<div align="center">**CAREER PLAN**</div>

1. INTRODUCTION

1.1 Career goal: My goal is to become a world-class health services investigator and expert in the treatment of patients with cardiac arrhythmias. I propose a mentorship plan and program of study that will enable me to 1) understand care of atrial fibrillation and atrial flutter (collectively referred to as "**AF**") in veterans; 2) develop interventions to improve care.

1.2 Clinical background: My research interests parallel my clinical expertise. I am a board-eligible cardiac electrophysiologist, board-certified cardiologist, and board-certified internist. My training includes three years of internal medicine residency at Harvard University's Brigham and Women's Hospital, three years of cardiology fellowship at the University of California San Francisco (UCSF), and two years of cardiac electrophysiology (EP) fellowship at UCSF. At the VA Palo Alto Healthcare System (VAPAHCS), I see patients in our new Arrhythmia Clinic, which is among the first of its kind in the VA system. I also perform invasive EP procedures for cardiac rhythm disorders, including catheter ablation and implantation of pacemakers, defibrillators, and cardiac resynchronization devices.

I am very fortunate to be recognized for my clinical expertise. In addition to 16 peer-reviewed research manuscripts, I have authored 11 review articles and book chapters. I have given 21 invited national and international talks on topics in cardiac electrophysiology. I was nominated for two consecutive two-year terms to the American Heart Association (AHA) Clinical Council Young Investigator's Committee and was a finalist for the AHA Laennec Society Young Clinical Award.

2. PREVIOUS RESEARCH EXPERIENCE AND FUNDING

2.1 Research experience

2.1.1 Pre-clinical experience: As an undergraduate biology and computer science student, I completed courses in engineering, computer science, mathematics, informatics, and physiology. I became interested in integrating these disciplines in medical research. I worked with Daniel I. Sessler MD (now Chair of the Department of Outcomes Research at the Cleveland Clinic) at the UCSF Outcomes Research Group and developed the first real-time signal processing system for human muscle electrograms and for measurement of cutaneous blood flow. My work led to co-authorship on five scientific papers[1-5] and the system is used by several research labs worldwide.

2.1.1. Experience during residency training

2.1.1.1 Hematologic biomarkers, angiographic risk scores, and myocardial tissue perfusion outcome in acute MI: During my medical residency, I became strongly interested in cardiovascular clinical trials and spent two years as a research associate with the Thrombolysis in Myocardial Infarction (TIMI) study group. Under the mentorship of C. Michael Gibson, MS, MD, I performed a pooled analysis of 1200 patients from 4 randomized trials investigating the relationship between serum biomarkers and TIMI flow grade to myocardial tissue perfusion. This work culminated in three manuscripts[6-8] (one first-author, one second-author, one middle-author), two presented abstracts, and one book chapter.[9] I created two Phase I and II research protocols to study novel therapies for atherosclerotic plaque stabilization and arrhythmia monitoring. I participated in regular research meetings with other senior TIMI investigators including Drs. Eugene Braunwald and Elliott Antman.

2.1.1.2 Validation of cardiac stress magnetic imaging to silent ischemia and tissue perfusion: I extended these lines of investigation during residency and worked with Scott Solomon, MD MPH, and Raymond Kwong, MD, MPH, to perform validation studies of magnetic resonance imaging for myocardial perfusion, leading to two presented abstracts. I also developed a research protocol to assess for silent myocardial ischemia in diabetic patients. I acquired hands-on experience in clinical trial design and operations, introductory biostatistics, clinical databases, manuscript writing and abstract presentation.

2.1.2 Experience during fellowship training

2.1.2.1 Formal research training and transition to outcomes and health services research: During my cardiology fellowship, I learned how to use cutting-edge technologies to treat heart disease.

Sometimes, these therapies were employed with limited clinical evidence to support their use. I became interested in studying efficacy and outcomes of arrhythmia therapies. With my program's support, I postponed my EP clinical training by one year to have protected research time and pursue formal research training.

2.1.2.2 Master's Degree in Clinical Research (refer to Appendix A for a list of courses): In 2005, I started a two-year program for a Master's in Advanced Studies in Clinical Research sponsored by the UCSF Department of Epidemiology and Biostatistics. My program advisors were Stephen Hulley MD MPH, Jeff Olgin MD and Mary Whooley MD. Over 8 quarters, I completed 24 courses in epidemiologic methods, clinical trial design, database management, biostatistics, statistical methods, systematic reviews, grant and manuscript writing, genetic epidemiology, outcomes research, ethics, and a biweekly Master's research and career development seminar. Through formal coursework, my own research projects, and independent study, I became facile with using STATA for data manipulation and regression techniques.

2.1.2.3. Recipient of American College of Cardiology-Merck Foundation Postdoctoral Research Award: Working with Jeff Olgin MD, my program director and research mentor, I developed a clinical research proposal to examine predictors of ventricular arrhythmias after myocardial infarction. I designed the study, drafted the research protocol and CHR applications, enrolled subjects, and performed preliminary analyses. My work was incorporated into a larger genetics study underway[10] and served as the foundation of my own projects evaluating utilization and outcomes of implantable cardioverter-defibrillators (ICDs).[11-13] I also completed a first-author review article on sudden cardiac death.[14]

2.1.2.4 Predictors of mortality in patients with implantable cardioverter-defibrillators (ICDs) for primary and secondary prevention: Working with Jeff Olgin, MD, I examined predictors of mortality in 500 subjects with ICDs implanted at UCSF over an 11-year period. I gained hands-on experience with complex data manipulation, including data merging from four different relational databases, and I independently performed the statistical analyses. My first project examined the influence of renal insufficiency on survival in patients with ICDs. This work led to one first-authored manuscript[15] and an invited lecture at the 2008 Heart Rhythm Society international meeting. In another study, we studied the impact of advanced age on outcomes and cost-effectiveness in patients with ICDs, leading to a third-authored manuscript.[11]

2.1.2.5 Predictors of sudden cardiac death in veterans with coronary disease and normal systolic function: The Heart & Soul Study: Working with Mary Whooley MD (co-mentor), I examined echocardiographic and electrical predictors of sudden cardiac death in a cohort with stable coronary artery disease. Under her mentorship, I independently performed all data manipulation, statistical analyses and writing, resulting in a first-authored manuscript.[12] I have submitted another first-authored manuscript evaluating ventricular volume reversal and mortality.

2.2. Previous Peer-Reviewed Research Funding

All of these grants provided less than $50,000 of funding support.

2.2.1 UCSF-Howard Hughes Medical Institute Instructional Technology Grant (1999-2000): During medical school, my interest in medical informatics motivated me to develop the first-ever online database of peer-reviewed medical education websites, for which I received an informatics grant. The website has expanded to be the central portal for the UCSF Medical School curriculum.

2.2.2 American College of Cardiology-Merck Foundation Postdoctoral Research Award (2005-2006): I received this fellow-level (postdoctoral) grant to spend one dedicated research year to pursue a Master's Degree in clinical research.

2.2.3 NIH Postdoctoral Clinical Research Educational Loan Repayment Program (2005-2008) L30 HL082386-01/02: This peer-reviewed award repays the educational debt of applicants who perform patient-oriented research. I received this award and a renewal (three years total) to perform the above-mentioned projects. This award provided no research or salary support. The NIH repays educational loan debt directly to lenders.

2.3. Other Research Accomplishments: In 2004, a small group of volunteer physicians and I created the non-profit *South Asian Heart Center* in Northern California to provide cardiovascular

screening to persons of origin from the Indian subcontinent, a population at high risk for premature coronary artery disease. As the Research Chair, I led a team of volunteer investigators to launch a large cohort study. I directed the study design, database creation, and I drafted the operating protocols and consent forms. Recently, I directed the creation of a tissue banking protocol for DNA and plasma storage. I independently performed interim data analyses. The study is privately funded and has enrolled 1800 participants. In order to focus on arrhythmia health services research, I am no longer the principal investigator but remain actively involved on a volunteer basis. This four-year experience has given me practical experience in implementing large cohort studies.

3. CURRENT RESEARCH INTERESTS

For specific research projects relevant to this proposal, please refer to section 5 (Preliminary Data) of the Research Plan (§5.1-5.5). My move to VAPAHCS and Stanford University has enabled me to pursue new lines of inquiry in EP that build upon work accomplished at UCSF. I remain active in ongoing research collaborations and projects only 40 minutes away at UCSF and the San Francisco VA Medical Center. The central theme of my research is quality of care and outcomes of treatment of heart rhythm disorders in veterans.

3.1. Adherence to anticoagulation guidelines in veterans with stable coronary heart disease: Antiplatelet therapy after percutaneous revascularization (stenting) for secondary prevention of coronary disease may inappropriately influence discontinuation of warfarin in patients with atrial fibrillation. Working with Mary Whooley MD, I am examining the relationship of stroke risk factors and antiplatelet use to the outcomes of anticoagulation use, guideline concordance, and incident stroke in a cohort of 1024 subjects with stable coronary disease.

3.2. Rate control and mortality in veterans with AF: Using three separate cohorts of veterans with atrial fibrillation during Holter monitoring, treadmill testing, and resting electrocardiograms, I am investigating the relationship of uncontrolled ventricular rate, antiarrhythmic drugs use, and rate control drug use to incident heart failure, ventricular arrhythmias, and mortality.

3.3 Stroke prevention in atrial fibrillation - impact of mental illness: Although this project was started in 2005, I joined the research team as a co-investigator in the summer of 2008 and am fully integrated into the project. For a secondary study, I am examining the association of VA facility anticoagulation care volume with time in therapeutic range.

3.4. Dual use and outcomes in AF: During our work on project **3.3**, we noticed that a large proportion of veterans were receiving anticoagulation in both VA and non-VA Medicare facilities. Veterans with dual care for anticoagulation monitoring had higher unadjusted mortality. With the same research team and mentors in project 3.1, we are submitting an IIR-MERIT (HSR&D, PI: Frayne) to further explore these findings. The project, for which I have proposed 10% effort as co-investigator, will fund the creation of an updated set of VA and Medicare administrative data. The work proposed in Objective 2 (Research Plan §6.3) will dovetail from this project and capitalize on the use of this new dataset.

3.5 Systematic review of microvolt T-wave alternans (MTWA) testing: Working with Leah Karliner MD MS and Jeffrey Tice MD at UCSF, I am first-authoring a systematic review and technology assessment evaluating the role of MTWA in risk stratification for sudden cardiac death.

3.6 Impact of gender on survival after primary prevention ICD implantation: Working with Jeff Olgin MD, I am completing a study to determine adjusted survival on women versus men in a cohort of 600 patients receiving ICDs from a single center.

4. VA SERVICE AND OTHER INVOLVEMENT

4.1. Previous VA Service: My introduction to the Veterans Health Administration was in 1997, when as a second-year UCSF medical student, I had the privilege of one-on-one weekly rounds with Dr. John Ziegler, Emeritus Professor of Medicine, at the San Francisco VA Medical Center (SFVAMC) skilled nursing facility. He taught me the importance of learning the stories of veteran patients. I began to appreciate how experience in the armed forces impacted the life and health of our servicemen and women. As a third-year medical student, I met Dr. Edmund Keung, Director of the SFVAMC Electrophysiology Service and Director of the VA National Implantable

Defibrillator Surveillance Registry. He was the first mentor to cultivate my interest in cardiac electrophysiology, and he allowed me to participate in his pacemaker clinic as a medical student. During my internal medicine residency at Brigham & Women's Hospital, I spent 30% of my clinical time at the West Roxbury VA Hospital on the medical, intensive care, and cardiology services. During a large winter storm of 2004, I volunteered to take consecutive overnight calls in the hospital to prevent closure of emergency services to veterans. As a cardiology and cardiac electrophysiology fellow at UCSF, I spent 30% of my clinical time at the SFVAMC, which included a 3-year longitudinal cardiology continuity clinic. These experiences have solidified my interest in continuing to care for veterans.

4.2 Current VA Service: In August 2008, I started as a full-time invasive cardiac electrophysiologist at the VAPAHCS (8/8ths). I see patients in our new VA Electrophysiology and Arrhythmia Clinic, and I perform invasive EP procedures. In my clinic, I precept medical students, residents, cardiology fellows, and EP fellows. I also run our weekly *"arrhythmia rounds"* for the housestaff. Our EP program includes one other full-time non-invasive electrophysiologist (Karen Friday MD), two additional part-time invasive electrophysiologists based at Stanford University (Henry Hsia MD, Paul Zei MD), one nurse practitioner, two electrocardiography technicians, two dedicated EP lab technicians

5. RELATIONSHIP BETWEEN APPLICANT'S INTERESTS & SKILLS AND MENTORS':
Additional details of the mentoring plans are outlined in support letters.

5.1 PRIMARY MENTOR: Paul Heidenreich, MD MS is a cardiologist at VAPAHCS and Associate Professor of Medicine and of Health Research and Policy at Stanford University. He is an HSR&D Career Development Award recipient and Director of the Echocardiography Laboratories of VAPAHCS. He is Research Director of the Chronic Heart Failure QUERI. Dr. Heidenreich is an investigator on four projects relevant to this proposal: 1) Stroke Prevention in Atrial Fibrillation - Impact of Mental Illness (HSR&D IIR 04-248; Co-investigator); 2) Variation in VA compliance with heart failure guidelines (LIP/OQP); 3) Dual Use: Safe in AF (HSR&D IIR proposal; Co-Investigator); 4) National implementation of a clinical reminder system in cardiac ultrasound reports for beta blocker use in heart failure (Funding: LIP). He has completed and published two randomized trials on the use of clinical reminders for medication guideline compliance in chronic heart failure.[16-19] He has 162 peer-reviewed publications and was the Chair of the Task force that oversaw publication of the ACC/AHA key data elements and definitions for measuring clinical management and outcomes of patients with Atrial Fibrillation.[20, 21]

Dr. Heidenreich will provide strong, broad, and detailed mentorship across several areas: content (health services research, processes and quality of care research), methods (administrative dataset manipulation, statistical methods, clinical trial design and implementation, clinical support instrument design and validation), professional development (research team management, manuscript and grant writing, VA leadership, society and guideline committee leadership, progression toward research independence). He will continue to meet with me weekly along with informal and ad-hoc meetings. Our research block schedules are well synchronized, and our offices are a 7-second walk from each other.

5.2 CO-MENTOR: Susan Frayne, MD MS is an internist at VAPAHCS, Associate Professor of Medicine at Stanford University, and an Associate of the Stanford Center for Health Policy and Center for Primary Care Outcomes Research. She is a prior HSR&D CDA recipient and has expertise in evaluating processes of care, quality measures, access to care[22], gender disparities[23, 24], and outcomes using administrative data. Her research focuses on health care disparities and quality of care in patients with mental health conditions. She is the PI on two relevant projects on which I am a co-investigator: 1) Stroke Prevention in Atrial Fibrillation - Impact of Mental Illness (HSR&D IIR 04-248); 2) Dual Use: Safe in AF (HSR&D IIR proposal). For Project 1, Dr. Frayne and her team constructed the Treatment of Atrial Fibrillation in Mental Health (TEAM) database, which I will use for Objective 1 of this proposed award. Project 2 will fund the creation of a new linked VA-Medicare dataset, which will be one of several data elements used for Objective 2 of this proposed award. Dr. Frayne will provide methodological expertise in administrative dataset linking and manipulation, variable construction, adjustment

methods, manuscript preparation, grant writing, and professional development. I will meet one-on-one with Dr. Frayne weekly, in addition to weekly investigator meetings for the above projects.

5.3 CO-MENTOR: Ciaran Phibbs, PhD is a health economist at the VA Health Economics Resource Center, Center for Health Care Evaluation, and the VA Cooperative Studies Program Coordinating Center. He is Consulting Associate Professor in the Department of Health Research and Policy at Stanford University. Dr. Phibbs has expertise in linking, manipulating, and analyzing large datasets for health services research. He has been a member of the VIREC's advisory panel, which oversees use of merged VA and Medicare data for VA research. Dr. Phibbs has a long-standing interest in facility-level predictors of quality of care[25-28] and in quality of anticoagulation care in AF. Dr. Phibbs is a co-investigator on Dr. Frayne's above-mentioned projects, for which he is responsible for database preparation and statistical analysis. He is also the health economist and Co-Investigator for a VA cooperative multi-center randomized trial of point-of-care anticoagulation monitoring in AF.[29] Dr. Phibbs will provide mentorship in manipulation of large databases, use of administrative data, statistical modeling and regression methods, case-mix adjustment, and sensitivity analysis. Dr. Phibbs will provide "hands-on" tutorial with database manipulation, linking, statistical analysis, and STATA and SAS programming. Dr. Phibbs and I will meet separately as needed (twice per month initially) following our research team's weekly meetings.

5.4 CO-MENTOR: Mary Whooley, MD MS is Professor of Medicine at the University of California, San Francisco, Staff Physician at the San Francisco VAMC, and PI of the Heart & Soul Study. She is a former recipient of VA HSR&D RCD (1998-2001) and ARCD (2001-2004) awards, two VA Epidemiology program MERIT awards (1998-2003; 2003-2009), and an NIH R01 (2005-2010). Since 2005, I have been working with Dr. Whooley on arrhythmia risk prediction and outcomes in the Heart and Soul Study. Dr. Whooley was a mentor and research advisor during my Master's Degree program. She will mentor me in areas of study design, outcomes adjudication, data collection techniques, survey instrument design, scientific writing, and general mentorship in becoming an independent academic investigator in the VA system. I will have periodic meetings with Dr. Whooley, at least once per month with additional meetings as needed.

5.5 CONSULTANTS:

5.5.1. Mary Goldstein MD, MS is an internist and Professor of Primary Care Outcomes Research and Health Research and Policy at Stanford University. She is Director of the Geriatrics Research Education and Clinical Center (GRECC) at the Palo Alto VA Health Care System. Dr. Goldstein has a strong background in analysis of VA pharmacy data for quality of care research[30-34], guideline implementation, and intervention studies of improving guideline adherence.[35] Dr. Goldstein is a co-investigator with Dr. Heidenreich on echocardiographic reminder studies in heart failure.[17] She will contribute her expertise in informatics, reminder instruments, and implementation research. In addition, she will maintain in advisory role regarding career development within HSR&D, funding, and leadership.

5.5.2. Dawn Bravata MS MD is an internist, Associate Professor of Medicine at the Indiana University School of Medicine and Clinical Coordinator of the VA HSR&D Stroke Quality Enhancement Research Initiative (QUERI). Dr. Bravata will be the primary link to the Stroke QUERI team. She will provide expertise diagnosis extraction for stroke and hemorrhagic outcomes and will help to facilitate cross-QUERI collaboration.

5.5.3. Vic Froelicher MD is a cardiologist and Professor of Medicine at Stanford University. He is Director of the Exercise Physiology Consortium and Director of the Electrocardiography, Holter Monitoring, and Exercise Testing Laboratories at the Palo Alto VA Health Care System. Dr. Froelicher has 327 peer-reviewed manuscripts and has extensive clinical and research experience in customizing Electrocardiogram and Holter Reports in the VA system for over 10 years. He will provide expertise and guidance in designing and implementing Electrocardiogram, and Holter-based reminder systems for Objective 3.

6. IMPACT ON VETERAN HEALTH CARE AND POLICY AND BENEFIT TO VA

There are numerous potential benefits. AF is exceptionally common among veterans, but care of AF is highly variable. Understanding these patterns of care and their impact on outcomes

(Objective 1) would be the first step in improving quality of AF care in the VHA. Determining the relationship of processes of care with outcomes will allow us to define best-practice guidelines for the VHA, which could lead to dramatic reductions in embolic stroke and hemorrhage. Objectives 2 and 3 address a major clinical dilemma, which is how AF arrhythmias should be managed in veterans. There are currently no VA guidelines on selection of arrhythmia management strategy, indications for referral to specialty care (cardiology or cardiac electrophysiology), or use of invasive therapies, such as catheter ablation or pacing. As the burden of AF expands in the VHA and as cardiac electrophysiology continues to grow as a specialty, the time is ripe to evaluate quality of AF care, determine the effectiveness of non-invasive and invasive therapies, and implement measures to improve outcomes.

In addition, current data suggests that select therapies may work well only in specific patients subgroups. Published guidelines for AF management are quite complicated; the joint cardiology society guideline is 97 pages.[36] Objective 3 would serve as the basis for developing simple, effective tools to guide primary care providers in AF patient stratification, therapy selection, and referral when appropriate. Our findings could help form new guidelines on treatment of AF, which in turn could lead to efficient allocation of resources within VA facilities, minimize expenditures, and improve veteran health.

7. EXPECTED RESULTS OF EXPERIENCE IN TERMS OF BENEFIT TO VA AND TO THE NOMINEE IN TERMS OF RESEARCH PROGRAM

The proposed projects will evaluate comprehensive care of AF, a highly prevalent condition in veterans, at a system-wide (VHA) level and develop instruments to improve care. Previous HSR&D projects have evaluated anticoagulation care in select veteran populations with AF, such as veterans with prior stroke or mental health conditions. Indeed, there is a relative paucity of arrhythmia health services research, which may be related to the low prevalence of overlap of HSR and EP training among scientists.

This HSR&D CDA would come at a critical point in my career. **The mentoring, career development plan, and protected research time is essential in allowing me to achieve my goals.** EP is a demanding and procedure-oriented clinical specialty where full-time clinical work of managing sick patients and performing long procedures could easily exceed 60 hours per week. Such a scenario would stifle any real chance of developing a robust scientific portfolio. **In addition, I will require additional didactic training, tutorial, and mentorship to address gaps in my prior training and experience.** For my proposed projects, I will require training in several core areas, including health services research methods, use of large administrative datasets for research, complex statistical modeling, and clinical trial design and implementation. Taking classes, meeting with mentors and consultants, and writing or revising IIR grants at every review cycle would be impossible without dedicated time. The protected research time is critical to complete my research objectives and gaining research independence. The CDA would serve as a vehicle for me to 1) acquire the additional research and scientific skills necessary to achieve to my research goals; 2) submit for VA MERIT, NIH, and foundation investigator-initiated research award proposals with regularity; 3) become a world-class VA health services investigator.

8. COMMITMENT TO VA INCLUDING FUTURE RESEARCH PLANS AND AMBITIONS

I am firmly committed to a long-term academic career in the VA system as a health services investigator, clinician scientist, and cardiac electrophysiologist. I made a deliberate choice to join the VA as medical staff with a mission to expand the scope of EP patient care and research for veterans. Their welfare is my priority.

I am committed to accomplishing the following milestones by the end of this five-year award: 1) be promoted to associate professor or on a clear path for promotion within a short period after the award; 2) mentor junior EP faculty on their own career development awards; 3) create a clinical and research consortium of VHA cardiac electrophysiologists and arrhythmia researchers; 4) be a national VHA leader to develop clinical guidelines for quality measures and treatment for cardiac arrhythmias; 5) serve as a content and methods expert within HSR&D for arrhythmia research and teach and mentor other VA investigators; 6) be an international leader on my research areas and develop guidelines and policy statements for the major cardiovascular

societies; 7) direct VA cooperative clinical studies in arrhythmia therapies. Within 7 years, my goal is to be Chief of a Cardiac Electrophysiology section of an academic VA medical center and Chief of a VA Cardiology service within 15 to 20 years.

10. TIME COMMITMENT TO RESEARCH

During the award period, I will devote 75% of my time to research and 25% of my time to clinical cardiac electrophysiology at the Palo Alto VA Healthcare System. These clinical activities will include one half-day per week in arrhythmia/device clinic, and one partial day per week in the electrophysiology laboratory performing device implantations, electrophysiology studies, and catheter ablations of arrhythmias. I expect to have the capacity to mentor to up to three trainees or junior investigators.

11. SPECIFIC FORMAL AND INFORMAL TRAINING ACTIVITIES

11.1 Overview: The proposed training plan is centered around three core areas: 1) advanced research methods and diversification of knowledge base; 2) research productivity; 3) professional development and leadership.

11.2 Regular meetings and guidance from mentors: I have already started working on projects with my mentors. I will have weekly, high-quality meetings with mentors Heidenreich, Frayne, and Phibbs. These weekly meetings have been ongoing with mentors since the summer of 2008, when I joined my mentors as a co-investigator on Dr. Frayne's AF-Mental Health project. Each week after our core group meeting, Dr. Frayne, Dr. Phibbs, and I meet together to discuss my CDA application and research projects. Twice per month, Dr. Heidenreich joins the core group meetings, which supplement my weekly individual meetings with him. In addition, I have had individual meetings with Dr. Phibbs and Dr. Frayne every two to four weeks. I will have periodic meetings with Dr. Whooley, initially once per month. These periodic meetings have been occurring since 2005 with Dr. Whooley. Although Dr. Whooley is at the San Francisco VA, she is a core member of our HSRD&D Center for Health Care Evaluation and her San Francisco office is only 10 minutes from my residence. My mentorship team has a long and strong history of working together. All mentors are affiliated with our HSR&D Center for Health Care Evaluation. Dr. Heidenreich and Dr. Whooley have worked together for years on HSR&D and VA research committees and know each other well.

11.2. Advanced Research Methods

11.2.1 Formal training will be accomplished by taking courses over the first four years of the CDA through the Stanford University Department of Health Research and Policy **(Table 1)**. Given my prior Master's training in Clinical Research, I have developed a curriculum that will supplement my prior education and enable me to develop skills in areas integral to my research.

11.2.2 Hands-on training and individual tutorial: All mentors and consultants have specialized, complementary skill sets. I will learn from them through individual tutorial and team meetings relating to projects and to career development. Expertise in dataset manipulation and complex statistical modeling will require "hands-on" training and Dr. Heidenreich and Dr. Phibbs will direct my learning of these tasks. Dr. Heidenreich will provide additional tutorial in clinical trial design and methods. Drafts of manuscripts and proposals will be reviewed with mentors and works-in-progress seminars with senior faculty and colleagues.
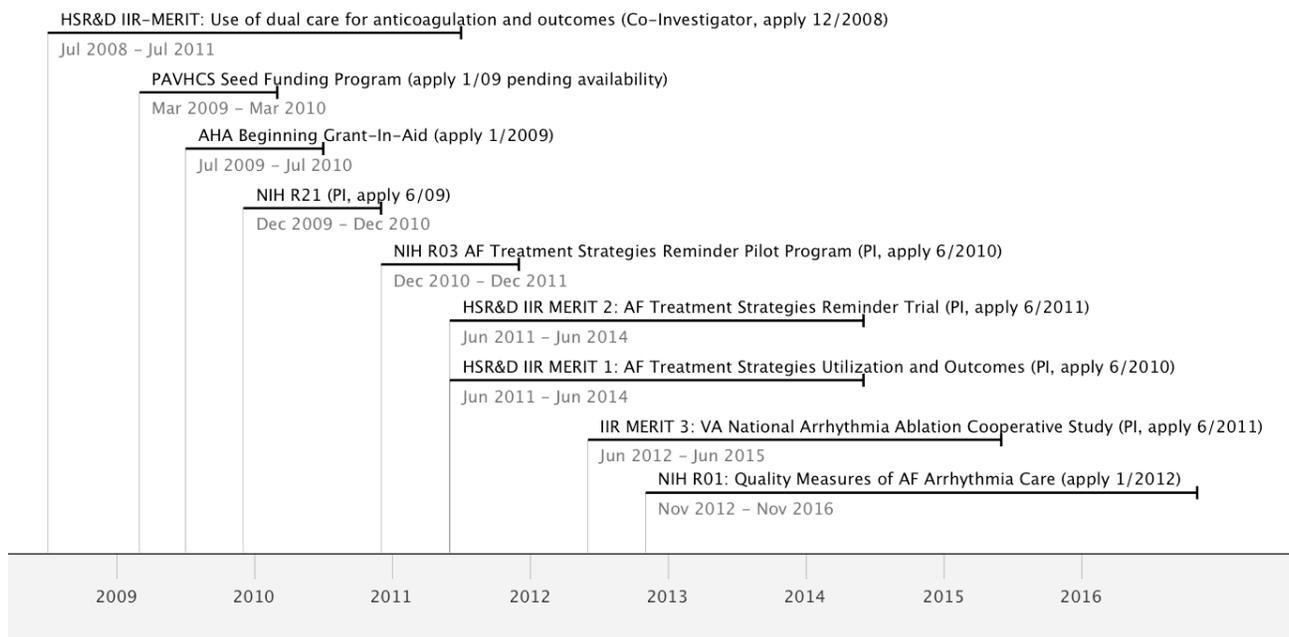
Table 1: Planned Courses During 5-year Career Development Award

First year: Center for Health Care Evaluation (CHCE) seminar. A forum where participants solicit regular feedback on works in progress and have access to invited faculty lectures in a small-group setting.
Fall 2009: HRP 207 Issues and Methods in Health Services Research and Policy. Introduces students to the scholarly concentration on health services and health policy research
Fall 2010: BMI 210 Introduction to Biomedical Informatics: Fundamental Methods. Building intelligent systems for decision support and web applications.
Spring 2010: HRP 252 Outcomes Analysis. Methods of conducting empirical studies with large existing medical, survey, and other databases to answer clinical and policy-related questions by using large databases and applying econometric and statistical models.
Winter 2010: MSE 292 Health Policy Modeling. Application of mathematical, statistical, economic, and systems models to problems in health policy.
Fall 2010: HRP 392 Analysis of Costs, Risks and Benefits of Health Care. Builds from a basic portrayal of decision problems, to more inclusive and sophisticated methods. Students will design and complete their cost effectiveness analysis project
VA Courses: I will take three online, self-paced courses offered by the Epidemiology Research and Information Center (ERIC) including 1) **Economic Analysis with VA Data**; 2) **Research and Improving Chronic Illness Care**; 3) **Cost and Outcomes Research**

11.2. Timeline for Research: A productive career development experience will require protected time, a timeline for research milestones, and discipline to adhere to these milestones. My mentors and I have crafted a timeline for funding applications as shown here. We will begin to submit grant proposals before the start of the proposed award. My mentors will work with me through our regular meetings to ensure adherence to this timetable.

The proposed timeline for funding affords for multiple new grant submissions each year, allowing for resubmissions during the Winter/Spring cycles. It is expected that by year 3 I will have multiple independent sources of funding as the principal investigator. The CDA project portfolio is the centerpoint of all proposed submissions; proposals in years 4 and 5 are for projects that we expect to develop from the CDA research aims.

HSR&D IIR-MERIT: Use of dual care for anticoagulation and outcomes (Co-Investigator, apply 12/2008)
Jul 2008 – Jul 2011

PAVHCS Seed Funding Program (apply 1/09 pending availability)
Mar 2009 – Mar 2010

AHA Beginning Grant-In-Aid (apply 1/2009)
Jul 2009 – Jul 2010

NIH R21 (PI, apply 6/09)
Dec 2009 – Dec 2010

NIH R03 AF Treatment Strategies Reminder Pilot Program (PI, apply 6/2010)
Dec 2010 – Dec 2011

HSR&D IIR MERIT 2: AF Treatment Strategies Reminder Trial (PI, apply 6/2011)
Jun 2011 – Jun 2014

HSR&D IIR MERIT 1: AF Treatment Strategies Utilization and Outcomes (PI, apply 6/2010)
Jun 2011 – Jun 2014

IIR MERIT 3: VA National Arrhythmia Ablation Cooperative Study (PI, apply 6/2011)
Jun 2012 – Jun 2015

NIH R01: Quality Measures of AF Arrhythmia Care (apply 1/2012)
Nov 2012 – Nov 2016

2009   2010   2011   2012   2013   2014   2015   2016

In addition, my mentors and the VA Chief of Cardiology expect firm deliverables for the investment in me. My mentors expect at least two first-author peer-reviewed papers per year from the proposed projects at least four additional publications per year including collaborative projects. Starting in year 3, as I gain funding and train other mentees, my mentors expect two senior author papers per year, which will increase to five per year by the end of the award.

11.3 Professional development and leadership: VA and society leadership experience will be gained from scientific presentations and meetings and by introduction to national leaders by my mentors. I will present research findings at national and regional meetings sponsored by PAVAHCS, HSR&D, Stanford Health Research & Policy, Heart Rhythm Society, American Heart Association, and American College of Cardiology. Many of these meetings are dedicated to health policy, quality of care, and outcomes research. My monthly meetings with Dr. Heidenreich and Dr. Whooley will emphasize the transition to becoming a senior VA investigator. Dr. Heidenreich is the chair or member of several task forces related to quality of care and outcomes in cardiovascular disease and he is committed to nominating me to relevant committees, editorial boards, and scientific meeting panels.

11.4 Clinical mastery: EP is a contemporary and fast-moving procedural specialty, and there is no substitute for clinical practice. I will continue seeing patients in clinic and performing EP procedures. I will continue to participate in scientific and clinical EP meetings, editorial journal review, and society clinical subcommittees.

<div align="center">**RESEARCH PLAN**</div>

1. RESEARCH OBJECTIVES
1.1. Overview of Objectives: Atrial fibrillation and atrial flutter (**AF**, collectively) are abnormal heart rhythms associated w ith increased morbidity, mortality, costs, and decreased quality of life. AF is very common, affecting 5-8.3% of all veterans.[37] Management of AF is aimed at stroke prevention and arrhythmia management, but treatment is difficult due to involvement of multiple care providers and facilities, multiple treatment strategies, complex management guidelines, and availability of procedural therapies. In the VHA, there is wide variation in the care of AF. The objectives of this career development proposal are: 1) to define a research agenda and analysis plan to understand how AF is cared for in the Veterans Affairs (VA) system and to develop measures to improve it; 2) to provide the applicant with the mentorship, research skills, training, and infrastructure required to become a highly successful and independent HSR&D investigator in the applicant's content area of clinical expertise, cardiac arrhythmias.

1.2. Study Objectives: The objectives will guide me through the five years of the award, help me acquire essential methodological skills, and serve as the foundation for independent research proposals for a portfolio of scholarly work. <u>The overarching goal of these projects is to optimize care of atrial fibrillation and flutter in the VHA, both for stroke prevention and for arrhythmia management.</u>

1.2.1 Objective 1: **To evaluate the quality of anticoagulation care in the Veterans Health Administration for stroke prevention in patients with atrial fibrillation or atrial flutter.** Our preliminary data suggests wide patient- and facility-level variation in quality of anticoagulation, which is consistent with non-VA studies.[38-40] Using an established database, I will 1) describe process of care measures for stroke prevention in the VA health care system; 2) identify predictors of variation at the patient, provider, and facility levels; 3) determine which measures best predict clinical outcomes.

1.2.2 Objective 2: **To evaluate the quality of arrhythmia management care in veterans with atrial fibrillation or atrial flutter.** In addition to stroke prevention, the mainstay of treatment of AF is to control heart rate and reduce symptoms caused by the arrhythmia, which may be accomplished by using a number of invasive and noninvasive treatments alone or in combination. Guidelines for use of these therapies are complex and newer therapies, such as left atrial catheter ablation have variable efficacy, are costly, and are performed at few VA centers. This project will define the use of different treatment strategies for AF in veterans, identify predictors of strategy selection, and compare outcomes across strategies, examining both VA and non-VA care for veterans.

1.2.3 Objective 3: **To develop a reminder instrument to guide VA care providers on evidence-based strategies for stroke prevention and arrhythmia management in patients.** This project will first pilot clinical tools attached to electrocardiograms and echocardiography reports to assist care providers in risk stratification for stroke prevention and selection of AF treatment strategy. The pilot study will form the basis of a subsequent IIR proposal for a randomized clinical trial of a reminder intervention to care providers. The goal is to improve care quality, guideline adherence, and clinical outcomes.

3. BACKGROUND
3.1 Introduction and definitions. **Atrial fibrillation** is an abnormal heart rhythm characterized by a rapid, disorganized, erratic electrical activation (fibrillation) of the left and right atria, the upper chambers of the heart. Clinical manifestations may vary from common symptoms of a rapid irregular pulse, palpitations, and exercise intolerance to more severe symptoms and signs of congestive heart failure. **Atrial flutter** is a counterpart arrhythmia characterized by organized, reentrant electrical activity resulting in an atrial rate of 300 beats per minute. Atrial flutter generally results in more severe symptoms due to much faster ventricular rates and longer duration of episodes. Some patients may experience only atrial fibrillation, while others experience atrial fibrillation alternating with flutter. Isolated atrial flutter may be more common in

younger patients. Because atrial fibrillation and atrial flutter have similar clinical manifestations and risk of stroke[36, 41], we refer to them to collectively as "**AF**".

3.2. AF is exceedingly common in veterans. In the United States, atrial fibrillation is the second-most common cardiovascular condition after hypertension[42], affecting 2.3 million Americans. AF will affect more than 4 million Americans by 2030.[43] The prevalence of AF is 4% in Americans over age 60 and 10% over age 80[44]; 70% of of individuals with AF are between ages 65 and 85 years. The absolute number of women and men with AF is equal, although above age 75, 60% of people with AF are women.[42] In veterans, the prevalence of AF among 29,587 outpatients receiving electrocardiograms in the VA Palo Alto Health Care System (VAPAHCS) was 8.3%.[37] Due to rising rates of obesity and hypertension in young adults, the age-adjusted incidence of AF increasing[45] and is therefore expected to affect more veterans at younger ages.

3.3 Stroke prevention: why is quality of care important?

3.3.1. AF causes stroke. The loss of coordinated electromechanical atrial activity predisposes to impaired atrial emptying, stasis of blood, and a prothrombotic state.[46] These factors cause blood clots to form in the heart and embolize systemically to cause stroke or other organ failure.[47, 48] AF is responsible for 15% of 700,000 strokes in the U.S. each year.[49] Among patients with AF, the annual incidence of stroke is 4.5%. The estimated annual direct and indirect cost of stroke in the U.S. is $57.9 billion.[50]

3.3.2. Stroke from AF is preventable, but therapy has risks. There are strong clinical data that long-term anticoagulation with oral warfarin, an inhibitor of Vitamin K-dependent clotting factors, can reduce the relative risk of stroke up to 60%.[51] The greatest clinical benefit of warfarin is in AF patients with prior stroke or associated co-morbid risk factors, including advanced age.[51] In one large pooled analysis of high-risk AF presenting with stroke, 39% presented with subtherapeutic anticoagulation levels and another 15% were not on warfarin.[52]

However, warfarin therapy may have serious or fatal hemorrhagic complications. The risk of hemorrhage is cumulative over time and increases with age.[53, 54] Furthermore, the absolute benefit of warfarin therapy in lower-risk patients may be clinically insignificant.[55] Aspirin is acceptable for AF patients with age <65 years who have no underlying structural heart disease or stroke risk factors and for selected other patients who cannot take warfarin.[56] Therefore, warfarin therapy is only useful when the risks of therapy are outweighed by the benefits.

3.3.3. Widely-disseminated stroke prevention guidelines are available. Because of the totality of evidence documenting strong benefit but potential harms of anticoagulation in AF, organizations have developed clinical practice guidelines. The most widely-disseminated guidelines in the United States are those of the American College of Cardiology and American Heart Association (ACC/AHA)[36, 41], the American College of Chest Physicians[56], the American College of Physicians[57], and VA/Department of Defense.[58] In 2006, the European Society of Cardiology (ESC) and Heart Rhythm Society (HRS) joined the AHA/ACC to create a new, unified international practice guideline statement for AF.[36] This guideline incorporates a simplified validated scoring system to determine risk of thromboembolism (e.g. stroke) for AF based on clinical risk factors **(Table 2)** including 1 point for each of **C**ongestive heart faliure, **A**ge > 75, **D**iabetes, and **2** points for prior **S**troke or transient ischemic attack

Table 2:
CHADS2 scoring:
1 point for each of the following (4 points max) Age > 75, hypertension, diabetes, heart failure.
2 points if prior stroke or transient ischemic attack
Guidelines: If prior stroke or TIA: Chronic warfarin If CHADS2 score ≥ 3: Chronic warfarin If CHADS2 score 2-3: Chronic warfarin or aspirin If CHADS2 score < 2: Aspirin only if age > 55
From 2006 AHA/ACC/ESC/HRS AF practice guidelines

("**CHADS2**").[59] In the derivation study, CHADS2 had better receiver-operating characteristics compared to other risk prediction schemes. However, a recent validation study from the Kaiser Permanente health care system demonstrated relatively similar performance of 5 risk schemes, including CHADS2 (*c* statistics 0.56-0.62).[60]

3.3.4. Current VA guidelines only address two high-risk subgroups. The VA/Department of Defense stroke rehabilitation practice document[58] recommends anticoagulation in patients who have experienced embolic stroke or transient ischemic attack (TIA). The 2003 updated VA

guidelines from the Office of Quality and Performance (OQP) for chronic heart failure recommend anticoagulation for AF in with reduced ejection fraction (<40%).[61, 62] These VA recommendations only address patients with prior stroke or heart failure, which represent a minority proportion of the total AF burden in the VHA. Furthermore, in contrast to VA-OQP guidelines, CHADS2 guidelines do not recommend anticoagulation in heart failure patients without other risk factors[36], although this is controversial. No published guidelines account for the consistent finding that compared to men, women have a higher risk for thromboembolism independent of other risk factors.[63] **Therefore, optimal care remains poorly defined for veterans with heart failure.** All statements do agree that warfarin should be used to target an international normalized ratio (INR) of 2.0-3.0 and that an INR < 2.0 does not confer adequate protection.[36, 41, 56, 57,64]

3.3.5 Adherence to guidelines and stroke prevention care in AF is variable. There is substantial variability in anticoagulation prescribing practices. In the ATRIA study, 13,000 non-VA managed care patients with AF were retrospectively studied.[40] Only 55% of 11,000 anticoagulation-eligible patients received therapy. Among the subgroup of anticoagulation-eligible patients at highest risk for stroke, only 59% were on warfarin therapy. Additional studies have validated these findings in large cohorts.[39, 40, 65-68 69]

In the VA system, there are conflicting data, which may suggest regional variation in care. A single-center cross-sectional study from the Pittsburgh VA Health Care System found that 69% of 1,289 veterans received at least one coumadin prescription.[39] Among the 31% not on coumadin, 213 patients had a history of AF but no documentation of AF in VA medical records. One study determined that warfarin use is higher in facilities with pharmacist-managed anticoagulation clinics[70], but this has not been examined in the VA system. These data underscore the need to 1) evaluate anticoagulation care across the entire VHA; 2) include non-VA care of AF in studies of VA users.

3.3.7 Prescription of anticoagulation alone is inadequate to prevent stroke. INR within range (2.0-3.0) predicts prevention of stroke or hemorrhagic complications,[64] and 90% of INRs are subtherapeutic at the time of a stroke.[52] Maintenance of a consistently therapeutic INR is difficult because of warfarin's slow-onset of action, long half-life, sensitivity to dietary vitamin K intake, and numerous drug-drug interactions. Although frequent dosage adjustment necessitates routine monitoring (often several times per week), this care may occur sporadically. Delays or inconsistency in monitoring and dose adjustment may promote hemorrhage or stroke.

Time in therapeutic INR range (TTR) has been previously used as process measure for quality of anticoagulation.[71] However, only recently has TTR been validated as an independent predictor of outcomes in AF in large cohorts.[38, 72] A substudy of a large randomized trial of anticoagulation in AF demonstrated no treatment benefit with warfarin compared to antiplatelet therapy in patients with a TTR < 58%.[72] Surprisingly, there was wide variation in TTR (46%-77%) across study centers. After adjustment of patient-level variables, most of the variability remained at the facility or geographic level. Since randomized trials generally provide best-case estimates of quality of care, TTR performance may be worse in real clinical practice. Multiple studies have shown that optimal TTR may be best achieved through use of anticoagulation clinics[71, 73, 74] However, in the VHA, anticoagulation clinics are not present at all facilities, which may contribute to these facility-level or geographic differences in thromboembolic risk. **Identification of mediators of TTR in the VHA would serve as the foundation to make systemwide improvements in quality of anticoagulation care for veterans with AF.**

3.3.6 Factors of poor guideline adherence and quality of anticoagulation are not well understood. Among 11,699 eligible Ohio Medicaid patients, only 12% received warfarin within 30 days of new onset AF. This use-rate, which is dramatically lower than rates observed in other HMO and Medicare studies[75], may suggest disparities in quality of AF care. Stroke is independently associated with lower income, educational attainment, and acculturation.[76] Older, warfarin-eligible patients with AF have lower rates of guideline-concordant stroke prevention.[77] African-Americans receive shorter courses of anticoagulation.[78] To our knowledge, the impact of race and socioeconomic status on AF care in across the entire VHA has not been determined.

3.4. AF arrhythmia management: why is it important?

3.4.1. AF increases morbidity, mortality, and hospitalizations independent of stroke risk.

AF doubles the risk of cardiovascular and all-cause mortality independent of anticoagulation status and AF risk factors.[79, 80] In addition, AF may cause or worsen heart failure due to left atrial mechanical dysfunction,[81] irregular ventricular contraction, or sustained tachycardia from poor rate control.[82] Correction of tachycardia or restoration of sinus rhythm may restore cardiac function.[83] Extreme tachycardia[14] or ventricular rate entropy (irregularity) during AF leads to increased vulnerability to ventricular fibrillation and sudden cardiac death.[84, 85] Effective management of the heart rhythm and rate therefore essential in patients with AF.

3.4.2. Symptoms from AF decrease quality of life.
AF can be highly symptomatic, and failure to control AF rate or rhythm is associated with decreased quality of life, recurrent hospitalizations, anxiety and depression.[86-89] Paroxysmal tachycardia, irregular beating, neck pulsations, non-anginal chest pain, extreme tachycardia, fatigue, exercise intolerance, and post-AF bradycardia and syncope are well-established symptoms of AF. A major treatment goal is to minimize or eliminate symptoms.

3.4.2. Multiple different strategies can be used to manage AF, but choice of strategy is controversial.
Strategies to manage AF include control of heart rate (**rate control**) or restoration of normal sinus rhythm (**rhythm control**) **(Table 3; Appendix A).** First-line therapy in both treatment strategies is prescription medication therapy. The landmark AFFIRM trial randomized 4060 subjects with atrial fibrillation to rate control medications versus rhythm control medications and demonstrated no overall mortality difference.[90] As a result, there has been widespread adoption of the view that rate control is adequate and that rhythm control is not justified.[91] However, the AFFIRM trial did not study patients with moderate to severe AF symptoms. In the AFFIRM study, 6% of patients failed to achieve adequate rate control.[90] Also, in a secondary on-treatment (per protocol) analysis, restoration of sinus rhythm achieved by antiarrhythmic drug therapy was associated with a lower disk of death.[92] This may suggest that the benefit in AFFIRM was tempered by limited efficacy of rhythm control strategies rather than by achievement of sinus rhythm. Certain rate control strategies, such as use of digitalis, increases mortality[93], which is consistent with our own preliminary data in veterans (see §5.5).

> **Table 3: Treatment strategies for AF**
> **1. Control or regularize ventricular rate**
> 1a) Medications (beta blockers, calcium channel blockers, digitalis)
> 1b) Catheter ablation of atrioventricular node with adjunctive right ventricular or biventricular pacing ("ablate & pace")
> **2. Restore normal sinus rhythm**
> 2a) Electrical or pharmacologic cardioversion
> 2b) Antiarrhythmic medications
> 2c) Catheter ablation for atrial fibrillation
> 2d) Catheter ablation of cavotricuspid isthmus (right atrial circuit) for atrial flutter

Older studies documenting increased mortality from antiarrhythmic drugs in patients with myocardial infarction have also reinforced a controversial view that antiarrhythmic drugs are uniformly dangerous in AF. A Cochrane systematic review studied 45 clinical trials of antiarrhyhmic drugs involving 12,559 patients and concluded that several class IA, IC, and III drugs are effective in maintaining sinus rhythm.[94] Specifically, amiodarone and propafenone, the two most commonly-used antiarrhythmics in the VHA formulary, did not increase mortality or proarrhythmia. However, the review concludes that, "any benefit on clinically-relevant outcomes remains to be established."[94] Although small studies demonstrate that restoration of sinus rhythm is associated with improvement in physical functioning, general health, social functioning, and exercise performance.[95, 96], randomized trials and meta-analyses have failed to identify an optimal medical strategy.[88, 89, 97, 98] There may also be ethnic variation in response. An AFFIRM substudy demonstrated higher efficacy of rhythm control compared to rate control in Hispanics.[99]

3.4.3. New, invasive electrophysiology procedures have expanded options for AF management.
Since 2000, there has been an exponential rise in the use of invasive electrophysiological testing and percutaneous radiofrequency catheter ablation to treat a variety of arrhythmias. The procedure is similar to coronary angioplasty or stenting. Using x-ray flouroscopy guidance, catheters with electrodes are inserted into the heart via the femoral or internal jugular veins. The electrical system can be mapped to determine the source of the arrhythmia. Radiofrequency energy can be applied from the catheter tip to cardiac tissue to ablate (eliminate) errant or pathologic electrical circuits. Efficacy varies based on type of arrhythmia, and

there are major differences in success rates between ablation of the antrioventricular junction (AVJ) or node, atrial fibrillation, and atrial flutter. AVJ ablation is used to create complete heart block. This simple, efficacious procedure does not eliminate AF but allows for rate control by using permanent ventricular pacing to modulate heart rate. In patients with chronic AF, this "ablate and pace" strategy is associated with improved quality of life and decreased use of health services[100], although chronic right (single) ventricular pacing may worsen systolic function.[101] Biventricular pacemakers, which pace the left and right ventricle simultaneously, improve the synchrony of the heart, which may prevent deterioration or improve ejection fraction and heart failure symptoms.[102]

"Typical" or cavotricuspid-isthmus dependent atrial flutter, which is the mechanism of 95% of all atrial flutters, is caused by a single reentrant circuit in the right atrium posterior to the tricuspid valve. The procedure to eliminate this circuit is technically easier and has a 95+% rate of cure.[103] In contrast, elimination of atrial fibrillation requires electrical isolation of large portions of the left atrium, pulmonary veins, and often other areas. Left atrial ablation is technically more demanding, more expensive, mandates more extensive operator training, requires cardiothoracic surgical backup, and may have higher complication rates. Left atrial isolation procedures for atrial fibrillation have a 1- to 3-year freedom from recurrence of 60-80%.[36, 104-106] Catheter ablation for atrial fibrillation and atrial flutter are more effective at restoring sinus rhythm than antiarrhythmic drugs[107] and have been shown to improve heart failure, ejection fraction, quality of life, and mortality, especially in patients with reduced systolic function.[106, 108]

3.4.3. Guidelines are complex and endorse multiple strategies.
AF management strategy selection remains controversial, largely because the totality of evidence is inconclusive. The cardiovascular society (AHA, ACC, HRS) 2001 guidelines recommend antiarrhythmic medications for AF for symptoms or to prevent heart failure, but these guidelines are backed by low levels (B and C) of evidence.[41] The 2006 guidelines now include catheter ablation, but do not endorse any single strategy as first-line or as preferred therapy.[36] The guideline document is almost 100 pages long, difficult to follow, and may be too complex for simplified integration into clinical practice. Furthermore, general practitioners may be critical of relevance and implementation of society-based guidelines.[109] The VA and OQP do not have guidelines on AF treatment strategies or antiarrhythmic therapies, including catheter ablation.[61, 62] The VA PBM Strategic Healthcare Group has created a patient handout for use of the antiarrhythmic medication sotalol[110] but to our knowledge has not published prescription guidelines.

3.4.3. Choice of strategy and variation in treatment may be influenced by VA facility resources.
Cardiac arrhythmia care is considered to be one of the most difficult content areas of internal medicine and cardiology, and the AFFIRM trial may support the view that rate control is universally sufficient. Our preliminary data suggests that over half of primary care providers do not refer AF to specialists for management (see §5.2). In fee-for-service systems such as Medicare, physician reimbursement incentives could be a contributing factor. Because of the potential risks of antiarrhythmic drugs[111, 112], physicians in facilities without on-site ECG, echocardiography, or cardiology or electrophysiology consultation may be more likely to use simpler strategies such as rate control. In the VHA, some larger facilities have a higher level of cardiology services, including electrical cardioversions, electrophysiology catheter ablation, and staff EP nurse practitioners and electrophysiologists. **Therefore, selection of strategy may be influenced by facility resources and availability of cardiology or electrophysiologist specialty care.** In these situations, patients who fail rate medical control may be less likely to be considered for other AF management strategies, particularly in the VHA.

3.4.4 Limited procedure availability may lead to disparities in care
Many veterans obtain cardiovascular healthcare from non-VA providers, particularly if they live far from VA care.[113-115] VHA enrollees have two to three times as many Medicare hospitalizations than VHA hospitalizations for coronary revascularization, even in urban settings.[116, 117] A seminal VA health services study found that elderly VA enrollees were six-times more likely to obtain cardiac surgery at non-VA hospitals, despite wide variation in non-VA procedure volume, quality, and standardized mortality estimates.[118] With the VHA's reorganization that began a decade ago,

its high-technology and high-cost specialty services are now provided through regional referral centers that are usually located in metropolitan areas. Catheter ablation and cardiac resynchronization therapy are newer treatments offered only at select VA medical centers. These centers are in large cities, primarily along the East or West coast, and are affiliated with academic medical centers with integrated cardiac electrophysiology programs (personal communication, Edmund Keung MD). Rural patients often must travel farther to access this care and rely on it less.[28, 119-122] The variability in services may lead to differences in care and practice patterns by facility or provider, and the impact on outcomes is not known. Furthermore, VA users with other insurance such as Medicare may seek these procedures outside of VA facilities. Reliance on supplemental insurance may lead to differential treatment of AF based on socioeconomic status and such disparity may impact outcomes. Rural veterans may also have limited access to high quality non-VA care.[120]

3.5 Conceptual framework: This framework for defining and evaluating quality rests upon the structure-process-outcome framework,[123] which has been shown to describe quality in health care
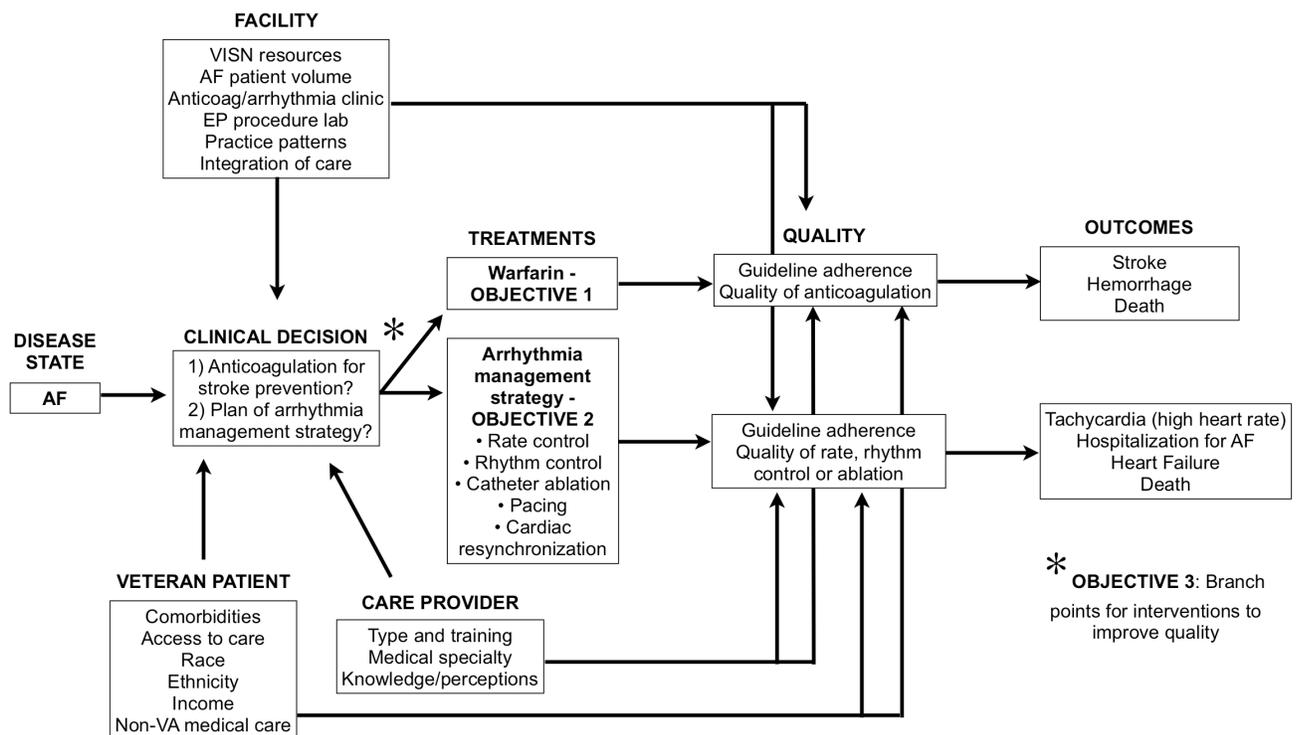
systems.[124] Treatment of AF is centered on stroke prevention **(Objective 1)** and strategies for arrhythmia management **(Objective 2)**. Risk of stroke is determined by comorbidities, and practice guidelines support warfarin therapy at a defined threshold of risk. However, there may be variation in guideline adherence and quality of this therapy **(Obj. 1, Aim 1.1)**. Patient-, facility- and provider level factors **(structure)** may explain this variability **(Obj. 1, Aim 1.2)**. These factors may also influence time in therapeutic range or other measures of quality of stroke prevention care **(process)** (**Obj. 1, Aim 1.2**), which may influence risk of stroke, bleeding or death **(outcome)** (**Obj. 1., Aim 1.3**). For selection of an arrhythmia management strategy **(process)**, multiple guideline-supported strategies exist, but their utilization is undefined in veterans (**Obj. 2, Aim 2.1**). Management strategy selection may also be determined by patient access to care disparities, socioeconomic status, facility resources, care provider, and use of non-VA care **(structure) (Obj 2, Aim 2.2)**. Each strategy may have differences in quality of care and **outcomes** (**Obj 2, Aim 2.3**). Understanding these relationships and mechanisms serve as the basis to develop provider-level interventions to guide AF treatment (**Objective 3**) and quality/performance guidelines for VA facilities, leading to improvements in outcomes**.**

Current ACC/AHA Clinical Practice Guidelines use the structure-process-outcome framework to identify process measures that are likely to influence outcomes based on face, content and construct validity[125], expert opinion[126], literature synthesis[127], and Bayesian post-test probability of benefit.[128] The ACC/AHA guidelines have specifically applied this model to propose monthly INR laboratory testing as key performance measure for AF care.[125] However, neither INR frequency nor other process measures have previously been validated as predictors in national care data. Our preliminary data demonstrates that facility volume and INR test frequency affect mean TTR by facility (see §5.3), thereby establishing a structure-process relationship. The link between TTR and stroke reduction in AF has only recently been retrospectively demonstrated in regional HMO administrative data[38] and in a randomized trial secondary data analysis.[72] **Therefore, more broadly stated, this proposal tests the validity of the current structure-process-outcome framework for assessing quality of AF care**. For example, if monthly INR testing does not predict stroke outcomes in veterans with AF, then why should it be mandated as a performance measure?

4. Significance

4.1 Relevance and rationale to examine care of AF in veterans

AF is extraordinarily common in veterans. Because of the rising prevalence of hypertension and obesity, the AF burden in the VHA is expected to rise, especially in younger patients (age < 65), who do not qualify for Medicare. Therapies for coronary disease, MI, and heart failure, have been successful in improving veteran morbidity and mortality. However, very little is known about the quality of anticoagulation care and AF rhythm management in the VHA. Although the Centers for Medicare & Medicaid Services (CMS) have issued specifications for 74 measures in the 2008 Physician Quality Reporting Initiative, none of these address quality of AF care.[129] Findings from Objectives 1 and 2 can foster creation of VA Office of Quality and Performance guidelines. Objective 3 will evaluate instruments that could later be implemented to improve or standardize quality of AF care. The knowledge gained from these projects could reduce stroke, heart failure, and death and may favorably impact quality of life. VA health care expenditures for these conditions would likely decline substantially. **These projects would serve as the foundation to make systemwide improvements in AF care in the VHA.**

5. WORK ACCOMPLISHED

5.1. AF treatment and stroke risk among veterans with stable coronary artery disease: The VA Heart & Soul Study.
Using data from the VA Heart & Soul Study (PI: Mary Whooley, co-mentor), I examined the stroke rates based on risk factors in a cohort of 1024 patients (50% with veteran status) with established coronary disease. I found that among patients with AF, age-adjusted stroke incidence was lower than rates from the derivation study of the CHADS2 guidelines **(Table 4)**. However, in our cohort, patients at high risk for stroke (CHADS2 score 4-5) had a higher stroke incidence than the cohort from which CHADS2 estimates were derived. Among high-risk patients, rates of anticoagualation use were markedly lower in minority groups (14% African-American, 14% Hispanic, 72% White, p < 0.05).

Table 4: Age-adjusted risk of incident stroke or transient ischemic attack, stratified by CHADS2 score (from VA Heart & Soul Study)

CHADS2 score	Age-adjusted annual incidence % (95% CI)	
	Arch Intern Med 2003;163:936–43	VA Heart & Soul Study
0	1.9 (1.2-3.0)	0.52 (0.19-1.41)
1	2.8 (2.0-3.8)	0.43 (0.20-0.90)
2	4.0 (3.1-5.1)	0.69 (0.36-1.3)
3	5.9 (4.6-7.3)	3.3 (1.8-5.9)
4	8.5 (6.3-11.1)	18.4 (9.9-34.1)
5	12.5 (8.2-17.5)	73.2 (17.3-309)

5.2. Knowledge and beliefs of cardiovascular disease management and atrial fibrillation among primary care providers (PCPs):
My colleagues and I surveyed 888 PCPs using case vignettes to demonstrate cardiovascular risk. Overall, respondents' adherence to cardiovascular prevention guidelines was low (56-59%) and was inversely related to years in practice and volume of patients seen.[130] In addition, PCPs cited medication cost, medication adherence, inadequate time for counseling, and lack of patient education tools as significant barriers to providing CVD risk management. This manuscript has been published.[130]

To address specific issues in management of AF, my colleagues and I surveyed 148 primary care, non-specialist physicians (PCP) from 36 states drawn from the American Medical

Association Masterfile (PI: Gregory Marcus MD MAS, UCSF). Respondents completed a 31-question online survey on preferences regarding AF management strategy (rate control vs. rhythm control) and anticoagulation. We used 5-point Likert scales that were later dichotimized for analysis. The study produced some striking findings (data unpublished, in preparation). Fifty percent (IQR 20%-90%) of primary care providers managed AF patients without referral to a cardiologist or cardiac electrophysiologist. Sixty percent of respondents believed that rate control was *superior* to rhythm control with regard to quality of life. Seventy-three percent of all respondents believed that rhythm control confers a reduction in risk of stroke, and 55% of respondents believe that rhythm control can be used to avoid long-term anticoagulation. These views are in opposition to published data, society practice guidelines, and consensus statements. Respondents whose practice beliefs opposed guidelines were older and had a longer time since completing residency. The study was not powered to assess for variation based on geography or practice setting (academic, VA, managed care). <u>Together these findings suggest: 1) that provider attitudes are not in agreement with guidelines for stroke prevention of AF rhythm control; 2) provider or facility characteristics may be contributors to AF care quality and strategy.</u>

5.3 Relationship of time in therapeutic range (TTR) to VA facility and AF case volume: The TEAM Database Study:
Yusuf and colleagues recently retrospectively identified TTR of INR 2.0-3.0 of 58% as a threshold for maximal protection against embolic events.[72] As part of the research team of Susan Frayne (co-mentor), I explored facility-level characteristics of anticoagulation care in the VHA using FY02-FY04 national VHA and Medicare data. Excluding two outliers with TTR < 1%, the mean TTR by facility was 55% ± 6% (range 31-66%). **Only 30 of 94 VA facilities (32%) had a mean TTR of 58% or higher.** Center volume, defined as # of veterans with INR values drawn at that facility, accounted for 23% of the variability (R^2) of mean facility TTR. The mean number of INR draws per patient over a 12-month period accounted for 19% of the variability (R^2, Figure 2). **These data indicate: 1) quality of anticoagulation by TTR is below accepted levels in the VHA; 2) TTR is related to patient volume and patient test frequency.**

Figure 2: VA Facility scatter plot of # INR checks per patient per year vs. mean time in therapeutic range
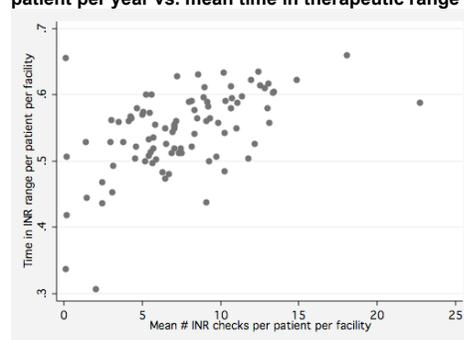
5.4 Variation in AF care based on VA-only or dual-use care:
Using the same database (see §6.2.1), we also performed pilot analyses to determine non-VA utilization for AF. Among 106,772 VHA patients with established AF on warfarin therapy in FY02-FY03, 72% used both VA and Medicare (MC) outpatient services. Among VHA patients with documented INR laboratory testing, 38% used the VA only, 26% used VA + MC, and 37% used Medicare only. **Based on these findings, it is likely that procedures for arrhythmia care, including cardioversion, catheter ablation, and pacemaker insertion, are frequently performed in VHA patients outside of VA hospitals, particularly in situations where VA facilities do not offer these services or have limited patient volume (§5.3)**. My primary mentor has found that economic incentives influence adoption of cardiovascular procedures, including coronary angioplasty and bypass surgery, and that central control of capital funding is negatively associated with adoption rates.[131] These data illustrate the importance of including Medicare data for Veteran patients. Objective 2 would aim to understand factors associated with non-VA AF care and outcomes.

5.5 Association of poor heart rate control, digitalis use to heart failure and mortality in veterans with AF:
We performed a retrospective cohort study of 577 veterans with Holter monitoring performed for clinical indications between 2004 and 2007 in the VA Palo Alto Health Care System. Outcomes were ascertained by trained, blinded adjudicators. The prevalence of AF by history was 17.5%. Patients with AF had significantly

Table 2: Adjusted hazard ratios for Veterans with AF receiving Holter monitors from 2004-2007 in the Palo Alto VA Health Care System*

	Heart failure hospitalization	Cardiovascular Death	All-Cause Death
Digitalis	7.1 (2.5-20)	30 (3.0-301)	5.2 (1.6-17)
Beta blockers	NS	NS	NS
Calcium blockers	NS	NS	NS
Anticoagulation	NS	NS	NS

*adjusted for age, comorbidities, and medications

higher resting heart rates (84±21 vs 69±15 BPM, p<0.001), but had low rates of antiarrhythmic therapy (13%) or rate control therapy (calcium-channel blockers 18%, beta-blockers 59%). Overall, the presence of a high resting heart rate (> 90) was independently associated with incident heart failure admission (OR 2.9, p=0.03), time to death (HR 2.4, p=0.007) and cardiovascular death (HR 2.53, p=0.05). Among patients with AF, digitalis therapy significantly increased the adjusted risk of these endpoints (**Table 2**). **These findings suggest: 1) AF patients have higher heart rates, which is associated with mortality; 2) antiarrhythmic and AV-nodal blocker drug use rates are low; 3) digitalis may be harmful** *(manuscript in preparation).* These results are consistent with my previous work that identified low use rates of beta blockers (58%) in veterans with coronary heart disease, which was associated with increased risk of sudden death.[12] The relationship of digitalis to adverse outcomes is consistent with a recent randomized trial substudy.[132]

5.6. Clinical reminder studies for beta blockers and angiotensin receptor blockers in heart failure: echocardiogram reminder study: My primary mentor has previously evaluated the impact of clinical reminders attached to echocardiography reports for endocarditis prophylaxis[133], beta blockers[18, 19, 133], and angiotensin receptor blockade[16] in heart disease. The largest of these studies was a VA funded (IIR-01-108) randomized trial of 1500-patients across three echocardiography laboratories at the Palo Alto VA Health Care System. Echocardiography reports of veterans with EF < 45% were randomized to include or not include a clinical reminder recommending: 1) beta blocker therapy (an AHA/ACC and VHA Class I indication) and 2) cardiology follow-up. The intervention resulted in a 10% absolute improvement in beta blocker use in heart failure. Seventy-six percent of physicians in the intervention arm recalled seeing the reminders. **This trial demonstrates the feasibility of intervention studies for cardiovascular care (Objective 3) and demonstrates success with cardiovascular care interventions directed at primary care providers.**

6. WORK PROPOSED

6.1. Overview of methods. For objectives 1 and 2, we will perform two observational studies using VA administrative data linked to Medicare data. The database for Objective 1 is ready for analysis. Objective 2 is an ancillary study using a combined dataset with data elements from another HSR&D IIR proposal for which I am a co-investigator. Objective 3 will pilot two intervention reminder studies that will form the basis of a larger randomized trial.

6.2. OBJECTIVE 1: To evaluate the quality of anticoagulation care in the Veterans Health Administration for stroke prevention in patients with atrial fibrillation or atrial flutter.

> *Specific Aim 1.1:* To characterize processes of care for stroke prevention for atrial fibrillation and atrial flutter.
>
> *Specific Aim 1.2:* To determine the relationship of patient-, provider-, and facility-level factors to processes of stroke prevention care in veterans with atrial fibrillation or atrial flutter.
>
> *Specific Aim 1.3:* To determine clinical outcomes associated with processes of stroke prevention care in veterans with atrial fibrillation or atrial flutter.

6.2.1. DATA SOURCES, AVAILABILITY, COMPONENTS:

6.2.1.1. TEAM database: The Treatment Equity for Atrial Fibrillation in the Mentally Ill (TEAM) database is a complex dataset with VA administrative data (NCPD, PBM, DSS) linked to Medicare data and VA stroke outcomes data for fiscal years (FY) 2001-2005. The dataset was conceived in 2004 by Susan Frayne MD MPH (co-mentor) to evaluate the impact of mental health conditions on stroke prevention in AF (IIR 04-248, PI: Frayne). The elegance of this dataset is that it captures a superset of **305,592 VA users with AF** and an extensive array of provider- and patient-level predictors linked to outcomes that are ascertained with well-validated methods. Many of my proposed variables have already been created. A major strength of the database is that linked Medicare data captures predictors and outcomes in these VA users that occurred outside of VA care. **The TEAM database is therefore remarkably well-suited to examine care of AF in veterans.**

Table 3: Data Sources*

Fiscal Yr	02	03	04	05
NPCD	x	x	x	x
PBM	x	x	x	x
DSS	x	x	x	
ISOD		x	x	x
BIRLS		x	x	x
CMS	x	x	x	x

*See Tbl 4 for more detail

6.2.1.2. DATA AVAILABILITY: The TEAM database is housed at the VA Health Economics Resource Center (Menlo Park, CA) and is **available for immediate use** for these projects. The database was constructed and is managed by co-mentor Ciaran Phibbs. **Database merging, linking, and cohort identification is complete and preliminary analyses have already been performed using this dataset.**

6.2.1.3. DATABASE COMPONENTS: Table 3 summarizes data sources used to constitute our cohort (FY02-03), examine processes of care (FY03-04) and their association with outcomes (FY04-05).

1) **VA National Patient Care Database (NCPD):** This is a centralized dataset that represents the universe of VHA users. Most VHA users are veterans and NCPD contains outpatient (OPC), inpatient (PTF), long-term care (ECT) administrative data. The dataset includes critical elements for addressing our study aims, including ICD-9 diagnosis codes, CPT procedure codes, clinic stop codes (provider and facility level data), demographics, and mortality (BIRLS) data. NCPD data have been used extensively for health services research,[134-136] and for administrative reports used to guide VA clinical, resource, and policy decisions. The VA remains committed to the quality of its administrative data[137] and since 1990 has detailed directions on coding and quality control of electrophysiology procedures[138]

2) **VA Pharmacy Benefits and Management (PBM) data:** This database contains complete VA pharmacy information (from every VA facility in the U.S.) and includes patient-level data on medications dispensed from within the VHA. At each VA facility, PBM software extracts individual patient-level dispensing elements monthly from outpatient medication records, including those dispensed by mail and those filled at the Consolidated Mail-out Pharmacies.[139, 140] Data elements include drug name, drug class, dosage, route, quantity dispensed, date dispensed, and consumption. Prior studies have shown that PBM data captures 99% of all VA prescriptions[76]. PBM data has exceptionally high agreement with DSS data[141], which explains a strong track record of use in multiple high-impact studies of VA prescribing practices. [142-147]

3) **VA Decision Support System (DSS) laboratory data:** This centralized information system contains extracts from each VA site of clinical and financial data for all inpatient and outpatient care, again representing the universe of VA users.[148] Since FY03, national data extracts include laboratory data for 59 blood tests, including laboratory measurements of therapeutic anticoagulation (prothrombin time and INR), thyroid function, and blood counts.

4) **VA Integrated Stroke Outcomes Database (ISOD):** This database was developed by the VA's Stroke QUERI in collaboration with the Rehabilitation Outcomes Research Center for Veterans with Central Nervous System Damage (RORC). This is a registry of all acute stroke patients in the VHA identified through the Functional Stroke Outcomes Database and NCPD data. The RORC has developed three definitions for stroke: the VHA Allocation Resource Center definition, a high sensitivity definition and a high specificity definition.[149, 150] The "high sensitivity" definition has a sensitivity of 91% and a specificity of 40% for stroke confirmed on chart review, and the "high specificity definition has a sensitivity of 54% and a specificity of 87%.[149]

5) **Medicare data (CMS):** Annual Medicare Part A & Part B data for every VA enrollee will is an essential component of our database, since 84% of U.S. patients with AF are over age 65 (Medicare eligible). Documented services (CPT) and diagnoses (ICD-9) in this dataset will capture a large-portion of AF and non-AF related care outside of the VA health care system. Medicare has successively updated its data quality standards,[151, 152] which are strictly enforced.[153] Despite limitations,[154] it has proved an important resource for health services research.[155-158]

6) **Vital status file 118, 119:** This carefully-validated fileset draws on mortality data from VA Inpatient PTF, BIRLS, Medicare Vital Status, and the Social Security Administration death file to create a "best" date of death for VA patients. It has 98.3% sensitivity for detection of deaths identified by the National Death Index, and 97.6% agreement with the National Death Index.[159, 160]

6.2.2. IDENTIFICATION OF STUDY COHORT:

We have created a main cohort of patients with AF and have specific subcohorts to be used in analyses. **Main cohort (C1):** We identified 140,589 veterans with established **AF** (subclassified as *atrial fibrillation only*, *atrial flutter only*, and *atrial fibrillation and flutter*) from FY02-FY03 NCPD and CMS ICD9 outpatient diagnosis codes. **Sub-cohort C2** is comprised of C1 patients who have no absolute contraindications to anticoagulation.[36] **Sub-cohort C3** includes C2 patients who have no relative contraindications to anticoagulation.[36] We will examine processes of care and quality indicators from FY03-FY04 data and their association to outcomes from FY03-FY05.

6.2.3. IDENTIFICATION OF PREDICTORS AND OUTCOMES:

6.2.3.1. Specific Aim 1.1: To characterize processes of care for stroke prevention for atrial fibrillation and atrial flutter. In this *descriptive* analysis, we will examine processes of care for stroke prevention in AF on cohorts C1, C2, and C3 over a twelve-month baseline period (FY03). We will examine the following processes of care: **P1) Prescription of anticoagulation**: a binary variable if anticoagulation was prescribed during FY03; **P2) Frequency of INR testing**: For each patient on anticoagulation, we will calculate the mean frequency of INR testing over a 12-month period in FY03; a crude binary predictor for **monthly INR testing (P3)**. These process measures are congruent with recent performance measure guidelines for AF published developed by the cardiovascular society task forces (AHA, ACC, HRS).[125] Since crude estimates may overestimate long-term (12-month) quality due to periodic clustering of laboratory testing, we will also examine **eligible outpatient days per INR test (P4)**, which excludes periods of inpatient, perioperative, or long-term VA or Medicare-coded care. We emphasize investigation of **time in therapeutic INR range (TTR) (P5)**, which is the preferred instrument variable for assessing quality of anticoagulation [71] and was recently demonstrated to be associated with stroke outcomes.[38, 72] We will also use **TTR ≥ 58% (P6)** as a binary predictor; this cutpoint was recently derived as a cutpoint at which anticoagulation confers benefit over antiplatelet therapy.[72] The TTR variable has already been created using a linear extrapolation-imputation method recommended by Samsa and Matchar[71], allowing us to readily proceed with its use in our defined cohorts. TTR is an excellent predictor of benefits (thromboembolism prevention) and harm (hemorrhage) of anticoagulation.[71] and has been used in a recent VA cooperative study randomized clinical trial.[161] We will also examine **adherence to anticoagulation guidelines (P7a-d)**: Since long-term anticoagulation is recommended only in medium- to high-risk patients with AF, we will examine adherence of coumadin prescription and non-prescription to four well established risk prediction guidelines: **a) CHADS2** (congestive heart failure, hypertension, age > 75, diabetes, prior TIA/stroke)[36],the **b)** stroke prevention in AF (**SPAF**) guidelines, **c) Framingham** risk score for AF[162], and **d)** American College of Chest Physicians (**ACCP**) guidelines. Because the VA, OQP, and NQF do not have established guidelines, these risk prediction schemes represent best practice guidelines for VA care. Although CHADS2 appears to be the most popular schema among cardiologist, guideline preferences among primary care providers is not known. **Warfarin refill compliance (P8)**[163, 164] will be calculated for FY2003 using the medication possession ratio (**MPR**)[142], which is an estimate of adherence to prescribed anticoagulation. This method has been successfully used on centralized PBM data[142, 165] and **our group has already calculated MPR in our TEAM dataset**. **P9) Nonadherence to clinic visits** using DSS outpatient no-show data will also be evaluated.

For all process measures, we will perform stratified and adjusted analyses based on patient gender, race, type of arrhythmia (fibrillation only, flutter only, both), and number and type of stroke risk factors (including age, heart failure, hypertension, diabetes, and prior stroke).[36] We will examine rates by facility and by prescribing provider type. Differences in processes of care in cohorts C1, C2, C3 will allow us to understand processes of care in VA patients across a spectrum of anticoagulation eligibility.

6.2.3.2. Specific Aim 1.2: To determine relationship of patient-, provider-, and facility-level factors to processes of stroke prevention care in veterans with atrial fibrillation or atrial flutter.

Hypothesis 1.2: Patient-, provider-, and facility- characteristics explain variation in processes of care for stroke prevention. Our purpose is to understand what factors explain variation in frequency of processes of care for stroke prevention. Therefore, we will perform a series of prespecified analyses evaluating process measures **P1**-**P9** as *dependent variables (outcomes)* in our defined cohorts using the following predictors:

　　　　　　1) Patient level: **V1) age**; **V2) sex**; **V3) race/ethnicity** will be ascertained using the "most frequent/most recent" algorithm applied over multiple years of VA and CMS data; **V4) socioeconomic status** will be estimated from **education** and **income levels** based on residential zip code from 2000 US Census Data. This well-established method[166] has been previously used by Dr. Frayne (co-mentor) for two large administrative dataset studies using VA and CMS data; **V5) comorbidities**: diabetes, hypertension, hypertension, myocardial infarction, coronary artery disease, prior stroke/TIA, and renal insufficiency will be individually examined because these factors affect risk of developing AF and risk of cardiovascular events (stroke, MI) and death independent of having AF.[45, 47, 49, 79, 80, 162, 167-169] In addition, because the presence of any other conditions may decrease intensity of care for unrelated conditions such as AF[170] , we will also examine the number of comorbid medical conditions using the Comorbidity Index. This scoring system was developed for case-mix adjustment for VA outpatients.[171] Derivation of this score using FY02 inpatient and outpatient ICD9 diagnoses has already been performed; **V6) use of VA outpatient cardiology services** based on clinic stop codes; **V7) VA priority status**; **V8) distance from VA** based on straight-line distances from the center of the patient's residential zip code to the center of the nearest VA facility's zip code. This distance construct[172] is highly correlated to actual travel time based on Dr. Phibbs' prior work.[173]

　　　　　　2) Facility level: **F1) primary VA facility** from clinic stop codes is the facility used most frequently in FY2003; **F2) presence of cardiac electrophysiologist or electrophysiology services** compiled by survey data from VA Cardiology Chiefs nationwide (EP consultation cannot be uniquely determined by clinic stop code, which is the same for all cardiology services); **F3) volume of AF** (# of patients with AF from that facility); **F4) presence of anticoagulation clinic at facility** based on compiled clinic stop codes validated by survey data (completed); **F5) volume of anticoagulation therapy** (# of warfarin prescriptions dispensed from that facility); **F6) presence or use of facility anticoagulation clinic** (based on % of AF patients on warfarin who have at least one visit to stop code 317)[161, 174, 175]**; F7)** presence of **facility academic affiliation**[176]; **F8)** whether the facility is **urban or rural**.[121, 177]. Most of the facility-indicator variables have already been created. We considered provider-level variables, but constructs such as provider type (physician, nurse practitioner) and specialty (internal medicine, cardiology) rely on identification of the provider who initiated warfarin therapy. This will be difficult to capture in administrative data, since warfarin prescriptions may dispensed by an anticoagulation clinic and may not be linked to the physician who actually requested or initiated anticoagulation services.

6.2.3.3. Specific Aim 1.3: To determine whether processes of stroke prevention care predict clinical outcomes in veterans with atrial fibrillation or atrial flutter. **Hypothesis 1.3a: process measures such as TTR are independently associated with reduction in stroke/TIA and mortality; 1.3b:** Time out of **therapeutic range (1-TTR) is independently associated with bleeding events.** Using **P1-P6 as predictor variables**, we will examine outcomes of **O1) stroke and TIA** based on ICD-9 codes in NCPD and CMS data. We will use the high-sensitivity and high-specificity methods for stroke data extraction; **O2) death** using data from VA BIRLS, PTF, and EXT[178] data which is 90% complete.[179] CMS data will be used to capture additional deaths; **O3) bleeding events** using a validated ICD9-based algorithm created by HSR&D investigator Dan Berlowitz MD[180-182] to capture any inpatient stay with an ICD9 code for hemorrhage as a primary diagnosis in NCPD and CMS data. This method has been successfully applied in identifying bleeding events in CHF patients.

6.2.4. Statistical analysis and power: Aim 1.1 is descriptive. We will use t-test (or analysis of variance) and chi-square testing for comparisions of continuous and dichotomous variables. We will compare across facility-level strata (region of U.S., VA facility size, rural/urban) to provide a comprehensive overview of AF care across the VHA. For Aim 1.2, we will use hierarchical, mixed-

effects models for the specified binary outcomes (patient and facility level). Provider characteristics will be modeled at the patient level. For Aim 1.3, after verifying assumptions of proportional hazards[183, 184], we will apply the Kaplan-Meier method and Cox regression for time to individual (not composite) outcomes (stroke/TIA, hemorrhage, death, new heart failure, and ventricular arrhythmias). For objective 1, we calculate statistical power from our most conservative hypothesis from aim 1.3, based on appropriate TTR (n=18,882) and low TTR (n=55,307) from the TEAM database. Assuming a conservative (very low) age-adjusted one-year stroke rate of 0.5%, we have power $(1-\beta)$ of 0.85 to detect a difference of 0.02% (two-tailed α = 0.05) using a Power and Precision approach. Power $(1-\beta)$ for this difference decreases to 0.80 when accounting for an effective 20% sample size reduction due to clustering. However, will use hierarchical models and first assess for clustering. Based on this conservative estimate, we will have ample power to test all hypotheses for larger, clinically meaningful differences. Most analyses will be performed using STATA based on experience of the applicant and mentors Heidenreich and Phibbs, with conversions from VA SAS format made using STAT-Transfer. Some mixed-effect and generalized linear-model (GLM) functions in SAS are more robust, and we will use these when required.

6.3. OBJECTIVE 2: To evaluate the quality of arrhythmia management care in veterans with atrial fibrillation or atrial flutter.

Specific Aim 2.1: To characterize the use of strategies for management of atrial fibrillation and flutter (rate control, antiarrhythmic therapy, electrophysiology ablation, pacing or cardiac resynchronization)

Specific Aim 2.2: To identify predictors of use of different strategies at the patient (clinical), provider, and facility level

Specific Aim 2.3: To determine clinical outcomes associated with each treatment strategy

6.3.1. DATA SOURCES, AVAILABILITY, COMPONENTS:

6.3.1.1 Database: Creation of the dataset for this objective will be performed as part of a proposed HSR&D IIR-MERIT project to examine the impact of dual use of VA and Medicare services on quality of stroke prevention (PI: Frayne (co-mentor); submitted 12/08). Dr. Heidenreich (primary mentor), Dr. Phibbs (co-mentor), and I are co-investigators for this proposal. Specifically, Dr. Phibbs will lead the study's database development team of which I will be a core member.

6.3.1.2 Data sources: The core data elements will be similar to the TEAM database (Obj 1). We will use VA **NPCD**, **DSS** (**Pharmacy**, **Lab**), **Vital Status** data for **FY06-FY07** linked to **Medicare (CMS)** data for the same period. The justification for using newer data is that more recent data (**FY06-FY07**) will have a higher prevalence of contemporary invasive procedures for AF such as catheter ablation and cardiac resynchronization therapy in VA and Medicare facilities, which better reflect the current conceptual framework of AF care. We will also append the superset data of the TEAM Database (Objective 1) to the new dataset to provide a continuous six-year period of observation for the cohort (Table 4). In addition, we proposed to link the **VA vital signs package**: This centralized dataset, housed at VA's Corporate Data Warehouse (CDW), includes heart rate and blood pressure obtained from each facility VISTA package.[185] The data for FY04-07 is available through VIReC.[186] Linking of vital sign extracts to VA NPCD data has been successfully performed by mentors Frayne and Phibbs on an unrelated project (NIMH 1R01 MH085799-01), demonstrating feasibility.

Table 4: Data sources and structure for Objective 2

Data Fiscal Year	TEAM Database (Obj 1) (Constructed, ready for use)				Dual Use DB (Proposed)	
	FY02	FY03	FY04	FY05	FY06	FY07
Key Construct:						
Identify AF subjects		x x	x x x x	x x x x		
Arrhythmia care processes*			x x x x	x x x x	x x	
Outcomes					x x x x	x x x x
Database components						
VA NPCD	x x x x	x x x x	x x x x	x x x x	x x x x	x x x x
Vital Status (cumulative)				x		x
DSS Pharmacy	x x x x	x x x x	x x x x	x x x x	x x x x	x x x x
Medicare	x x x x	x x x x	x x x x	x x x x	x x x x	x x x x
Additonal sources:						
Vitals Signs			x x x x	x x x x	x x x x	x x x x

* medical rate control, medical rhythm control, antiarrhythmic therapy, pacing

This new, expanded dataset has multiple advantages: 1) a longer period for determining chronicity of AF, since invasive therapies are more frequently used in recurrent or long-standing AF; 2) a longer time window for evaluating processes of care; 3) a longer follow-up for outcomes; **4) preliminary and baseline analyses can be performed without dependence on funding of the AF-Dual Use proposal, funding of my own planned MERIT proposal for this project, or acquisition of FY06-FY07 VA or Medicare data**.

6.3.2. Specific Aim 2.1: To characterize use of strategies for management of atrial fibrillation and flutter (rate control, antiarrhythmic therapy, electrophysiology ablation, pacing or cardiac resynchronization). This *descriptive* analysis parallels Aim 1A. In veterans with AF, we will examine the frequency of the following arrhythmia management strategies in the VHA and Medicare: **S1) rate control** with atrioventricular nodal drug therapy by drug name, dose, and class (DSS data); **S2) rhythm control** with antiarrhythmic drug therapy by drug name, dose, and class (DSS data); **S3) catheter ablation** of atrial fibrillation or flutter defined by NCPD and Medicare CPT codes; **S4)** catheter **ablation of AV node** (CPT code); **S5)** permanent single- or dual-chamber **pacemaker** implantation (CPT codes); **S6) cardiac resynchronization therapy** (CPT code); **S7)** electrical **cardioversion** (CPT code)**; S7) combined strategies based** on face validity from clinical relevance since therapies are not mutually exclusive; **S8)** no therapies (defined by absence of all codes in NCPD and Medicare data). Stratification methods are similar to those of Aim 1A. In addition, we will also stratify based on duration of AF.

6.3.3. Specific Aim 2.2: To identify predictors of use of different strategies at the patient (clinical), provider, and facility level. This analysis plan parallels Aim 1.2. We will use variables **V1-V7** as patient-level predictors and also **V9) mean heart rate, averaged from vital sign data over 4 quarters**. We wil use **F1-F3, F7-F8** as facility-level predictors. In addition, we will examine **provider medical specialty** of the provider who prescribes initial (non-refill) rate control or rhythm control medications for AF. We will examine the strategies **S1-S8** as *dependent variables* (outcomes) in our defined cohorts both individually and by grouping them as medical rate-control strategies (S1,S4,S5) and rhythm control strategies (S2, S3, S7).

6.3.4. Specific Aim 2.3: To determine clinical outcomes associated with each treatment strategy. This analysis parallels Aim 1.3. Using strategies **S1-S8** as predictor variables, we will examine the following outcomes: **1) hospitalization for AF** is determined when AF-related ICD-9 codes are the primary code for hospitalization; **2) frequency of tachycardia** (HR > 90 or 100) is determined by outpatient vital sign data; **3) incident heart failure** is determined by inpatient and outpatient ICD-9 codes using well-validated ICD-9 extraction algorithms; **4) hospitalization for heart failure** is determined when heart failure-related ICD-9 codes are the primary code for hospitalization; **5) ventricular arrhythmia** is determined by ICD-9 codes; **6) stroke/TIA** using methods in aim 1.3; **7) death** from vital status files.

6.3.5. Statistical analysis and power: Our plan parallels the analysis plan for Objective 1. Aims 2.1 and 2.2 will use the approaches outlined for Aims 1.1 and 1.2, respectively. Aim 2.3 will use the survival anaysis methods described for 1.3. In addition, for Aim 2.3 some repeated outcomes (tachycardia episodes, AF hospitalization, heart failure hospitalization) will be tallied through the end of follow-up and presented as means for each strata (arrhythmia management strategy) and as continuous outcomes in regression models. We performed conservative power calculations based on our prevalence of medical rate control (59%) and medical rhythm control (13%) in our VAPAHCS holter cohort. Using our smallest subcohort (74,149 veterans in whom TTR data is complete), and assuming a very low AF hospitalization rate of 1.5% through the end of follow-up, we have power (1-ß) of 0.98 (or 0.94 with 20% clustering) to detect a difference of 0.05% (two-tailed α = 0.05) using a Power and Precision approach. For invasive procedures, whose prevalence will be much lower, we require analysis of a minimum of 150 procedures to be able to demonstrate a clinically-meaningful absolute risk difference of 5% (above a background rate of 1%) compared to medical rate control, with two-tailed α = 0.05 and power of 0.85. This corresponds to a conservative 0.05% prevalence or penetration of invasive EP procedures in non-rate control patients.

6.3.6. Potential problems and alternative approaches:

6.3.6.1. Lack of CPT procedure codes in Medicare managed care patients, whose plans are capitated rather than true fee-for-service. This situation could lead to informative missingness in veterans in whom Medicare procedure data is unavailable, although patients with VA insurance may be less likely to use Medicare managed care for elective procedures. We will perform sensitivity analyses by comparing point estimates in subcohorts based on VA priority status and designation of Medicare HMO care. We will also include these indicators as variables in our models to assess for informative missingness and potential interaction.

6.3.6.2. Lack of captured information for electrophysiology ablation procedures. Differential coding of VA encounters for ablation procedures could confound perceived facility variation in care. Although Medicare data usually reflects accurate coding because of linked reimbursements, there may be more variation in the VHA, particularly if there is a lag in availability of newer CPT codes related to AF ablation in the VA Computerized Patient Records System. Among facilities performing ablations, we will look for clustering of CPT cardiovascular procedure codes. If there is clustering, then we will survey VA centers performing ablations to inquire about encounter coding practices. We can then screen our data using facility-specific codes and compare point estimates to results using standardized codes across VHA. For device implants (single-chamber, dual-chamber, and biventricular pacemakers), we expect less variation because these procedures have been performed longer and VHA has implemented pacemaker coding and data quality control guidelines since 1990.[138] Coding validation for device implants could be performed by linking our dataset to the VA Pacemaker Surveillance Registry (Director: Edmund Keung), but we do not expect this to be necessary.

6.3.6.3. Availability of data. The database for Objective 2 will combine the TEAM dataset from Objective 1, which is already in our possession, with elements from new data sources that have been requested as part of a separate MERIT proposal on which I am a co-investigator (§ 6.3.1). If that project does not get funded, then I will still be able to generate preliminary and baseline data from the TEAM dataset. These findings could serve as the basis for my own IIR-proposal, in which I would then request funds for dataset expansion. Also, if there are unanticipated delays in obtaining additional Medicare data, then we can still readily proceed with planned analyses using VA and Medicare data (FY02-FY04) already in our possession.

6.4 OBJECTIVE 3: To develop a reminder instrument to guide VA care providers on evidence-based strategies for stroke prevention and arrhythmia management in patients.

> *Specific Aim 3.1: To pilot two simplified, guideline-based reminder instruments directed at providers for stroke prevention and arrhythmia management in veterans with AF.*
> *Specific Aim 3.2: To **design** a randomized-clinical trial to evaluate an optimal reminder instrument.*

6.4.1. Specific Aim 3.1: Hypothesis 3.1: Cardiology report-based reminders for anticoagulation and arrhythmia management for AF will be viewed by providers who manage AF care. We will pilot two instruments 1) to facilitate rapid calculation of the patient's risk of stroke, based on guidelines; 2) to recognize high resting heart rates in AF; 3) to advise providers on guideline-based strategies for management. **Instrument A will be attached to the patient's cardiac ultrasound (echocardiogram) report**; **Instrument B will be attached to the patient's electrocardiogram (ECG) report.** We selected these platforms for reminders because these tests are generally prompted by AF diagnosis and are

> **Proposed reminder attachment:**
> *"1) Patients with atrial fibrillation or atrial flutter are at risk of stroke and other thromboembolic events. Oral anticoagulation with warfarin (Coumadin) is recommended in patients with prior stroke (including transient ischemic attack) or with two or more of the following risk factors: age > 75 years, hypertension, diabetes, heart failure symptoms or EF ≤ 35%. Aspirin or warfarin is recommended for one or two of these factors. No therapy is recommended if there are contraindications or zero risk factors. Consider referral to Cardiology service if your patient does not meet these guidelines.*
>
> *2) [The patient's heart rate in AF is _____.] Control of heart rate with medications including select beta blockers and calcium channel blockers is recommended for patients with persistent or recurrent paroxysmal atrial fibrillation or flutter. In patients with poor heart rate control despite medications or with AF symptoms despite heart rate control, antiarrhythmic drug therapy or catheter ablation may be beneficial. Consider referral to Cardiology service if your patient does not meet these guidelines."*

typically ordered by care providers that manage AF. As a result, we believe that reminder fatigue is less likely. Pretesting of pilot instruments will be conducted via interviews with VA primary care providers and cardiologists. We will then pilot the instruments at the VAPAHCS ECG and echocardiography laboratories in 50 consecutive outpatient ECGs and 50 outpatient echocardiograms in which AF is the indication for the test or is the rhythm during the study. The primary outcome at 60 days will be provider awareness of the reminder based on an e-mail survey to the provider (1 additional e-mail if no response). As part of the pretesting process for the planned clinical trial, we will also survey providers for their opinion of the reminder and its language and content. Secondary outcomes at 3 months are: 1) proportion of patients with guideline-concordant anticoagulation therapy; 2) proportion of patients prescribed rate control medications, antiarrhythmic drug therapy, or referred to cardiology.

6.4.2. Specific Aim 3.2: To **design** a randomized-clinical trial to evaluate an optimal reminder instrument. **Hypothesis 3.2: An optimal clinical reminder instrument will improve guideline adherence and quality of AF care.** Our goal is to design a randomized clinical trial to evaluate optimal instrument(s) based on results from Aim 3.1. This project will enable me to gain experience in designing and conducting a clinical trial. I will also learn methods unique to provider intervention studies. The experience would help fill an important gap in my research background, as this would be the first clinical trial that I conduct.

We expect the trial to be feasible for a variety of reasons. First, a similar study design has been previously used by the primary mentor for an IIR-MERIT project to study clinical reminders for heart failure medications[16, 17] and to evaluate other echo-reminder systems.[19, 133] The largest and most recent of these randomized trials evaluated a reminder for beta-blocker therapy in veterans with heart failure at three echocardiography labs in VAPAHCS (PI: Heidenreich (mentor); Co-investigator: Goldstein (advisor/consultant). We believe that starting the trial during the 5-year CDA period may even be possible for a number of reasons. First, the Institutional Review Board (IRB) approved a waiver of consent on these studies. Such a waiver will dramatically boost enrollment, improve efficiency, and reduce project costs. This will also allow us to complete enrollment in a relatively short time frame. Second, the mentor has created an automated computerized system that, with only a few mouse clicks, will instantly determine patient eligibility and randomize the patient. The system then automatically performs the intervention based on randomization (attaches or omits the clinical reminder to the echocardiography report).[17] As a result, this trial, like the mentor's previous reminder studies, can be performed cheaply and efficiently with minimal overhead or research staff.

Still, there are complex methodological issues that are unique to this study. I will be challenged to craft a study design and research protocol that address issues of multi-arm design, multi-level randomization (patient, provider, or both), contamination, reminder fatigue, reminder persistence, dropout, and informative censoring. I will also gain experience in survey analysis, project management, team organization, and collaboration.

6.4.3. Statistical analysis and power: For Aim 3.1, the goal is to demonstrate feasibility of meeting a provider awareness rate of 75% for one or both instruments, based on results from the mentor's previous study.[17] With 30 reports per pilot instrument, we have 85% power to achieve this (two-tailed α = 0.05). We have increased the size to 50 reports per instrument to account for provider nonresponders and for potential contamination. For Aim 3.2, our sample size of 400 subjects per arm may change based on pilot findings. We determined that 346 subjects per arm is powered to detect a 10% difference, assuming a baseline guideline-concordance rate of 60%, with two-tailed α = 0.05 and ß = 0.80. These numbers are based on data from Dr. Heidenreich and Dr. Goldstein's beta blocker study, which randomized 1546 patients and found a beta-blocker prescription rate of 66% in the control arm and 74% in the intervention arm.[17]

6.4.4. Potential problems and alternative approaches:

6.4.4.1 Contamination: A small proportion of providers will have patients included in both the ECG and echocardiogram reminder pilot studies. For the primary outcome, awareness of one study (e.g. ECG) may contaminate their awareness of the other (e.g. echocardiogram). For the primary analysis, we will calculate the primary outcome with and without providers exposed to

both types of interventions. We will also examine this provider group separately to estimate the magnitude of contamination. These estimates will allow us to determine the magnitude of contamination effect which will useful in designing the randomized trial.

6.4.4.2 Low provider survey response rate. The response rate was 81% in the beta blocker reminder trial.[17] Our sample size is powered for a response rate as low as 60%. Indeed, we can extend our pilot studies (with IRB approval) to include more subjects if needed.

6.4.4.3 Low impact of pilot reminders. This is unlikely but would indicate that the reminder is poorly designed, has poor penetrance, or is directed at the wrong providers. We would then redirect our efforts to develop new constructs or explore different reminder platforms. Alternatives include VISTA or CPRS-based reminders, real-time calculators of patient stroke risk, and real-time assessments for patient time in therapeutic range (TTR). Dr. Goldstein's expertise in this area will be very valuable if alternative approaches must be considered.

6.5 TIMELINE AND FEASIBILITY FOR ALL OBJECTIVES: Given the limited resources available from a career development award, feasibility is always a concern. Therefore, we have carefully considered the appropriate scope of work for this proposal, and we have designed the studies in a manner that we believe to be both meaningful and eminently feasible within the context of this five-year award. Because **Objective 1** takes advantage of a parent study with an existing dataset that is ready for analysis, Aims 1.1, 1.2, and 1.3 can be completed within the first two years. **Objective 2** will require more time for data preparation due to receipt and linkage of multiple data sources. However, because most baseline and predictor variables are already in hand as part of the TEAM dataset, we can readily proceed with preliminary and baseline analyses for Aims 2.1 and portions of Aim 2.2, even in the first or early part of the second year. **Objective 3** is a clinical study and independent of methods and results of the other projects. Therefore, planning and implementation of the pilot reminder studies can be performed concurrently with Objectives 1 and 2. We believe that the pilot reminder studies are feasible based on our

Table 5: Project Management Plan (Refer to Career Plan for funding timeline)	Pre CDA	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Related work						
Holter cohort manuscript	X					
Heart & Soul cohort AF study	X					
AF-Mental Health Conditions Co-investigator	X	X				
Dual Use: Safe in AF Co-investigator	X	X	X	X		
Objective 1:						
Merge data sources, perform data checks, identify cohort	X					
Create baseline, predictor, and process of care variables	X	X				
Create dependent variables		X				
Analyses for Aims 1.1, 1.2, 1.3		X	X			
Abstract presentation and manuscript preparation			X	(X)		
Objective 2:						
Obtain data sources, merge data sources		X	X			
Perform data checks, identify cohort			X	X		
Create baseline, predictor, and process of care variables		(X)	X	X		
Create dependent variables				X	X	
Analyses for Aims 2.1, 2.2, 2.3				X	X	
Abstract presentation and manuscript preparation					X	X
Objective 3:						
CHR application and IRB approval		X				
Design, pretesting, and refining of pilot instruments		(X)	X			
Modification of automated reminder system		X	X			
Pilot study implementation and enrollment			X	X		
End of pilot study, physician survey, study analysis				X		
Abstract presentation, possible methods paper				X		
Reminder intervention refinement					X	
Randomized trial design					X	X
Randomized trial enrollment						(X)

group's prior work, experience, infrastructure, and resources. IIR funding proposals for the randomized trial will occur during the third year of the award and we believe that enrollment can start in the beginning of the fifth year, perhaps earlier.