mortality than Whites, nor why some regions of the US have much higher acute CHD mortality than others.[59] While the REGARDS-MI study's main aims are focused on racial and regional differences in CHD, it also serves as a rich resource for a wide range of additional analyses. Dr. Safford has already successfully encouraged a range of investigators, including many trainees, to conduct studies using REGARDS and REGARDS-MI data. The time and resources made available through this K24 award will enhance the already rich REGARDS resource with additional data, including Medicare, Area Resource File data and chart abstraction data, to advance Dr. Safford's program of research, providing excellent preliminary data to serve as pilot data for new projects for extramural funding, while further expanding training and career development opportunities. We describe the new research proposed under this award next, which will be supported by the REGARDS infrastructure, now extended for another 5 years, as well as the funds available from this award.

Table 2. REGARDS participant characteristics, by race, gender and CDC-defined CHD mortality region.

Characteristic	Low Mortality Region				Medium Mortality Region				High Mortality Region			
	BM	BW	WM	WW	BM	BW	WM	WW	BM	BW	WM	WW
N	1315	2237	3213	3303	1580	2573	3232	3171	1841	2944	2351	2384
%<65 years of age	58.1	57.4	44.6	51.2	53.2	56.3	44.8	50.8	48.5	52.3	47.2	52.0
% Annual Income <$20,000	19.5	32.5	6.5	14.2	20.1	32.8	8.6	16.9	20.5	28.2	8.3	18.1
% College Educated	27.3	25.3	51.4	39.5	24.8	23.0	46.0	33.0	27.1	26.8	43.2	32.2
% BP>140/90 mmHg	28.8	23.3	18.1	13.7	23.4	19.7	16.7	13.7	31.3	28.3	19.1	13.6
% with Diabetes	33.8	34.2	19.9	13.8	35.4	33.1	21.2	17.2	32.7	30.9	23.0	16.1
% Current Cigarette Smoker	21.8	14.8	10.9	12.1	21.1	16.0	12.4	13.9	18.0	16.7	12.1	14.6
% Never Exercise	29.2	39.7	26.2	35.8	30.8	41.6	25.3	37.6	32.8	43.4	28.5	40.7
% Obese (BMI >30 mg/kg^2)	38.3	55.8	28.6	30.0	36.9	55.3	30.4	34.8	35.2	55.0	32.2	33.4
% CRP >3 mg/dl	35.9	50.0	26.5	36.3	37.0	49.4	28.0	39.7	34.0	52.3	29.8	38.1
% Albuminuria >30 mg/dl	24.1	20.1	15.8	10.0	26.1	21.6	15.6	11.0	28.8	20.3	18.4	11.9

CHD=Coronary Heart Disease. BP=Blood Pressure. BMI=Body Mass Index. CRP=C-Reactive Protein. BM=Black Men. BW=Black Women. WM=White Men. WW=White Women. Mortality Regions=counties in low, medium and high mortality tertiles using CDC data.

New Study: The relationship between quality of care during acute coronary syndrome (ACS) and heart failure (HF) admissions and subsequent CHD outcomes (Trainees: Drs. Brown, Levitan [ACS] and Durant and Redmond [HF]).

Significance: As the experience with pay-for-performance (P4P) grows, evaluations of outcomes associated with better performance on the P4P quality indicators (QI) are beginning to emerge, revealing a mixed picture. Dr. Safford coauthored one of the first reports to demonstrate that high performance on QIs for diabetes are not necessarily associated with better outcomes,[27] an observation subsequently confirmed in other disease areas,[27, 60-63] resulting in calls for use of QIs that are tightly linked to outcomes.[63, 64] However, long-term outcomes studies to inform this policy discussion are difficult to conduct in the US because the health care system is so fragmented; REGARDS, with adjudicated outcomes and longitudinal follow-up on 30,239 individuals, linked with CMS data on a large subsample, offers such an opportunity. We propose to evaluate the relationship between hospital-based processes of care for ACS and HF, including CMS's 10 P4P QIs, and short- and long-term outcomes. While CMS's QIs are based on clinical trial *efficacy* evidence, there are limited data on the *effectiveness* of these QIs in under-studied subgroups such as women, Blacks, elders and individuals with chronic kidney disease (CKD), diabetes, or multiple conditions. Our results are designed to

inform the future selection of QIs with demonstrable impact on outcomes for broad groups of patients. Therefore, our **Specific Aims** are:

Aim 1) To examine variations in guideline-concordant processes of care for a) ACS and b) HF.
We **hypothesize (H1)** that guideline concordant care will vary by region (with lower concordance in areas of high acute CHD mortality); by hospital (with lower concordance among non-teaching hospitals and those with lower "report card" scores for ACS and HF QIs); and by patient factors (with lower concordance among Blacks, women, older individuals, or individuals with CKD, diabetes, or multiple conditions).
Aim 2) To better determine which QIs are most tightly linked with outcomes, we will examine associations between processes of a) ACS and b) acute HF management and short and long-term outcomes.
We **hypothesize (H2)** that following ACS or HF hospitalization, guideline-concordant care is associated with (for ACS) lower recurrent MI, stroke, HF, or CVD mortality (primary composite outcome); and (for HF) the same composite outcome, plus overall rehospitalization (primary outcomes). We also **hypothesize (H3)** that guideline-concordant care will be as effective in reducing longitudinal outcomes in individuals with CKD, diabetes or both, as in individuals with neither; and in older vs. younger patients.

Innovations include the unselected group of hospitals available for study; other studies are either limited to a single health system, i.e., Kaiser or the VA, or rely on voluntary reporting, i.e., the Get With the Guidelines initiative. The use of the REGARDS cohort for this project is also innovative due to the national reach including individuals who live far from academic medical centers in both urban and rural areas; the availability of self-reported and physiologic baseline data not available in database studies; the large proportion of Blacks, who are at high risk for poor outcomes; and adjudicated CVD endpoints, also not available in database studies.

Approach:

REGARDS data. The REGARDS study collected a wide variety of data at baseline, including patient-reported medical history, measures of stress and depression, health status and health behaviors (smoking, alcohol, exercise, medication adherence, diet); and physiologic data (blood pressure, lipids, glucose, creatinine, c-reactive protein, albuminuria, ECG, body mass index, waist circumference). These data will be critical in the complex covariance adjustment required to result in meaningful comparisons for studies of quality of care. Dr. Safford's extensive background and leadership on several studies of quality of care and the construction of novel quality indicators will be a strong foundation for this work.

We will also use REGARDS adjudicated outcomes data, including stroke, myocardial infarction, ACS, HF, CVD death and all-cause mortality to carry out the studies proposed in Aim 2.

Medical record review data. We will expand the medical record abstraction tool developed by Dr. Mundkur (see below and Appendix 4) that captures medications prescribed at hospital discharge to abstract additional data elements, shown in Table 3. We selected those that are most feasible within the limitations of the resources available under this award and within the REGARDS study. We will examine approximately 2000 ACS and 750 HF records that have already been collected by the REGARDS study, spreading the work over 3 years.

CMS data. REGARDS has purchased CMS data from the Research Data Assistance Center (ResDAC, University of Minnesota) for 2001-9 (with a contract to extend through 2012) including claims for inpatient, outpatient and physician services; hospice care; home health care; and skilled nursing facilities from 2001-2012; plus enrollment files including information on CMS eligibility, entitlements, HMO enrollment and vital status. We have been able to link data for 95.6% of CMS-enrolled REGARDS participants using data received to date (2003-2008). CMS data are usually available within ~2 years; 62% of REGARDS participants are expected to have at least one year of CMS data available by 2009.

While CMS claims data provide valuable information on medical illnesses, health services utilization and costs, they have limitations. For example, the 10-15% of CMS beneficiaries enrolled in HMOs will not have claims data available.[65] Since CMS data are collected for billing, reliability is an issue. The REGARDS informed consent included consent to link CMS data to REGARDS study data.

We will also obtain data on hospital-level QIs that have been voluntarily submitted to CMS, available through the Hospital Quality Alliance on-line (the source of "report card" data on each hospital).

The Area Resource File (ARF) is a collection of data from more than 50 sources, including the American Medical Association, the American Hospital Association, the US Census Bureau, CMS and the Bureau of Labor Statistics, and provides data at the county level on a host of variables that reflect available medical services, utilization of those services, and area-level environmental indicators. The ARFs are available from the Health Resources and Services Administration. ARF data will also expand the opportunities for future trainees to conduct additional studies relating access to care to high quality care and acute CHD outcomes.

Table 3. CMS, ACC/AHA and other QIs for ACS and HF, with current average rates at US hospitals.

Quality Indicator	Description	Rate
ACS		
BB at D/C[ab]	Documentation of BB Rx in D/C instructions or D/C summary	75%
Assessment of LVSF[a]	*See description under HF measures*	70
ACEI/ARB for LVEF <40%[ab]	*See description under HF measures*	65
Cardiac rehabilitation referral[a]	Documentation of referral in D/C summary or orders	59
Statin at D/C [a]	Documentation of statin prescription in D/C instructions or D/C summary	59
Counseling to quit smoking[ab]	Documentation of tobacco cessation counseling	59
Coronary angiography	Coronary angiography during hospitalization or within year prior to admission	50-60
Aspirin on arrival[ab]	Documentation of aspirin administration <24 hours from hospital admission or having received aspirin on the day of presentation at home or en route to the hospital	77
Timely reperfusion[ab]	Time from ED Triage to fibrinolytic administration <30 minutes Time from ED Triage to first device utilization in catheterization lab <90 minutes	35-45
Aspirin at D/C[ab]	Documentation of aspirin Rx in D/C instructions or D/C summary	90
Clopidogrel at D/C	Documentation of clopidogrel Rx in D/C instructions or D/C summary	40-50
Spironolactone for LVEF≤40% and DM/HF	Documentation of spironolactone Rx in D/C instructions or D/C summary if LVEF ≤40% in pts with either DM or HF	20
HF		
Assessment of LVSF[ab]	Echocardiogram, nuclear medicine test, or cardiac catheterization with LV-gram performed during hospital stay; one of above diagnostic test performed before arrival; LVSF documented, either as LVEF or as narrative qualitative description; plan to assess LVSF after D/C	86
ACEI/ARB in pts with LVSD[ab]	ACEI/ARB Rx at D/C in pts with EF <40% (or moderate-severe LVSD described)	72
Counseling to quit smoking[ab]	Documentation of tobacco cessation counseling in yr PTA OR Rx on D/C	43
HF D/C instructions[ab]	Written instructions/educational materials given to pt/caregiver at D/C for all 6: activity level, diet, D/C meds, f/u appointments, weight monitoring, what to do if sx worsen	24
BB Rx'd if LVEF≤35%	BB Rx at D/C in pts with EF <40% (or moderate-severe LVSD described)	83
Spironolactone Rx if LVEF≤35%	Spironolactone Rx at D/C in pts with EF <35% (or moderate-severe LVSD described)	20
Warfarin for pts with AF	Warfarin Rx for pts with AF or contraindication documented	30-40
Evaluation for ischemia	Documentation of coronary angiography or stress test	
Daily weights	Documentation of daily weights measured on at least ½ days during hospitalization	20-40
BP control	LV≤40% SBP<120 mmHg and DBP≤ 80; LV<40% SBP≤140 and DBP≤90	
ISDN+ hydralazine among AA[e]	ISDN/hydralazine combination Rx for AA with moderate-severe HF symptoms	5

ACC=American College of Cardiology. ACEI=angiotensin converting enzyme inhibitor. AF=atrial fibrillation. ARB=angiotensin receptor blocker. BB=beta-blocker. DBP=diastolic blood pressure. D/C=Discharge. DM=diabetes mellitus. ED=Emergency Department. ISDN= isosorbide dinitrate. ISDN=isosorbide dinitrate, LVEF=left ventricular ejection fraction. LVSD=LVS dysfunction. LVSF=LVS function. Pt=patient, Rx=prescribed. SBP=systolic BP. Yr=year. [a]ACC/AHA Performance Measure.[66, 67] [b]CMS hospital quality indicator for ACS or HF.[68] [c]Adherence based on available data from CMS and hospital registries.[69-72]

Preliminary work:

For many years, several organizations have endorsed a standard approach to reporting of troponin results by hospital laboratories, recommending that either the upper limit of normal or the lowest reliable level should be used in making decisions about troponin elevations, since even low elevations are clinically relevant.[58, 73-79]

Table 4. Odds ratios for receipt of medications among low vs. high troponin elevation groups

	Unadjusted		Adjusted[1]	
Medication Type	OR (95% CI)	p	OR (95% CI)	p
Beta Blocker	**2.5 (1.1, 5.5)**	**0.03**	**2.6 (1.1, 6.0)**	**0.02**
ASA/Plavix	1.7 (0.6, 4.3)	0.30	1.8 (0.7, 4.7)	0.25
ACEI/ARB	0.9 (0.5, 1.8)	0.84	1.0 (0.5, 2.0)	0.99
Lipid lowering agent	1.3 (0.6, 2.7)	0.44	1.5 (0.7, 3.2)	0.29

[1]Models adjusted for age, sex and history of MI. ASA=aspirin. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker.

However, we found that hospitals are continuing to use "indeterminate" ranges, which are no longer recommended; this complicates the clinical detection of low-troponin elevation MIs, or 'microsize' MIs. Dr. Brown led a study that showed that secondary prevention is less common in individuals with microsize MIs than in those with usual MIs (Table 4). The chart abstraction tool already includes 4 of the 10 ACS QIs, and we will expand it to add the remaining 6 and the 4 HF QIs, in addition to QIs as informed by Dr. Bittner (Appendix 4).

For Aim 2, 3291 REGARDS participants had CKD at baseline (CKD-EPI-estimated glomerular filtration rate <60 ml/min/1.73m^2), 6070 had diabetes, 1214 had both, and 1806 were over age 80.

Hypothesis testing:

For H1, we will construct a series of multi-level logistic regression models, with the dependent variable being each QI listed in Table 3 (and others as recommended by Dr. Bittner) among individuals who did not have a documented exclusion, and the independent variables being the exposures of interest (region, hospital type, patient factors). Additional patient-level covariates related to case-mix will be added to these models (Table 5). Power was estimated using the expected number of 2000 ACS cases and 750 HF cases. We anticipate that many regional, hospital and individual exposure prevalences will be near 50% or greater (see Table 3 for estimated adherence), providing 80% power to detect OR as low as 1.3 for ACS and 1.7 for HF. Clearly, some QIs with more restricted denominators, such as spironolactone for patients with low EF, will have more limited power; additional cases accrued over time will improve power.

The approach to testing the hypotheses proposed in Aim 2 will be a series of Cox proportional hazards models analyzing the time to first recurrent event for the composite outcome of recurrent MI, stroke, HF or CVD mortality. Analogous models will be constructed to analyze the time to first recurrent hospitalization for the HF QIs. The main independent variable will be whether the participant received the QI of interest. Separate models will be conducted for each of the QIs listed in Table 3. These models will be conducted initially without covariate adjustment, and then repeated with adjustment for confounders as listed in Table 5 to determine the independent association of adherence with the QI and longitudinal outcomes. With an expected number of ACS patients of 2000 and for the composite outcome, we will have 80% power to detect HR as low as 1.2-1.3 depending on QI adherence rates (Table 3) and median follow-up time. For 750 HF cases, we have 80% power to detect HR as low as 1.4-1.7 depending on QI adherence rates and median follow-up time. QIs with smaller samples will have more limited power. The renewal of the candidate's R01 for another 5 years will provide additional events, eventually permitting examination of each component of the composite outcome separately.

Table 5. Variables to be used to test hypotheses, by Aim and data source.

Aim	Hypothesis	Dependent Variables	Independent Variables
1. Variations in care	H1. Variations at regional, hospital and patient levels	Processes of care for ACS and HF(see Table 3)[a]	Region: acute CHD mortality region,[c] HPSA,[e] urban/rural[d] Hospital[d]: acute care beds, geographic location, intern:bed ratio, number of nurses, profit status, private status, academic affiliation, reports to GWTG, proportion of non-white patients Patient: *Biological factors*: Baseline[c] renal disease, diabetes, chronic lung disease, depression (CES-D), ECG, functional status (Short Form-12), BMI Medical record[a] [prior cardiac surgery, history of ischemic heart disease, pneumonia, BNP, LVEF, ECG, cardiac catheterization before index hospitalization, admission blood pressure, radiographic results, admission exam, daily weights] *Environmental factors:* distance between home and hospital[c] *Cultural factors*: gender, race[c] *Socioeconomic factors*: education, income, insurance type *Behavioral factors*: tobacco, alcohol, illicit drug use[a,c]
2. Process - outcome link	H2, H3. Process and longer term outcomes	*ACS:* CVD Mortality[a]; recurrent MI, stroke, or HF;[a,b] Revasc;[a] Comp's[a] *HF:* As for ACS, plus any readmission;[a,b] HF readmission;[a,b] HF mortality;[a] all-cause mortality[a]	Inpatient processes of care (Table 3)[a] Region: as for Aim 1 Hospital: as for Aim 1 Patient: as for Aim 1 Utilization: readmission,[a,b] ED/office visits after discharge,[b] medications in subsample with CMS and Part D

ACS=Acute coronary syndrome. BMI=body mass index. BNP=Brain-type natriuretic peptide. CES-D= Centers for Epidemiologic Studies Depression scale. CHD=Coronary Heart Disease. CKD=Chronic kidney disease. CMS=Centers for Medicare and Medicaid Services. Comp's=In-hospital complications. CVD= Cardiovascular disease. ED=Emergency Department. HF=Heart failure. HPSA=Health Professional Shortage Area. GWTG=Get With The Guidelines. LVEF=Left Ventricular Ejection Fraction. MI=Myocardial Infarction. Pt=Patient. QOL=Quality of life. Revasc=Revascularization. [a]Record review. [b]CMS data. [c]REGARDS baseline data. [d]Area level data. Shaded dependent variables for ACS are combined as the primary composite outcome, and will be examined separately as secondary outcomes. For HF, an additional primary outcome is any readmission.

Potential limitations, alternatives, future directions: As in all observational studies, these analyses will only establish associations and not causality. Self-reported data collected at REGARDS baseline, like all self-reported data, have well-known limitations. Although REGARDS used innovative approaches to recruit individuals from geographic regions distant from academic research institutions, participants may nevertheless not be representative of US blacks and whites. We anticipate that the large sample and wide geographic reach

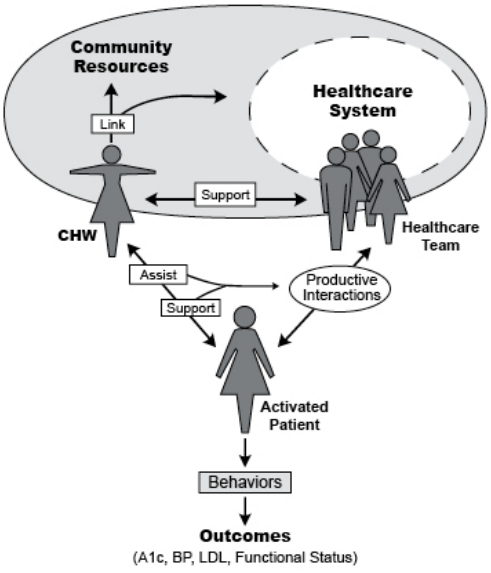
may improve on generalizability relative to past epidemiologic studies. The feasibility of the proposed study is well-demonstrated, since all the records are being collected through the infrastructure of the REGARDS-MI study, and the recent refunding for another 5 years assures ample additional records, which will boost the power estimated for the analyses above. Alternatives may be to use health insurance plan data, but these are not readily available. VA data could be used, but studies on veterans may be difficult to generalize. These proposed analyses build on the candidate's expertise in studies of the quality of care and limitations of currently used QIs, and will provide strong foundational studies for the candidate's future studies, as well as for mentees to establish their careers in patient-oriented CHD outcomes research.

The results of these studies will generate pilot data for a larger study that will include patient-reported outcomes such as functional status. Importantly, although the candidate has been part of teams using CMS and ARF data for analysis, she has never led teams in the use of these data. Thus, her skills in conducting research will be augmented through these new studies (see Career Development above). Mentees will learn principles of analyzing quality of care, including issues related to case-mix adjustment and outcomes; multivariable multi-level modeling techniques for cross-sectional analyses; time-to-event analyses; as well as issues related to the use of Medicare and ARF data.

b. Encourage.

The Encourage-1 and Encourage-2 implementation trials.

Figure 2. The CHW assisting, supporting and linking the client within the context of the Chronic Care Model.



These 2 trials are being conducted in the Alabama Black Belt, characterized by its rich soil, deep poverty and rural setting. Barriers to optimal chronic disease self-management faced by its predominately black residents (1/3 with diabetes) are substantial. Peer-delivered coaching interventions have shown promise in asthma, cancer and HIV, but there is less robust evidence of benefit for diabetes. Peer coaches provide assistance and support to community members, and their activities can be viewed within the context of the Chronic Care Model (Figure 1), linking individuals into the healthcare system and facilitating productive interactions with the healthcare team. Peer coaching is based on principles of empowerment with the goal of activating patients to become more engaged in their healthcare.

Encourage-1 is a randomized, controlled implementation trial testing the hypothesis that a peer-delivered coaching intervention will be superior to usual care in improving cardiometabolic parameters (BP, LDL-cholesterol, A1c) and quality of life among individuals with type 2 diabetes. We enrolled 423 adult participants (target: 400, see Table 6); all received a 1-hour diabetes education class, a culturally tailored cookbook with familiar healthy recipes, and additional educational materials. Participants randomized to the intervention arm also received a 10-month peer-delivered coaching intervention based on empowerment principles, with an 8-week intensive intervention phase of weekly telephone contacts with the peer coach, followed by a maintenance phase of monthly telephone calls thereafter. Additional calls before and after each physician visit were designed to optimize the interactions with the healthcare provider. Data were collected at baseline, 6 and 12 months, including a 1-hour face-to-face interview (see Appendix 4 for a copy), plus biometric data. We included in the assessments several items of interest to trainees, e.g., racial discrimination (Dr. Halanych) and cost data (Ms. Campbell). Peer advisors were trained over 2 days on motivational interviewing skills, diabetes basics, healthy eating, physical activity, stress reduction, human subjects in research, and the protocol and study forms.

Encourage-2 will be fielded in 2012-13, will also include 400 individuals, and is currently in the intervention development phase. It is also a randomized, controlled implementation trial and it will test the hypothesis that a peer coach-delivered intervention designed to improve functional status and empowerment will be superior in improving cardiometabolic parameters (BP, LDL-c, A1c) and functional status in individuals with type 2

diabetes and chronic pain, compared with usual care. Chronic pain is extraordinarily common in adults with type 2 diabetes, stems mostly from osteoarthritis, and is often overlooked by primary care providers.

New study: Intervention to optimize generic medication utilization (Trainees: Halanych, Cherrington, Sewell, Campbell).

Table 6. Characteristics of the 423 Encourage-1 trial participants.

Characteristic	All N=420	Intervention N=198	Control N=226
Mean age±SD, years	59.6 ± 12.8	59.4 ± 12.2	59.84 ± 13.3
% Women	75.9%	78.8%	73.4%
% Black	86.7%	94.0%	80.0%
% < High School Education	29.8%	31.3%	27.9%
% Income <$10,000/year	34.8%	36.9%	32.3%
% BP >130/80 mmHg	73.6%	76.6%	71.0%
% A1c ≥ 7.0%	60.9%	61.5%	60.3%
% LDL-cholesterol ≥100 mg/dl	58.9%	57.6%	60.0%

Significance: Effective interventions to improve medication compliance for chronic diseases are needed, since 50% of individuals with chronic diseases do not take medications as directed.[80-82] A recent Cochrane review observed that the existing literature on interventions to optimize medication adherence is "surprisingly weak."[83] The need for effective strategies is especially urgent in the Southeastern US (the site of our study), where risk factor levels are in worse control, and where chronic disease and CVD outcomes are worse than elsewhere in the country (see also REGARDS).[37, 84, 85] Medication costs are well described barriers to optimal adherence, contributing to suboptimal risk factor control.[86-88]

Pre-doctoral mentee Ms. Campbell observed that a large number of Encourage-1 participants were using costly brand-name diabetes medications with lower cost options, despite reporting very low income (see Table 6 and below). Consistent with past reports in other populations,[89-93] Ms. Sewell conducted focus groups with members of our target largely Black rural communities, revealing beliefs about lower effectiveness of generics and higher risk for side effects (see below). Based on Social Cognitive theory, overcoming such beliefs may best be accomplished by the use of peer coaches from the same communities. These observations form the foundation for the new study with peer coaches. A recent systematic review of 37 interventions to improve medication adherence found only one that used lay health workers, reporting sustained differences in adherence at 12 months among patients with ischemic heart disease;[94] many other interventions delivered by professionals were ineffective. Further, the use of peer testimonials was recently reported to be effective in lowering blood pressure in a Southern hospital.[95] We now propose to study whether an intervention designed to improve medication adherence delivered by peer coaches can improve adherence and generic medication use, and, thereby, cardiometabolic risk factors. Mentees were instrumental in collecting the preliminary data for this new study, in which they will learn principles of implementation trial design and collaborative, theory-driven intervention development, as well as community-based recruitment and retention strategies.

The **Specific Aims** of this new project will be to:

1) Work with community members to develop a culturally sensitive intervention designed to be delivered by peer coaches based on principles of empowerment, and including peer testimonials.
2) Pilot test the intervention among Black Belt residents with diabetes and uncontrolled blood sugar, hypertension or high cholesterol. If promising, a full intervention trial will be proposed for future funding.

We **hypothesize** that compared with general health counseling, a peer coach-delivered intervention based on principles of empowerment and including peer testimonials will result in 1) a significant increase in the prescription of generic pharmacologic alternatives and 2) improved medication adherence. If the pilot shows promise for the intervention, we will use these data to propose a larger study testing the effectiveness of the intervention in improving cardiometabolic risk factor levels, including A1c, blood pressure and lipid levels in this under-studied high-risk population living at the epicenter of not only the obesity and diabetes epidemics, but also a region of high stroke and acute CHD mortality.

Innovation: The use of peer supporters to encourage switches to generic medications is novel and innovative. The targeted population, rural Blacks living in the Southeast, is under-studied despite being at very high risks for poor health outcomes. The use of Diffusions of Innovation theory (see below) to guide the development of an intervention to enhance generic medication use is innovative in this population. The targeting of beliefs about generic medications as a strategy to enhance medication adherence is highly innovative.

Approach:

Preliminary data: *Adherence and A1c in Encourage-1.* We found that 51% (n=204) of Encourage-1 participants reported suboptimal medication adherence, and Ms. Campbell reported that 62% (n=127) of these 204 had opportunities for generic medication substitutions. On Morisky's adherence scale of 0-4, those with a 0 score (perfect adherence) had A1c=7.6%, those with scores of 1 had A1c=8.2%, scores of 2 had A1c=8.7%, and scores of 3 or 4 had A1c=10.0% (p for trend <.001). These data demonstrate that medication nonadherence is common in this population, as are substitution opportunities among the nonadherent, suggesting that improving adherence by making medicines more affordable could improve A1c.

Attitudes and beliefs about generic medicines. In June 2011, Ms. Sewell conducted 4 focus groups of Black Belt residents with a chronic disease and on at least one medication. No new themes emerged by the 3rd group, demonstrating saturation. Themes included the perception that generic medications were less effective than brand name medications; that the lower effectiveness required higher dosing resulting in more side effects; that "poor people have to settle" for generics; and that doctors were "experimenting on them" when they switched medications (manuscript under review). This qualitative work provides an excellent basis from which to design an intervention to encourage generic substitutions in this population.

Attitudes toward AHRQ Comparative Effectiveness Consumer Guides. Dr. Safford held discussion groups with Black Belt community members with diabetes to obtain feedback on the AHRQ Consumer Guides for oral diabetes medications and premixed insulin. Discussion group members expressed high interest in the Consumer Guides, which include comparisons between available medications on effectiveness, cost and side effect profiles. Community members valued the government source of the information, and rated the prices and side effect comparisons as being particularly helpful. They also expressed high confidence in generic medications after reading through the guides together. This qualitative work suggests that AHRQ Consumer Guides may be useful to provide content for an intervention designed to encourage generic substitutions.

Theoretical basis for the intervention: We plan to use Roger's Diffusion of Innovations and Bandura's Social Cognitive theories to guide intervention development. Roger's Diffusion of Innovations theory posits that innovations, including new ideas, beliefs, attitudes or practices spread through communication channels over time within a social system.[96] Black Belt communities have very closely knit social systems, making the use of this theory particularly attractive there. Many of our peer coaches are opinion leaders, creating a compelling setting for the use of peer coaches as the innovators and early adopters that can diffuse the "innovation", here the use of generics. Bandura's Social Cognitive theory is also relevant, since the coaches are members of participants' own communities, and their testimonials model the targeted behavior, facilitating to the participant's own movement toward change.[97]

Methods: To carry out Aim 1, we will work within our established community infrastructure to engage community members in a participatory, iterative process of intervention development over the course of six months. Community member perspectives are essential in the successful design of a culturally relevant, engaging intervention. We accomplish this by inviting onto the research team two members of the targeted community who now live and work in Birmingham. These team members provide ongoing input at investigator meetings and help us to shape the intervention. Our second strategy is to have a series of discussion groups with our peer coaches, presenting draft portions of the intervention for feedback and guidance, redrafting based on this feedback and continuing until few new suggestions are made.

Because this is an iterative process, the final form of the intervention is not yet known. However we do anticipate that the intervention will be delivered by peer coaches via telephone, given the distance barriers in these rural communities and how well-received this was in Encourage-1. We plan to videotape community members telling stories about their own use of generic medications, provided as part of the intervention on DVD's, as in Encourage-2. We preliminarily envision 6 weekly contacts, 4 before and 2 after a scheduled office follow-up visit. The initial contact will establish rapport and provide information on generic medications from trusted sources (e.g., AHRQ Guides). The next contacts will include watching peer testimonials as the prompt for discussions about the client's own issues related to medication adherence. The peer will use motivational interviewing to help the client establish and work towards realistic goals to improve medication adherence. A contact will occur within the week of the next scheduled office visit, and will include encouragement to plan to speak with the physician about identified barriers to adherence that could be overcome with the help of the physician, such as generic switches. Post-visit follow-up will likely focus on identifying unmet needs and

working collaboratively to problem-solve and develop plans to address needs, including linking back in to the doctor or pharmacist (see Figure 2).

To carry out Aim 2, we plan to conduct a pilot feasibility test of the intervention over the course of a year. We will train five peer coaches to deliver the intervention, modeled on our successful Encourage approaches, which included a two-day in-person training with telephone reinforcement monthly throughout the intervention period. Preliminarily, we anticipate that training will include education on generic medications, common misconceptions about generics from the focus groups, and the process of medication adjustment as an important strategy to create an acceptable regimen that achieves risk factor control. Coaches will be trained on the study protocol, motivational interviewing techniques, and principles of human subjects in research.

We will recruit 60 patients for the pilot trial. Targeted individuals will have diabetes and report poor medication adherence, with exclusions for advanced illness or pregnancy, or inability to speak English (rare in these communities). Our preliminary data (see above) indicate that about 60% of individuals with poor medication adherence will have generic switching opportunities for diabetes medications. We will use community-based recruitment as in our other studies, with preliminary screening eligibility cards administered by our community recruitment staff. Research team members conduct formal screening and eligibility checks. Consenting participants will be randomized, 30 to the peer coaching intervention, and 30 to the control condition (telephonic counseling sessions on general health issues).

Data will be collected at enrollment and 6 months after the intervention has been delivered. Medication adherence will be assessed using a validated self-reported scale at each data collection point, such as the Morisky scale.[98] A complete medication inventory, diabetes knowledge, and psychosocial factors will be collected at baseline and at follow-up, taking care to note brand vs. generic medications (Appendix 4), detecting medication changes. We will use an in-home data collection method adapted from the REGARDS study to collect data on A1c, blood pressure and lipids. Process data will permit assessment of how the intervention exerted its effects, including the workbooks used by coaches in their interactions with clients as well as interviews with clients and coaches both during the intervention phase and after its conclusion.

Analysis/Hypothesis test: Recruitment of 30 individuals per group will enable us to detect a group Morisky score difference of 0.33 with $\geq$80% power with 2-tailed alpha=0.05. The larger trial to be proposed after demonstrating feasibility will include multivariable analyses of the study outcomes, including cardiometabolic risk factor levels. The larger trial will be designed to detect clinically important group differences in A1c (0.4%), blood pressure (4 mm Hg systolic) and low density lipoprotein cholesterol (6 mg/dL) between the intervention and control arms. Because individuals are clustered within communities, the design will be a group-randomized trial. Accounting for clustering and attrition during follow-up, we anticipate a trial of 400 individuals.

Limitations, challenges and alternatives include the study's modest size and scope, in keeping with its pilot nature. We will use self-reported medication adherence because pharmacy data based adherence measures are not available. Dr. Muntner, a collaborator, is an expert in adherence studies (see letter).[99-106] We will examine new self-reported tools as they become available, since the Morisky scale has only modest internal consistency. Challenges include the rural setting and use of community members who are not trained research staff, but our previous studies demonstrate the feasibility of these partnerships. Intervention fidelity is always a challenge in community-based studies, and we will approach this in several ways. We develop notebooks for peer coaches that facilitate intervention delivery while doubling as process data collection tools. We conduct monthly booster training sessions to reinforce the protocol and provide additional training on skills. However, coaches do not always attend, and community coordinators provide one-on-one updating in these cases; the training may not be as effective when done by community coordinators. We also use the participants to assess intervention fidelity, asking them to report on the quantity of their interactions with their peer coaches, as well as their perceptions on several domains that reflect adherence to nondirective counseling. Alternatives to a peer-delivered intervention include a professional-delivered intervention, which generally achieves greater fidelity. However, professional-delivered interventions have had relatively disappointing results,[83, 94] and would be difficult to implement in rural Alabama. Furthermore, the beliefs about generic medications may be difficult to dispel by a professional, given the mistrust we observed in the focus group results. We considered quasi-experimental designs, which are an alternative when randomized trials are not feasible in community settings, but our past work has demonstrated the feasibility of the more robust design, thus we plan to use it again.

REFERENCES

1. Safford M, Eaton L, Hawley G, et al. Disparities in use of lipid-lowering medications among people with type 2 diabetes mellitus. *Arch Intern Med.* Apr 28 2003;163(8):922-928.
2. Safford MM, Halanych JH, Lewis CE, Levine D, Houser S, Howard G. Understanding racial disparities in hypertension control: intensity of hypertension medication treatment in the REGARDS study. *Ethn Dis.* Summer 2007;17(3):421-426.
3. Howard BV, Criqui MH, Curb JD, et al. Risk factor clustering in the insulin resistance syndrome and its relationship to cardiovascular disease in postmenopausal white, black, hispanic, and Asian/Pacific Islander women. *Metabolism.* Mar 2003;52(3):362-371.
4. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA.* May 28 2003;289(20):2673-2684.
5. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol.* Dec 15 2004;160(12):1152-1158.
6. Margolis KL, Manson JE, Greenland P, et al. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Arch Intern Med.* Mar 14 2005;165(5):500-508.
7. Valiyeva E, Russell LB, Miller JE, Safford MM. Lifestyle-related risk factors and risk of future nursing home admission. *Arch Intern Med.* May 8 2006;166(9):985-990.
8. Gold R, Michael YL, Whitlock EP, et al. Race/ethnicity, socioeconomic status, and lifetime morbidity burden in the women's health initiative: a cross-sectional analysis. *J Womens Health (Larchmt).* Dec 2006;15(10):1161-1173.
9. Tinker LF, Bonds DE, Margolis KL, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. *Arch Intern Med.* Jul 28 2008;168(14):1500-1511.
10. Brown TM, Hernandez AF, Bittner V, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program. *J Am Coll Cardiol.* Aug 4 2009;54(6):515-521.
11. Li R, O'Sullivan MJ, Robinson J, Safford MM, Curb D, Johnson KC. Family history of myocardial infarction predicts incident coronary heart disease in postmenopausal women with diabetes: the Women's Health Initiative Observational Study. *Diabetes Metab Res Rev.* Nov 2009;25(8):725-732.
12. Halanych JH, Safford MM, Kertesz SG, et al. Alcohol consumption in young adults and incident hypertension: 20-year follow-up from the Coronary Artery Risk Development in Young Adults Study. *Am J Epidemiol.* Mar 1;171(5):532-539.
13. Halanych JH, Shuaib F, Parmar G, et al. Agreement on cause of death between proxies, death certificates and clinician adjudicators in the REGARDS study. *Am J Epidemiology.* In press 2011.
14. Robinson JG, Wallace R, Safford MM, et al. Another Treatment Gap: Restarting Secondary Prevention Medications The Women's Health Initiative. *J Clin Lipidol.* Jan;4(1):36-45.
15. Salanitro AH, Funkhouser E, Agee BS, et al. Multiple uncontrolled conditions and blood pressure medication intensification: an observational study. *Implement Sci.*5:55.
16. Brown AF, Gerzoff RB, Karter AJ, et al. Health behaviors and quality of care among Latinos with diabetes in managed care. *Am J Public Health.* Oct 2003;93(10):1694-1698.
17. Duru OK, Mangione CM, Steers NW, et al. The association between clinical care strategies and the attenuation of racial/ethnic disparities in diabetes care: the Translating Research Into Action for Diabetes (TRIAD) Study. *Med Care.* Dec 2006;44(12):1121-1128.
18. Zhang Q, Safford M, Ottenweller J, et al. Performance status of health care facilities changes with risk adjustment of HbA1c. *Diabetes Care.* Jul 2000;23(7):919-927.

19. Kim C, Williamson DF, Herman WH, et al. Referral management and the care of patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) study. *Am J Manag Care.* Feb 2004;10(2 Pt 2):137-143.

20. Kim C, Williamson DF, Mangione CM, et al. Managed care organization and the quality of diabetes care: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care.* Jul 2004;27(7):1529-1534.

21. Kerr EA, Gerzoff RB, Krein SL, et al. Diabetes care quality in the Veterans Affairs Health Care System and commercial managed care: the TRIAD study. *Ann Intern Med.* Aug 17 2004;141(4):272-281.

22. Tseng CL, Helmer D, Rajan M, et al. Evaluation of regional variation in total, major, and minor amputation rates in a national health-care system. *Int J Qual Health Care.* Dec 2007;19(6):368-376.

23. Tseng CL, Rajan M, Miller DR, et al. Use of administrative data to risk adjust amputation rates in a national cohort of medicare-enrolled veterans with diabetes. *Med Care.* Jan 2005;43(1):88-92.

24. Thompson W, Wang H, Xie M, et al. Assessing quality of diabetes care by measuring longitudinal changes in hemoglobin A1c in the Veterans Health Administration. *Health Serv Res.* Dec 2005;40(6 Pt 1):1818-1835.

25. Brown AF, Gregg EW, Stevens MR, et al. Race, ethnicity, socioeconomic position, and quality of care for adults with diabetes enrolled in managed care: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care.* Dec 2005;28(12):2864-2870.

26. Pogach L, Xie M, Shentue Y, et al. Diabetes healthcare quality report cards: how accurate are the grades? *Am J Manag Care.* Dec 2005;11(12):797-804.

27. Mangione CM, Gerzoff RB, Williamson DF, et al. The association between quality of care and the intensity of diabetes disease management programs. *Ann Intern Med.* Jul 18 2006;145(2):107-116.

28. Ackermann RT, Thompson TJ, Selby JV, et al. Is the number of documented diabetes process-of-care indicators associated with cardiometabolic risk factor levels, patient satisfaction, or self-rated quality of diabetes care? The Translating Research into Action for Diabetes (TRIAD) study. *Diabetes Care.* Sep 2006;29(9):2108-2113.

29. Maney M, Tseng CL, Safford MM, Miller DR, Pogach LM. Impact of self-reported patient characteristics upon assessment of glycemic control in the Veterans Health Administration. *Diabetes Care.* Feb 2007;30(2):245-251.

30. Zhang Q, Safford M, Miller D, et al. Short-term statin exposure is associated with reduced all-cause mortality in persons with diabetes. *Med Care.* Apr 2007;45(4):308-314.

31. Heisler M, Tierney E, Ackermann RT, et al. Physicians' participatory decision-making and quality of diabetes care processes and outcomes: results from the triad study. *Chronic Illn.* Sep 2009;5(3):165-176.

32. Helmer DA, Tseng CL, Rajan M, et al. Can ambulatory care prevent hospitalization for metabolic decompensation? *Med Care.* Feb 2008;46(2):148-157.

33. Gregg EW, Karter AJ, Gerzoff RB, et al. Characteristics of insured patients with persistent gaps in diabetes care services: the Translating Research into Action for Diabetes (TRIAD) study. *Med Care.* Jan;48(1):31-37.

34. Safford MM, Allison JJ, Kiefe CI. Patient complexity: more than comorbidity. the vector model of complexity. *J Gen Intern Med.* Dec 2007;22 Suppl 3:382-390.

35. Safford MM, Brimacombe M, Zhang Q, et al. Patient complexity in quality comparisons for glycemic control: an observational study. *Implement Sci.* 2009;4:2.

36. Safford MM, Shewchuk R, Qu H, et al. Reasons for not intensifying medications: differentiating "clinical inertia" from appropriate care. *J Gen Intern Med.* Dec 2007;22(12):1648-1655.

37. Howard G, Cushman M, Prineas RJ, et al. Advancing the hypothesis that geographic variations in risk factors contribute relatively little to observed geographic variations in heart disease and stroke mortality. *Prev Med.* Aug-Sep 2009;49(2-3):129-132.

38. Howard G, Safford MM, Meschia JF, et al. Stroke symptoms in individuals reporting no prior stroke or transient ischemic attack are associated with a decrease in indices of mental and physical functioning. *Stroke.* Sep 2007;38(9):2446-2452.

39. Houser SH, Howard VJ, Hovater MK, Safford MM. Obtaining medical records from healthcare facilities under the HIPAA Privacy Rule: the experience of a national longitudinal cohort study. *Neuroepidemiology.* 2007;28(3):162-168.

40. Pullicino PM, McClure LA, Wadley VG, et al. Blood pressure and stroke in heart failure in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Stroke.* Dec 2009;40(12):3706-3710.

41. Pullicino PM, Wadley VG, McClure LA, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail.* May 2008;14(4):290-295.

42. Curtis JR, McClure LA, Delzell E, et al. Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender. *J Gen Intern Med.* Aug 2009;24(8):956-962.

43. Haley WE, Roth DL, Howard G, Safford MM. Caregiving strain and estimated risk for stroke and coronary heart disease among spouse caregivers: differential effects by race and sex. *Stroke.* Feb;41(2):331-336.

44. Cummings DM, Doherty L, Howard G, et al. Blood pressure control in diabetes: temporal progress yet persistent racial disparities: national results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Diabetes Care.* Apr 2010;33(4):798-803.

45. Meschia JF, Merrill P, Soliman EZ, et al. Racial disparities in awareness and treatment of atrial fibrillation: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke.* Apr 2010;41(4):581-587.

46. Brown TM, Voeks JH, Bittner V, Safford MM. Variations in prevalent cardiovascular disease and future risk by metabolic syndrome classification in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am Heart J.* Mar 2010;159(3):385-391.

47. Glasser SP, Wadley V, Judd S, et al. The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. *Clin Cardiol.* May 2010;33(5):280-288.

48. Muntner P, Judd SE, Krousel-Wood M, McClellan WM, Safford MM. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis.* Sep 2010;56(3):447-457.

49. Parmar G, Ghuge P, Halanych JH, Funkhouser E, Safford MM. Cardiovascular outcome ascertainment was similar using blinded and unblinded adjudicators in a national prospective study. *J Clin Epidemiol.* Oct 2010;63(10):1159-1163.

50. Durant RW, McClure LA, Halanych JH, et al. Trust in physicians and blood pressure control in blacks and whites being treated for hypertension in the REGARDS study. *Ethn Dis.* Summer 2010;20(3):282-289.

51. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care.* May 2004;27 Suppl 2:B10-21.

52. Curtis JR, Arora T, Matthews RS, et al. Is withholding osteoporosis medication after fracture sometimes rational? A comparison of the risk for second fracture versus death. *J Am Med Dir Assoc.* Oct;11(8):584-591.

53. Curtis JR, Arora T, Narongroeknawin P, et al. The delivery of evidence-based preventive care for older Americans with arthritis. *Arthritis Res Ther.*12(4):R144.

54. Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis.* Sep;17(9):1664-1669.

55. Yun H, Delzell E, Ensrud KE, et al. Predicting hip and major osteoporotic fractures using administrative data. *Arch Intern Med.* Nov 22;170(21):1940-1942.

56. Morton LM, Cahill J, Hartge P. Reporting participation in epidemiologic studies: a survey of practice. *Am J Epidemiol.* Feb 1 2006;163(3):197-203.

57. Mesa Public Search. Participation_10-13-2004.doc. http://www.mesa-nhlbi.org/MESASearch.aspx. Accessed April, 3, 2010.

58. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: A statement from the AHA Council on Epidemiology and Prevention, AHA Statistics Committee, World Heart Federation Council on Epidemiology and Prevention, European Society of Cardiology Working Group on Epidemiology and Prevention, Centers for Disease Control and Prevention, and the National Heart Lung and Blood Institute. *Circulation.* 2003;108(20):2543-2549.

59. Association AH. Heart Disease and Stroke Statistics - 2010 Update. http://www.americanheart.org/downloadable/heart/1265665152970DS-3241%20HeartStrokeUpdate_2010.pdf. Accessed October 15, 2010.

60. Serumaga B, Ross-Degnan D, Avery AJ, et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *BMJ.*342:d108.

61. Nicholas LH, Osborne NH, Birkmeyer JD, Dimick JB. Hospital process compliance and surgical outcomes in medicare beneficiaries. *Arch Surg.* Oct;145(10):999-1004.

62. Osborne NH, Nicholas LH, Ghaferi AA, Upchurch GR, Jr., Dimick JB. Do popular media and internet-based hospital quality ratings identify hospitals with better cardiovascular surgery outcomes? *J Am Coll Surg.* Jan;210(1):87-92.

63. Hawn MT, Vick CC, Richman J, et al. Surgical site infection prevention: time to move beyond the surgical care improvement program. *Ann Surg.* Sep;254(3):494-499; discussion 499-501.

64. Werner RM, Bradlow ET. Relationship Between Medicare's Hospital Compare Performance Measures and Mortality Rates. *JAMA.* December 13, 2006 2006;296(22):2694-2702.

65. Dafny L, Dranove D. Do report cards tell consumers anything they don't already know? The case of Medicare HMOs. *National Bureau of Economics Research* 2005. http://www.nber.org/papers/w11420.pdf. Published Last Modified Date|. Accessed Dated Accessed|.

66. Krumholz HM, Anderson JL, Bachelder BL, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction) Developed in Collaboration With the American Academy of Family Physicians and American College of Emergency Physicians Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. *J Am Coll Cardiol.* Dec 9 2008;52(24):2046-2099.

67. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics--2010 Update. A Report From the American Heart Association. *Circulation.* December 17, 2009 2009:CIRCULATIONAHA.109.192667.

68. Hospital Quality Compare - A quality tool provided by Medicare http://www.hospitalcompare.hhs.gov/Hospital. Accessed January 17, 2010, 2010.

69. Fonarow GC, Yancy CW, Heywood JT. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. *Arch Intern Med.* Jul 11 2005;165(13):1469-1477.

70. Yancy CW, Abraham WT, Albert NM, et al. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. *J Am Coll Cardiol.* Apr 29 2008;51(17):1675-1684.

71. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *Jama.* Nov 8 2006;296(18):2217-2226.

72. Krumholz HM, Baker DW, Ashton CM, et al. Evaluating quality of care for patients with heart failure. *Circulation.* Mar 28 2000;101(12):E122-140.

73. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* Nov 27 2007;50(22):2173-2195.

74. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* Oct 2007;28(20):2525-2538.

75. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation.* Nov 27 2007;116(22):2634-2653.
76. Urban P, Radovanovic D, Erne P, et al. Impact of changing definitions for myocardial infarction: a report from the AMIS registry. *Am J Med.* Dec 2008;121(12):1065-1071.
77. Morrow DA. Evidence-based decision limits for cardiac troponin: low-level elevation and prognosis. *Am Heart J.* Nov 2004;148(5):739-742.
78. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality. *Circulation.* Oct 23 2007;116(17):1907-1914.
79. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. *Circulation.* Feb 28 2006;113(8):1071-1078.
80. Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. *Annu Rev Nurs Res.* 2000;18:48-90.
81. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. *J Clin Epidemiol.* Dec 2001;54 Suppl 1:S57-60.
82. Rybacki JJ. Improving cardiovascular health in postmenopausal women by addressing medication adherence issues. *J Am Pharm Assoc (Wash).* Jan-Feb 2002;42(1):63-71; quiz 72-63.
83. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2008(2):CD000011.
84. Howard G. Why do we have a Stroke Belt in the Southeastern United States? A review of unlikely and univestigated potential causes. *Am J Med Sci.* 1999;317:160-167.
85. Howard G, Labarthe DR, Hu J, Yoon S, Howard VJ. Regional differences in African Americans' high risk for stroke: the remarkable burden of stroke for Southern African Americans. *Ann Epidemiol.* Sep 2007;17(9):689-696.
86. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA.* Jul 4 2007;298(1):61-69.
87. Gibson TB, McLaughlin CG, Smith DG. A copayment increase for prescription drugs: the long-term and short-term effects on use and expenditures. *Inquiry.* Fall 2005;42(3):293-310.
88. Gibson TB, Ozminkowski RJ, Goetzel RZ. The effects of prescription drug cost sharing: a review of the evidence. *Am J Manag Care.* Nov 2005;11(11):730-740.
89. Iosifescu A, Halm EA, McGinn T, Siu AL, Federman AD. Beliefs about generic drugs among elderly adults in hospital-based primary care practices. *Patient Educ Couns.* Nov 2008;73(2):377-383.
90. Huang ES, Brown SE, Thakur N, et al. Racial/ethnic differences in concerns about current and future medications among patients with type 2 diabetes. *Diabetes Care.* Feb 2009;32(2):311-316.
91. Shrank WH, Cadarette SM, Cox E, et al. Is there a relationship between patient beliefs or communication about generic drugs and medication utilization? *Med Care.* Mar 2009;47(3):319-325.
92. Babar ZU, Stewart J, Reddy S, et al. An evaluation of consumers' knowledge, perceptions and attitudes regarding generic medicines in Auckland. *Pharm World Sci.* Aug;32(4):440-448.
93. Piette JD, Heisler M, Harand A, Juip M. Beliefs about prescription medications among patients with diabetes: variation across racial groups and influences on cost-related medication underuse. *J Health Care Poor Underserved.* Feb;21(1):349-361.
94. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med.* Mar 26 2007;167(6):540-550.
95. Houston TK, Allison JJ, Sussman M, et al. Culturally appropriate storytelling to improve blood pressure: a randomized trial. *Ann Intern Med.* Jan 18;154(2):77-84.
96. Rogers E. *Diffusion of Innovations*. 4th ed. New York: The Free Press; 1995.
97. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Englewood Cliffs: Prentice Hall; 1986.
98. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care.* Jan 1986;24(1):67-74.

99. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. *Age Ageing.* Jul;39(4):481-487.
100. Krousel-Wood M, Islam T, Muntner P, et al. Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. *Ann Behav Med.* Dec;40(3):248-257.
101. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. *Am J Manag Care.* Jan 2009;15(1):59-66.
102. Krousel-Wood MA, Muntner P, Islam T, Morisky DE, Webber LS. Barriers to and determinants of medication adherence in hypertension management: perspective of the cohort study of medication adherence among older adults. *Med Clin North Am.* May 2009;93(3):753-769.
103. Krousel-Wood MA, Muntner P, Joyce CJ, et al. Adverse effects of complementary and alternative medicine on antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. *J Am Geriatr Soc.* Jan;58(1):54-61.
104. Muntner P, Joyce C, Holt E, et al. Defining the minimal detectable change in scores on the eight-item Morisky Medication Adherence Scale. *Ann Pharmacother.* May;45(5):569-575.
105. Muntner P, Judd SE, Krousel-Wood M, McClellan WM, Safford MM. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis.* Sep;56(3):447-457.
106. Muntner P, Mann DM, Woodward M, et al. Predictors of low clopidogrel adherence following percutaneous coronary intervention. *Am J Cardiol.* Sep 15;108(6):822-827.