

Atrial fibrillation affects over 2 million people in the United States and accounts for 1% of all emergency department visits and nearly \$7 billion in healthcare expenditures. Emergency department physicians have little information to guide the management of patients with symptomatic atrial fibrillation and, largely as a result, admit more than 65% for an inpatient stay. Studies suggest that nearly half of these admissions could be safely avoided. Emergency physicians need improved methods to identify the low risk atrial fibrillation patient who does not require hospitalization.

We hypothesize that readily available emergency department data can be utilized in an atrial fibrillation clinical prediction rule to identify those patients at low or high risk for adverse outcome. We propose developing and validating a multivariable clinical prediction rule that accurately estimates risk for adverse outcome in emergency department patients with atrial fibrillation. We will describe and analyze the rule's utility by the distribution of assigned risk and its impact on physician decision-making.

To develop our prediction rule, we will measure nineteen independent variables that are routinely available to the emergency physician within the first two hours of emergency department management. These variables will include patient history and physical examination findings, vital signs, and common laboratory studies. These data will be incorporated into the development of our prediction rule, while adhering to established clinical and biostatistical standards. Our proposed rule will predict risk for both 5-day and 30-day adverse outcomes. This 5-day outcome is more applicable to the emergency department setting where standard 30-day outcomes are highly dependent on unpredictable, post-visit patient and provider behavior. This proposed study will also collect and store blood and plasma samples for future analysis.

The development of a highly accurate prediction rule will significantly advance the treatment of atrial fibrillation and reduce unnecessary hospitalizations. This is the initial step toward our goal of improving the emergency department management of atrial fibrillation and reducing unnecessary resource utilization through more appropriate dispositions and individualized pharmacologic treatment.

Atrial fibrillation, a disorder in which the heart beats irregularly, affects over two million Americans and is associated with a four-fold increase in the risk of stroke. Nearly 75% of patients treated in emergency departments for atrial fibrillation are hospitalized and the annual treatment costs exceed \$6.65 billion. Our clinical study will enhance management of patients with acute atrial fibrillation by improving physician disposition decisions and reducing unnecessary costly hospitalizations.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME Barrett, Tyler Warren		POSITION TITLE Assistant Professor of Emergency Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) BARRETTTW			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.S.	September 1993-May 1997	Psychology
Vanderbilt University School of Medicine	M.D.	Aug 1997- May 2001	Medicine
Vanderbilt University School of Medicine	M. Sc	August 2008-pres.	Clinical Investigation

A. Positions and Honors.

Positions and Employment

2001-2002 Transitional Year Intern, Los Angeles County Harbor-UCLA Medical Center
2002-2004 Emergency Medicine Residency, UCLA Medical Center, Los Angeles, CA
2004-2005 Chief Emergency Medicine Resident, UCLA Medical Center, Los Angeles, CA
July 2005- Attending Physician, Department of Emergency Medicine, Vanderbilt University
Medicine Center, Nashville, TN
July 2005- Assistant Professor of Emergency Medicine, Vanderbilt University School of Medicine,
Nashville, TN

Other Experience and Professional Memberships

2000-Present American College of Emergency Physicians
2001-2005 Society of Academic Emergency Medicine
2003-2005 Emergency Physician, Kaiser-Permanente, Baldwin Hills Emergency Department,
Baldwin Park, CA
July 2004 Emergency Physician Lecturer and Consultant, British-American Family Medicine Clinic
and Urgent Care, Saint Petersburg, Russia
Dec. 2004 Emergency Physician Lecturer and Consultant, Project HOPE-UCLA Center for
International Emergency Medicine, Shanghai, China
2005-Present State of Tennessee Medical Doctor
2006-Present Diplomat, American Board of Emergency Medicine
2008-Present Society of Academic Emergency Medicine
2008-Present Editorial Board, *Annals of Emergency Medicine*
2009-Present American Heart Association

Honors

1994-1995 **GCRC Clinical Study Unit Student Research Award**
National Institutes of Health, New England Medical Center, Boston, MA
1994-1997 **LS&A College Honors**
University of Michigan, Ann Arbor, Michigan

1996-1997	Order of Angell Senior Honor Society University of Michigan, Ann Arbor, Michigan
1998	Canby Robinson Research Fellowship in Emergency Medicine Vanderbilt University School of Medicine
1999-2001	Microbes and Defense Society Vanderbilt School of Medicine Honor society
2001	Excellence in Emergency Medicine Society for Academic Emergency Medicine
2004-2005	Chief Resident in Emergency Medicine UCLA/Olive View-UCLA Emergency Medicine Residency
2005	Nurses Choice Award Olive View-UCLA Emergency Department Nursing Staff
2008	Top Peer Reviewer - 2007 <i>Annals of Emergency Medicine</i>
2008	Vanderbilt Physician-Scientist Development Program Award Vanderbilt University Medical Center
2008	Fellow of the American College of Emergency Physicians American College of Emergency Physicians
2009	Top Peer Reviewer - 2008 <i>Annals of Emergency Medicine</i>

B. Selected peer-reviewed publications (in chronological order).

Original research and theoretical treatises (Peer reviewed).

1. Sundaram S, **Barrett TW**, Cendroglo M, King AJ, Pereira BJG. Transmembrane passage of cytokine inducing bacterial products across new and reprocessed polysulfone dialyzers. *J Amer Soc Nephrol* 1996; 7: 2183-2191. PMID: 8915979
2. Sundaram S, **Barrett TW**, Butt NK, Porat R, Hogan P, King AJ, Pereira BJG. Cytokine production by human peripheral blood mononuclear cells stimulated by a *pseudomonas aeruginosa* culture filtrate: role of plasma and polymixin B. *Int J Artif Org* 1996; 19: 276-283. PMID: 8791147
3. Pereira BJG, Sundaram S, **Barrett TW**, Butt NK, Porat R, King AJ, Dinarello CA. Transfer of cytokine-inducing bacterial products across hemodialysis membranes: role of bacterial species, plasma and whole blood. *Clin Nephrol* 1996; 46: 394-401. PMID: 8982556
4. Jaber BL, **Barrett TW**, Cendoroglo NM, Sundaram S, King AJ, Pereira BJ. Removal of cytokine inducing substances by polymixin-B immobilized polystyrene-derivative fibers during in vitro hemoperfusion of 10% human plasma containing staphylococcus aureus challenge. *ASAIO J.* 1998; 44: 48-53. PMID: 9466501
5. Jaber BL, **Barrett TW**, Cendoroglo NM, Sundaram S, King AJ, Pereira BJ. Endotoxin removal by polymixin-B immobilized polystyrene-derivative fibers during in vitro hemoperfusion of 10% human plasma containing staphylococcus aureus challenge. *ASAIO J.* 1998; 44: 54-61. PMID: 9466502
6. **Barrett TW**, Norton VC. Parental knowledge of different acetaminophen concentrations for infants and children. *Acad Emerg Med.* 2000; 7:718-721. PMID: 10905654
7. **Barrett TW**, Norton VC, Slovis CM, Maron DJ, Busam M, Boyd J. Self-reported cardiac risk factors in emergency department nurses and paramedics. *Prehospital and Disaster Medicine.* 2000; 15: 14-17. PMID: 10905654
8. **Barrett TW**, Moran GJ. Commentary (CDC Update) Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants-Colorado, Indiana, Pennsylvania, and Los Angeles County, 2002-2003. *Ann Emerg Med* 2004; 43: 43-47. PMID: 14707939
9. **Barrett TW**, Mower WM, Zucker MI, Hoffman JR. Injuries missed by limited computed tomographic imaging of patients with cervical spine injuries. *Ann Emerg Med* 2006; 47: 129-133. PMID: 16431221
10. Brywczyński JJ, **Barrett TW**, Lyon JA, Cotton BA. A Structured Literature Review of Penetrating Neck Injury Management in the Emergency Department. *Emerg Med J* 2008; 25:711-5. PMID: 18955599

11. **Barrett TW**, Schierling M, Zhou C, Colfax JD, Russ S, Conatser P, Lancaster P, Wrenn K. Prevalence of Incidental Findings in Trauma Patients Detected by Computed Tomography Imaging. *Am J Emerg Med*; 2009; 27(4): 428-435.
12. Moran GJ, **Barrett TW**, Mower WR, Krishnadasan A, Abrahamian F, Ong S, Nakase JY, Pinner RW, Kuehnert MJ, Jarvis WR, Talan DA for the EMERGENCY ID NET Study Group. Decision Instrument for the Isolation of Pneumonia Patients with Suspected Pulmonary Tuberculosis Admitted through U.S. Emergency Departments. *Ann Emerg Med*; 2009; 53(5): 625-632. PMID: 18760503

Non-experimental articles *Annals of Emergency Medicine Journal Club – Papers Authored*

1. **Barrett TW**, Schriger DL. Pines JM, Hollander JE Emergency Department Crowding is Associated with Poor Care for Patients with Severe Pain. *Ann Emerg Med* 2008; 51:6-7.
2. **Barrett TW**, Schriger DL. Haukoos JS, Hopkins E, Byyny, RL, for the Denver Emergency Department HIV Testing Study Group. Patient acceptance of Rapid HIV testing practices in an urban emergency department: assessment of the 2006 CDC recommendations for HIV Screening in Health Care Settings. *Ann Emerg Med* 2008; 51:310-311.
3. **Barrett TW**, Schriger DL. Miller AH, Nazeer S, Pepe P, et al Acutely Decompensated Heart Failure in a County Emergency Department: A Double Blind Randomized Controlled Comparison of Nesiritide Versus Placebo Treatment. *Ann Emerg Med* 2008; 51: 580-582.
4. **Barrett TW**, Schriger DL. Measures of Emergency Department Crowding, Odds Ratios, and the Dangers of Making Continuous Data Categorical: Answers to January 2008 Journal Club Questions. *Ann Emerg Med* 2008; 51: 782-789.
5. **Barrett TW**, Schriger DL. Practical considerations in HIV testing in the emergency department, characteristics of diagnostic tests and the role of sensitivity analysis in observational studies: Answers to March 2008 Journal Club Questions. *Ann Emerg Med* 2008; 52: 170-181.
6. Brywczyński JJ, **Barrett TW**, Schriger DL. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ Out-of-Hospital Continuous Positive Airway Pressure Ventilation Versus Usual Care in Acute Respiratory Failure: A Randomized Controlled Trial. *Ann Emerg Med* 2008; 52: 242-243.
7. **Barrett TW**, Schriger DL. Acutely Decompensated Heart Failure in a County Emergency Department: A Double-Blind Randomized Controlled Comparison of Nesiritide Versus Placebo Treatment Answers to May 2008 Journal Club Questions. *Ann Emerg Med* 2008;52(4):458-472.
8. Heavrin BS, **Barrett TW**, Schriger DL. The National Report Card on the State of Emergency Medicine: Evaluating the Emergency Care Environment State by State 2009 Edition. *Ann Emerg Med* 2009;53:155-156.

Textbooks:

1. Seamens C, **Barrett T**. DRUGology 2006. *Vanderbilt University Press*.
2. Seamens C, **Barrett T**. DRUGology 2007. *Vanderbilt University Press*.
3. Seamens C, **Barrett T**. DRUGology 2008. *Vanderbilt University Press*.

Abstracts

1. Boyd J, Norton VC, Busam M, **Barrett T**. Comparison of manual and automatic blood pressure measurements in trauma patients. *Acad Emerg Med*. 1999; 482- 483.
2. Boyd J, Norton VC, Busam M, **Barrett T**, Wright S. Patient attitudes regarding the performance of procedures on the newly dead. *Acad Emerg Med*. 1999; 6:545-546.
3. Norton VC, Zimmerman G, Busam M, **Barrett TW**, Boyd J. EMLA cream reduces the pain of IV starts in adult ED patients when applied at triage. *Acad Emerg Med*. 2000; 7:531.
4. Berger C, Smith C, **Barrett T**, Thurman R, Wrenn K. Ability of Emergency Physicians to Predict Clinically Significant Traumatic Injury-Physician Assessment Versus Computed Tomography. *Acad Emerg Med*. 2007; 14:S138.
5. Brywczyński J, **Barrett TW**, Estrada C, Jenkins C, Johnson M, Zhou C, Abramo T. Cerebral And Somatic Tissue Oxygenation Monitoring In Major Trauma Patients During Aeromedical Transport. *Acad Emerg Med*. 2009; 16: S192.
6. **Barrett TW**, Brywczyński J, Estrada C, Jenkins C, Johnson M, Zhou C, Abramo T. The Utility Of Near-Infrared Spectroscopy In The Prehospital Evaluation Of Trauma Patients. *Acad Emerg Med*. 2009; 16: S184.

10. Specific Aims

Over 2 million people in the United States have atrial fibrillation (**AF**), the most common sustained cardiac arrhythmia in clinical practice.¹ This number is expected to increase to 5.6 million by 2050.¹ AF is associated with a 5-fold increase in the risk of stroke and 1.5 to 1.9 increased risk of death.¹⁻⁶ One percent of all US emergency department (**ED**) visits are for complaints related to AF.⁷ Our ability to accurately risk-stratify AF patients presenting to the ED is poor and more than 65% of these ED visits result in hospital admission and contribute to the \$6.65 billion in healthcare expenditures.⁸ Studies have shown that nearly half of these admissions could be avoided and patients safely discharged home.⁹⁻¹¹ The National Heart, Lung, and Blood Institute (**NHLBI**) recently identified AF prevention and treatment as a major priority, especially the development of AF prediction risk models.¹² A major challenge for emergency physicians is to differentiate between patients who are at low risk for adverse outcomes and thereby safe to discharge from the ED and those at high risk who require inpatient monitoring and treatment. However, an ED-based AF prediction risk model for this very common arrhythmia has thus far not been reported. We propose the development of a multivariable emergency department AF prediction rule (**AFPR**) based on established clinical and biostatistical standards.¹³⁻²³ We will target *symptomatic AF* defined as ED patients with a new or established diagnosis of AF or atrial flutter that require ED evaluation for a complaint thought related to their rhythm disturbance.

Our AFPR will be an accurate, objective, validated, reliable clinical prediction rule to risk-stratify ED patients presenting with AF exacerbations. It will incorporate patient history and examination findings, vital signs, and laboratory studies obtained upon ED presentation, as well as trends over the first 2 *hours* of care. Our AFPR will incorporate those determinants that are statistically demonstrated to identify low risk of 5-day and 30-day adverse outcomes. In addition, we will identify high-risk patients early in their ED evaluation that should be admitted. ***Our long-term goals are to improve emergency department management of AF through highly accurate risk stratification and appropriate patient disposition, followed by development of individualized pharmacologic treatment protocols, such that we can reduce resource use and improve patient care.*** Such risk models and individualized treatment plans for symptomatic AF requiring emergent care will be of significant value given the increasing incidence and high admission rate of this common problem.²⁴

We propose the following:

SPECIFIC AIM #1

To develop and validate a multivariable clinical prediction rule that accurately estimates risk for adverse outcomes in patients presenting to the ED with symptomatic AF.

We hypothesize that readily available ED data can be utilized in an AF clinical prediction rule to identify those patients at low or high risk for adverse outcomes.

SPECIFIC AIM #2

2.a. To describe and analyze the rule's utility by the distribution of assigned risk and its impact on physician decision-making.

We hypothesize that assigned risk can be utilized to drive physician decision-making by identifying patients who do not require hospital admission (**low risk**) and patients needing hospitalization (**high risk**).

2.b. To translate our results into a clinically useful format. We hypothesize that a facile version of the AFPR will be easily incorporated into standard ED patient management systems and assist physicians with risk stratification of patients presenting with AF.

2. Candidate's Background

Undergraduate, Medical School, and Residency: My interest in medical research originated during a period of financial support and mentorship while I was an undergraduate at the University of Michigan. I was the recipient of a National Institutes of Health GCRC Clinical Study Unit Student Research Award in 1994 and 1995. I worked for 3 summers in Dr. Brian Pereira's laboratory measuring plasma cytokine response and the transfer of bacterial products across in vitro hemodialysis systems. These projects resulted in five peer-reviewed publications and confirmed my decision to pursue a medical career. After graduating with a B.S. in Psychology, I attended medical school at Vanderbilt University and subsequently became interested in a diverse array of medical disciplines with the common link of acute care. During my first year of medical school, I surveyed parents in the Pediatric Emergency Department regarding their knowledge of acetaminophen dosing and administration. This sparked my interest in studying the best ways to treat acutely ill patients. I was awarded a Vanderbilt Canby Robinson Research Fellowship the summer after my first year of medical school. My subsequent participation in multiple clinical studies in the Emergency Department (ED) confirmed my decision to train in Emergency Medicine and to seek a residency that would prepare me for a career in clinical research.

I completed a Transitional Year internship at Harbor-UCLA Medical Center followed by residency, including a Chief Resident year, at the UCLA/Olive View-UCLA Emergency Medicine program. UCLA is a prominent leader in academic Emergency Medicine with a particular focus on training future clinical research leaders. Throughout my residency, I collaborated with federally funded Emergency Medicine research faculty on a triage prediction model for pulmonary tuberculosis and a subgroup analysis of the National Emergency X-ray Utilization Study. Results from both studies were published in *Annals of Emergency Medicine*. I believe that my initial training in clinical care and ED investigation ideally position me to have a positive impact on acute illness related decision-making, health policy, and healthcare resource utilization.

Faculty Development: After completing my Chief Resident year, I returned to Vanderbilt as a faculty member and joined the rapidly growing Emergency Medicine Research Division. Vanderbilt University Medical Center has a rich history of highly successful clinical research and Dr. Corey Slovis, the department chair, recruited me to fill a role as a developing physician scientist. He subsequently hired Dr. Alan Storrow as Vice-Chair for Research and Academic Affairs and assisted Dr. Storrow in establishing one of the best Emergency Medicine clinical research division infrastructures in the nation. To further support my development, Dr. Slovis reduced my clinical duties allowing my primary focus to become research. In June 2007, I began enrolling patients in the largest randomized clinical trial conducted in the Vanderbilt Emergency Department to date. In April 2008, I was grateful to receive a highly competitive two-year Vanderbilt Physician-Scientist Development Program (VPSD) award that has greatly assisted me in applying for a K23 funding. In August 2008, my department funded my enrollment in the Master of Science in Clinical Investigation (MSCI) program. In the short time that Drs. Storrow and Slovis have been leading Emergency Medicine research activities, our department has soared to sixth place in NIH funded research support among emergency medicine departments nationally.

During my initial years as a faculty member, I considered several areas of research focus. Prior to beginning my MSCI coursework, I decided on atrial fibrillation (AF) as my research area based on my fascination with the arrhythmia, clinical frustrations treating ED patients with AF, the lack of ED-based patient oriented AF research and the increasing prevalence of the disease. The diagnosis of AF is based on well-defined electrocardiogram findings unlike other common ED disease processes such as hypertension or hyperglycemia. These clear and objective diagnostic criteria make AF an excellent disease for ED-based research. My review of the ED-based literature confirmed that emergency physician decision-making for AF treatment and disposition is often based on the clinician's anecdotal experience. Emergency physicians, without clear guidelines on patient management, hospitalize nearly 3 of 4 ED patients with AF leading to substantial use of healthcare resources. My career goal is to study AF with the ultimate goal of improving the ED management, initially by this proposed risk stratification prediction rule, and eventually by implementing a personalized ED treatment approach for AF.

My interest in clinical prognostic research and AF led to collaboration with Dr. Alan Storrow, Dr. Dan Roden, Dr. Dawood Darbar, and Dr. Frank Harrell to develop prognostic models for ED patients with AF. With their support, and time granted from the VPSD award, I performed the pilot analysis presented in *Preliminary Studies* and will present this work as a plenary abstract at the American College of Emergency Physicians Research Forum in October. The results of our work are novel and suggest that objective variables obtained in the ED predict subsequent events. While this research experience was beneficial, I recognize the critical need for further coursework in complex modeling techniques and medical decision-making, as well as further

mentorship from senior cardiovascular, emergency medicine, and biostatistical experts, if I am to become an independent investigator and national leader in this area.

I chose Dr. Storrow as my mentor given his NIH RO1 supported research of risk stratification in heart failure, a disease often associated with AF, his more than 20 years of experience as an emergency medicine research physician, and his successful mentorship of two funded young investigators. The ED is a challenging environment to conduct high-quality, patient-oriented research yet Dr. Storrow has demonstrated a mastery of ED cardiovascular investigations. In addition to this experience, Dr. Storrow has shown a personal interest in my academic development over the past three years. We meet weekly to discuss my research progress and Dr. Storrow is readily available to me at other times since his office is located on the same floor as my own. As an emergency physician, Dr. Storrow has an understanding of the unique characteristics of the ED setting as well as the barriers and solutions that exist to conducting cardiovascular emergency medicine research. Recognizing that the reviewers may perceive a weakness in Dr. Storrow's specific experience in AF, I have enlisted the active collaboration of two internationally known cardiologists, Dr. Darbar and Dr. Roden, who have this expertise. They have invested substantial time in my preliminary studies and the preparation of this application. Their active participation on my mentorship team will complement Dr. Storrow's expertise.

My personal research record and commitment to an academic career are exemplified by twelve peer-reviewed papers (five first authors), eight presented abstracts, eight peer-reviewed Journal Club reviews, and selection to the Editorial Board of *Annals of Emergency Medicine*. I am a co-investigator for RELY, an international registry of patients with atrial fibrillation. We have enrolled over 100 ED patients with AF in the first 6 months since study initiation. I will devote 75% effort to the research proposed in this application, as my clinical responsibilities as an ED attending physician will be limited to 25% effort. Working clinically in the ED provides critical insights into AF questions requiring further study. It also allows me to assess the clinical applicability and feasibility of research and medical advances in real-time and maintains my ability to routinely interact with AF experts. Because the majority of patients with symptomatic AF enter the hospital system through the ED, working clinically is fundamental to understanding the context of a patient's work-up and care.

It is increasingly apparent that ED-based risk-stratification for patients with AF is rarely evidence-based and highly risk-averse. Attempts at risk-stratification in AF have been made but have not been successfully implemented. This failure may be due to the limited clinical utility of the studies conducted to date. Studies have historically focused on identifying high-risk patients, but the ability to accurately identify low-risk patients remains elusive. A prediction rule based on prospectively collected data could improve admission and discharge decision-making. Examples of previous successful endeavors include the APACHE score for the critically ill and PORT pneumonia score. These approaches have improved outcomes and decreased intensive care unit LOS in ED patients with trauma, sepsis and acute lung injury. *Because the majority of symptomatic AF admissions originate in the ED, an emergency physician appropriately trained in research and cardiac emergencies is ideally positioned to advance the science of decision-making during the presentation and early course of treatment for AF.*

Traditionally, there has been a lack of research-trained, NIH-funded emergency physicians specializing in cardiac emergencies. As an emergency physician with training in research methodology, excellent mentoring, and access to an extensive research infrastructure, I am ideally positioned to initiate this program of mentored research.

4. Career Development/Training Activities During Award Period

My broad training and development goals for this K23 are: **a)** enhance my methodological skills and knowledge of decision-making issues related to ED patients with AF and **b)** obtain the necessary professional and academic skills to succeed as an independent investigator. My proposed Career Development Timeline is presented in Table 1. My three specific goals of the award are:

Goal 1: Improve my qualitative and quantitative methodological skills in research design, protocol management, and data analysis.

I am presently completing my Master of Science in Clinical Investigation at Vanderbilt University School of Medicine. I have completed coursework in Biostatistics, Epidemiology, Clinical Trials, Molecular Medicine with an emphasis on AF etiologies, Responsible Conduct of Research and Data Management during the first year of this program. I have also completed a one-week seminar on Clinical Prediction Modeling taught by Dr. Harrell. While the MSCI coursework that I have completed has provided me with a strong foundation, I recognize that I need additional didactic courses to be a successful independent AF investigator. Specifically, I intend to further develop my skills in prognostic research by enrolling in Epidemiology II course in year 1 followed by clinical prediction modeling seminars during year 2 and 3. I will advance my knowledge in AF electrophysiology. In addition, as my long-term goal is to study personalized AF treatment, I will improve my knowledge of pharmacogenomics by enrolling in the human genetics, proteomics, and clinical pharmacology courses described below.

Course 1: Epidemiology II (MPH 514-5508) Dr. Wayne Ray, PhD. This course teaches the proper design of observational studies, assembly and follow-up, exposure measurement, outcome ascertainment, confounding and effect modification, calculation of measures of occurrence and effect, and summary of multivariate statistical analyses. This course will enhance my knowledge in advanced clinical epidemiology, as those skills are important in prognostic research.

Seminar 1 and 2: Short Courses in Medical Decision-Making and Clinical Prediction Modeling. I will enroll in the Basic Psychology of Medical Decision-Making course offered by the Society for Medical Decision-Making. I will also study advanced prediction modeling short courses recommended by Dr. Harrell in Years 3 and 4.

Lecture Series 1: Vanderbilt Electrophysiology Core Curriculum Series. I will actively participate in this twice-monthly series of lectures that focuses on major topics in the Arrhythmia field including management of AF.

Course 2: Human Genetics (MSCI 524-5004) Kelly Taylor, MS CGC. The course will provide me with an up-to-date overview of basic human genetics concepts, molecular genetics, genotyping, mutation detection, approaches for genetic study design and ethical issues regarding genetic studies and the use of DNA samples. This course will update my knowledge on the latest advances in basic genetics and improve my understanding of AF genomic research.

Course 3: Proteomics (MSCI 524-5026) Dr. Lorraine Ware, MD, The objective for this course will be to further my education in clinical proteomics including rationale and description of past studies, selection of candidate biomarkers, assay development, biostatistics analysis and clinical application of proteomic research.

Course 4: Cardiovascular Pharmacology (Pharm 325-1) Dr. Joey V. Barnett, Ph.D. This course will improve my knowledge of cardiovascular pathophysiology, the mechanisms of action of current cardiovascular medications, rationale for drug therapy, and emerging therapies for cardiovascular diseases including AF.

Goal 2: Further my understanding of decision-making issues related to patients with AF

During the period of this award, I will focus on gaining further expertise in the risk stratification of AF, AF epidemiology, investigational AF treatments including the genetic, proteomic and molecular remodeling associations with AF. These associations will be important not only in future risk models but also in the personalized treatment of AF in the ED. Clinical prediction rules are intended to help physicians interpret clinical information to estimate the probability of an outcome. They are meant to augment, not replace, clinical gestalt. Several activities are planned to enhance my understanding of the complex interplay of AF symptoms, response to therapy and their impact on physician disposition decision-making. The first activity will occur via interactions with my cardiology collaborators. My meetings with Drs. Darbar and Roden will broaden my understanding regarding the continuum of AF care from ED admission through hospital discharge. Decision-making in the ED and hospital based on response to therapy, subjective and objective symptoms and health behavior will be discussed in detail. Specifically, we will discuss how the development and implementations of the prediction rule satisfy the unmet needs of AF physicians in the ED and hospital. These issues will be extremely important to ensure the development of a readily implementable prediction rule.

In addition to mentoring, I will annually attend 2 national conferences specifically relevant to emergency physicians and cardiologists. Attending conferences will allow me to network with others conducting AF

research and will inform me of the field's latest research findings. Meetings will be selected from the American Heart Association (cutting-edge international heart failure research), American College of Emergency Physicians (clinically oriented research for emergency physicians), the Heart Rhythm Society (clinically oriented research for management of cardiac arrhythmias), and the Society of Academic Emergency Medicine (a predominance of basic science research in emergency medicine).

Table 1: Career Development Outline (5 years of CDA)

Year	Career Development Plan	Research Project	
		Specific Aims	Manuscripts/ Presentations
Year one	<ul style="list-style-type: none"> ▪ Ongoing Activities: 1. Weekly mentor & quarterly SAC meetings 2. Critical literature review and synthesis (Drs Storrow, Han and other VUMC experts) 3. AF Clinic 4. Conferences/Seminars ▪ Coursework: 5. Pharmacogenomics Coursework 6. EP Core Curriculum 	1st & 2nd Aims: Atrial Fibrillation Risk Stratification in the ED 1) Continue enrollment 2) Create database	
Year two	<ul style="list-style-type: none"> ▪ Ongoing Activities as above ▪ Coursework: 7. Additional Coursework ▪ Clinical Prediction Rules: 8. Preceptorship with Drs. Harrell, Storrow & Darbar 9. Directed reading 	1st & 2nd Aims Continuation: 1) Continue enrollment 2) Clean up database 3) Statistical analysis	1st & 2nd Aims: 1) Prepare abstract for submission 2) EBM Review: For ongoing study
Year three	<ul style="list-style-type: none"> ▪ Ongoing Activities as noted above ▪ Initial preparation of R01 10. Additional coursework in Clinical pharmacology & Statistics 	1st & 2nd Aims Continuation 1) Continue enrollment 2) Statistical analysis R01: Continue preparation of application	1st & 2nd Aims: 1) Prepare first manuscript from initial data.
Year four	<ul style="list-style-type: none"> ▪ Ongoing Activities as noted above ▪ Additional Genetics and Prediction Rule Coursework ▪ Mentors/SAC oversight of R01 Application 	Sub-aim 2.b.: Work with Dr. Russ to develop clinical useful format of AFPR 1st – 2nd Aims: Completion and manuscript preparation Development of future Hypotheses and Studies: 1) Multicenter validation and impact analysis of AFPR 2) Analysis of common genetic polymorphisms risk of ED outcomes 3) Comparison of efficacy and adverse effects of common AF treatments used in special populations (e.g. elderly, lone AF) 4) Evaluation of the use of personalized drug treatment for acute management of AF episodes R01: Revise and resubmit application	
Year five	<ul style="list-style-type: none"> ▪ Ongoing Activities as noted above ▪ Mentors/SAC oversight of R01 Resubmission 	R01: Planned resubmissions, if necessary IRB submissions for future studies	

Clinical Educational Experience

I will attend the Vanderbilt Atrial Fibrillation clinic at least twice a month and work with Dr. Darbar in order to gain a greater understanding of the epidemiology and routine management of AF. This clinic will also often be the designated follow-up for patients enrolled in my proposed project. Therefore, my participation in the clinic will provide me with an additional opportunity for following the patient's clinical course.

Goal 3: Strengthen my academic and professional development skills, including scientific writing, presentations, and grant preparation.

To achieve this goal, I will participate in multiple activities during the K23 grant period. In my academic department, I will attend the weekly Emergency Medicine Division of Research meetings, with in depth discussion on research projects, idea development, and practical research implementation. In addition, I plan on presenting preliminary data, pilot work, and final findings from the proposed projects at national meetings. Finally, structured meetings with my mentor, Dr. Storrow, will focus on grant writing skills and subsequent grant submissions.

Emergency Medicine Research Division Meetings

The Emergency Medicine Research Division has weekly executive meetings to review the progress of ongoing studies, discuss recent pertinent literature, and plan future research studies. I attend these weekly meetings and discuss my projects with Dr. Storrow and the other members of the research division. The Research division also holds a monthly meeting at which investigators present current projects or discuss future studies. These meetings are a forum for valuable discussion about study design, statistical analysis, and manuscript and grant preparation.

Mentorship and Collaboration

I have developed strong relationships with researchers and mentors in outcomes research, cardiology, emergency medicine, epidemiology, nursing and biostatistics. This multi-disciplinary team forms a cohesive unit of mentors ideal for supporting an emergency medicine-based AF outcomes researcher (*Table 2*). Dr. Alan Storrow is an expert in EM cardiovascular research, has a track record of successful funding, and possesses the protected time and EM expertise for mentoring. Further, I have assembled a team of emergency medicine, AF, and decision analysis experts on a Scientific Advisory Committee (SAC) to ensure my development as an independent investigator and outcomes researcher. They will assist in the development of a concise, accurate prediction rule that, once validated, will be adapted into clinical practice.

Table 2. Roles of Mentors and Scientific Advisory Committee Members

Member	Role	Expertise Provided to K23
Alan B. Storrow, MD	Mentor	EM research, cardiac emergencies, grantsmanship, mentoring success
Dawood Darbar, MD	Advisory Committee	Cardiology, AF management, AF Pharmacogenomics
Daniel Roden, MD	Advisory Committee	Cardiology, AF, AF Pharmacogenomics
Frank Harrell, PhD	Advisory Committee	Methodology/Modeling, Analysis Strategies

My SAC will meet on a quarterly basis to discuss issues pertinent to that stage of the project. The following members will comprise the SAC:

Alan B. Storrow, M.D., Associate Professor and Vice Chair for Research and Academic Affairs, Department of Emergency Medicine. I will take advantage of his expertise in successfully completing ED-based cardiovascular research studies. As my primary mentor, he will also supervise my career development.

Dawood Darbar, M.D., Associate Professor of Medicine and Pharmacology; Director, Vanderbilt Arrhythmia Service; and Director, Clinical Cardiac Electrophysiology Fellowship. Dr. Darbar directs the Vanderbilt AF Registry and his research focus is on the genetics associations with AF development and treatment. He is dedicated to expanding AF research to the ED and will supervise my continuing education in pharmacogenomics and the epidemiology of AF.

Frank E. Harrell, Ph.D., Chairman, Department of Biostatistics; Director, Design, Biostatistics, and Clinical Research Ethics Program, Vanderbilt Institute for Clinical and Translational Research, NIH CTSA. Dr. Harrell is an internationally renowned clinical prediction modeling expert. He will further my prediction modeling education through direct instruction, recommended statistical seminars, and ongoing discussion of the proposed project.

Dan M. Roden, M.D., Professor of Medicine and Pharmacology; Director, Oates Institute for Experimental Therapeutics; Asst. Vice Chancellor for Personalized Medicine; Principal Investigator for the Pharmacogenomics of Arrhythmia Therapy (PAT) Center. Dr. Roden is a world-renowned expert in molecular mechanisms of arrhythmias and he will advise me in pharmacogenomic study design and direct me to additional collaborators interested in AF personalized treatment.

In these meetings, we will cover the following objectives:

1. Review the study progress according to fulfillment of the project's Specific Aims, planned interim analyses, and discussion about responsible conduct of research as it applies to the project stage at that time
2. Evaluate the project's productivity by manuscript submission and acceptance, presentation of results at national scientific research conferences, and incorporation of results into future novel research ideas
3. Review my progress toward acquiring expertise in advanced clinical prediction modeling strategies and potential genetic and molecular associations with AF
4. Incorporate expert advice into successfully completing this project and securing independent extramural funding.

8. ENVIRONMENT AND INSTITUTIONAL COMMITMENT TO CANDIDATE

Description of Institutional Environment

Vanderbilt University School of Medicine and Medical Center

Vanderbilt University School of Medicine is a private institution with a mission to perform research that will advance the science and practice of medicine. Through this commitment to research Vanderbilt has attracted world class research faculty and trainees whose efforts have placed Vanderbilt 10th place nationally for attracting extramural funding. This funding has enabled Vanderbilt to develop a robust research infrastructure that will greatly enhance the candidate's potential to succeed in his research and training goals. Resources of particular relevance to Dr. Barrett's research are highlighted below.

The Department of Emergency Medicine

The candidate's department chair, Dr. Corey Slovis is enthusiastically committed to establishing the department as a premier site for emergency medicine research. This is demonstrated by his commissioning in 2006 of the Research Division (below). The department currently ranks sixth in NIH research funding among all emergency medicine departments. His attached letter outlines the support available for the candidate's research and training. The candidate will have access to the shared departmental research resources which include a research nurse, six clinical trials associates, a grants manager, and administrative support for his research efforts as well as a Ph.D. and Masters level biostatistician. This infrastructure has proven highly efficient at identifying and enrolling subjects with atrial fibrillation within the challenging ED environment. Over the past 6 months over 100 ED patients with AF have been enrolled in RELY, an international registry of patients with atrial fibrillation for which Dr. Barrett serves as site co-investigator. In addition, the department will financially support any tuition costs for the candidate's career plan and has committed to subsidize any non standard-of-care lab work that is necessary for this project.

The Research Division of the Department of Emergency Medicine

During his research and career development, Dr. Barrett will have full access to the resources within the Research Division of the Department of Emergency Medicine. The division is charged with supporting ED faculty in research related activities and is a source of information for funding opportunities, research conferences, and other research related activities. The Research Division facilitates research proposal development and provides training in research methodology and grantwriting. Though the Research Division is relatively young (~3 years old), they have been aggressive in obtaining various research and funding opportunities. Currently, this division is actively enrolling in five clinical trials and have recently been awarded a K23 (Dr. Don Arnold, 1K23HL080005), an R01 (Dr. Storrow, 1R01HL088459-01) from the National Lung, Heart, and Blood Institute and an Emergency Medicine Foundation Career Development award (Dr. Jin Han). The Research Division's rapid growth is attributable to the strong leadership provided by Dr. Alan Storrow who is the Vice Chair for Research and Academic Affairs and Dr. Barrett's mentor.

Department of Biostatistics

The Department of Biostatistics is directed by Frank Harrell, Jr., PhD, a co-investigator of Dr. Barrett. This department is centrally located on campus adjacent to the Eskin Biomedical Library. The department offers a full array of biostatistical support with an emphasis on establishing long-term collaborative relationships with investigators to accomplish the research mission of the institution. The department has 22 Ph.D. faculty, 3 senior M.S.-level biostatistician faculty, 14 M.S. staff biostatisticians, 10 computer systems analysts, and 7 administrative staff members. The department operates three server computers: a custom-built system with two Intel Xeon processors, 3 GB of main memory, and 120 GB of mirrored disk storage and a custom-built system with two 64-bit AMD Opteron 250 (2.4 GHz) processors, 16 GB main memory, and 250 GB of mirrored disk storage. Dr. Frank Harrell Ph.D., the department chair will serve on Dr. Barrett's Scientific Advisory Committee and will guide the implementation and analysis of the research. Cathy Jenkins, a Masters level biostatistician, will also work on the project with Dr. Harrell, along with a Ph.D. level Biostatistician who's effort is supported by the Department of Emergency Medicine.

Clinical Research Center

The Vanderbilt Clinical Research Center provides space, hospitalization cost, laboratories, equipment and supplies for clinical research by faculty members in any department of the Medical School. The Clinical Research Center also serves as a training resource for young clinical investigators. The CRC includes 21 inpatient beds, 7 outpatient rooms, 2 biostatisticians, biomedical informatics support, a computer laboratory, cardiovascular-, metabolic-, and neuroscience-procedure rooms and a core laboratory.

Office of Research

The Office of Research provides professional guidance and administrative expertise to all VUMC investigators and provides comprehensive services to assist faculty in their efforts to secure funding and conduct research of the highest quality and worldwide impact.

RELEVANT FACULTY EXPERTISE

The centers listed above represent a small portion of the vast collaborative network that Dr. Barrett will have access to. Vanderbilt University Medical Center prides itself on its collegial and cooperative environment and the candidate will have opportunities to work with many world class researchers. The faculty listed below have committed to supporting the candidate in his training and research endeavors.

Mentors: Dr. Barrett's mentor, Dr. Alan B. Storrow, is a highly successful NIH funded clinical investigator with a strong track record of mentorship. Dr. Storrow is a nationally renowned heart failure researcher who has expertise with developing clinical prediction models in ED patients with heart failure. Dr. Storrow has worked with Dr. Barrett on preliminary studies directly relevant to the proposed project and co-authored abstracts and manuscripts submitted for publication. A detailed biography of Dr. Storrow is provided below:

Alan B. Storrow, M.D. is an Associate Professor and Vice Chair for Research and Academic Affairs, Department of Emergency Medicine. Dr. Storrow is nationally recognized for his research in the emergency department management and treatment of heart failure. He has extensive experience with successful clinical trials and has recently been awarded an ED based R01. Dr. Storrow's research has focused on improving emergency department management of heart failure. He is the principal investigator for a 5-year NHLBI-sponsored RO1 studying heart failure risk stratification in the emergency department. Dr. Storrow has authored over 85 peer-reviewed papers in addition to authoring 19 published book chapters and editorials. In addition to serving on the candidate's SAC, Dr. Storrow has committed operational support for Dr. Barrett's research project in the form of directing research personnel effort toward patient enrollment. Dr. Storrow has demonstrated superb ED cardiovascular research talents and productivity which uniquely qualify him to serve as Dr. Barrett's mentor for the proposed study.

Scientific Advisory Committee: The individuals below have agreed to serve on the Scientific Advisory Committee (SAC). This committee will comprise of Dr. Dawood Darbar (Medicine), Dr. Frank Harrell (Biostatistics), and Dr. Dan Roden (Medicine). Dr. Darbar and Dr. Harrell are also co-investigators on the proposed research project. The SAC will meet quarterly. Between meetings, the members of the committee will be easily accessible to the candidate in person and by e-mail.

Dawood Darbar, M.D., Associate Professor of Medicine and Pharmacology; Director, Vanderbilt Arrhythmia Service; Director, Cardiac Electrophysiology Laboratory; and Director, Clinical Cardiac Electrophysiology Fellowship. Dr. Darbar has been a cardiovascular clinical investigator for over a decade and was the recipient of the 2009 American Heart Association Established Investigator Award. His research interests include clinical and genetic predictors of ventricular rate control in atrial fibrillation, the genetic basis of atrial fibrillation and the Pharmacogenomics of atrial fibrillation therapy. He currently is the principal investigator for 2 NHLBI-supported RO1 studies on atrial fibrillation. Dr. Darbar has actively participated in the proposed project design and review of preliminary study data. He will also supervise Dr. Barrett's further training in the genetics of atrial fibrillation and general pharmacogenomics.

Frank E. Harrell, PhD, Chairman, Department of Biostatistics; Director, Design, Biostatistics, and Clinical Research Ethics Program, Vanderbilt Institute for Clinical and Translational Research, NIH CTSA; Director, Statistics and Methodology Core, Vanderbilt Kennedy Center for Research on Human Development; Fellow, American Statistical Association; Editorial Board, Medical Decision Making; and

Associate Editor, Statistics in Medicine. Dr. Harrell is a leading expert in the biostatistical aspects of clinical prediction rule development and has published over 180 peer-reviewed articles and a textbook on the subject. In addition to guiding the biostatistical analysis on this project in conjunction with Cathy Jenkins, M.S. and a TBN Ph.D. Biostatistician, Dr. Harrell will participate in the Scientific Advisory Committee and oversee Dr. Barrett's education in biostatistics.

Dan M. Roden, M.D., Professor of Medicine and Pharmacology; Director, Oates Institute for Experimental Therapeutics; Asst. Vice Chancellor for Personalized Medicine; Principal Investigator for the Pharmacogenomics of Arrhythmia Therapy (PAT) Center; Section Editor (Drug Therapy), Circulation; Recipient of 2005 Distinguished Scientist Award, Heart Rhythm Society; and the 2008 Rawls Palmer Award for Progress in Medicine, American Society for Clinical Pharmacology And Therapeutics. Dr. Roden has published over 200 peer-reviewed manuscripts and is the principal investigator for 3 NHLBI and NHGRI RO1 projects focusing on the pharmacogenomics of arrhythmia therapy, modulation of cardiac repolarization and the Vanderbilt Genome–Electronics Records Project. Dr. Roden has a long history of mentoring successful early clinical investigators.

Other Faculty

Stephan Russ, M.D. M.P.H., Assistant Professor, Department of Emergency Medicine. Dr. Russ works both with the Department of Emergency Medicine and Bioinformatics and has designed software programs to assist in patient data collection. Dr. Russ also works clinical shifts in the adult and pediatric emergency departments. His unique skill sets include clinical emergency medicine expertise, bioinformatics and computer programming, and his M.P.H. training, make him an ideal consultant to assist Dr. Barrett with developing a clinically useful format for his atrial fibrillation risk prediction rule. Dr. Russ has collaborated with Dr. Barrett on the preliminary studies and is a co-author on abstracts and manuscripts submitted for publication.

FACILITIES AND OTHER RESOURCES

A detailed list of facilities and other resources that will be available to the candidate have been provided in the *Facilities and Resources* section of this application, briefly: the candidate will enroll subjects at the Vanderbilt Emergency Department. This is trauma ED with an annual census of 55,000. The ED is equipped with an electronic whiteboard system that provides minute by minute patient data which is an invaluable tool for subject identification. Multiple laboratories are accessible to the candidate. His project will use the Vanderbilt General Clinical Research Center core laboratory, an esoteric clinical laboratory and the emergency medicine research division's own research lab. All study personnel are equipped with desktop or notebook computers with intranet and internet access. The candidate will have Technical Support from the Informatics Center. This center provides central support for all faculty as well as software access and clinical information systems. Specialized informatics support is also available through the Department of Biostatistics, the Center for Health Services Research, and the Informatics Core of the Department of Emergency Medicine. The candidate will also have access to several personnel whose salary support is provided by the department of emergency medicine's research division. These personnel include a research nurse, 6 full time Clinical Trials Associates (CTAs), a Grants Manager, and an Administrative Assistant. Each of these individuals will provide support for Dr. Barrett's training and research by assisting with patient enrollment, IRB and grant applications, and research methodology.

EDUCATION AND OPPORTUNITIES FOR INTELLECTUAL INTERACTIONS

Dr. Barrett will have a wide variety of opportunities to interact with other investigators. In addition to regular meetings with his advisors and advisory committee members, the candidate will have opportunities to attend seminars, journal clubs and professional conferences. A selection of those opportunities are listed below.

The Emergency Medicine Research Committee

The Emergency Medicine Research Committee provides a monthly opportunity for emergency medicine researchers to present their ideas for research and get valuable feedback from fellow researchers. Poster and

oral presentations are presented following national presentation format. These simulations prepare the researcher to present their findings in the national arena.

Future Coursework

Dr. Barrett has selected a curriculum of classes from those offered by the Master of Public Health (MPH) and the Master of Science in Clinical Investigation (MSCI) Programs at Vanderbilt University. These classes will build on his existing educational background and will focus on advanced epidemiology, genetics, proteomics and medical writing. A detailed list of coursework is provided in the training plan.

Electrophysiology Core Curriculum Series

Dr. Barrett will actively participate in this twice-monthly series of lectures that focuses on major topics in the Arrhythmia field including management of patients with acute and chronic AF.

Emergency Medicine and Cardiology Journal Club

Dr. Barrett will participate in the Department of Emergency Medicine and Division of Cardiology Journal Clubs throughout the award period. Journal clubs discuss seminal articles in the field medicine, and will expose the candidate to cutting edge research in the fields of emergency medicine and cardiology. Dr. Barrett's responsibility will be to critically analyze journal articles; this process will provide him practical exposure to the various research methods, study designs, and statistical analyses utilized by these studies. He will better understand the strength and limitations of each study design, research methods, and statistical analyses.

Department of Emergency Medicine Grand Rounds and Specialty Conferences. Dr. Barrett will have opportunities to present the development of this project and the available results and to obtain valuable insight on study design and future directions. The opportunity to present at these conferences on a frequent and ongoing basis will provide Dr. Barrett multiple opportunities to prepare presentations for national meetings.

National Research Meetings

Dr. Barrett will attend the Society for Academic Emergency Medicine, the American Heart Association, the American College of Emergency Physicians, and the Heart Rhythm Society National Meetings. In addition to presenting his research, he will attend interest groups meetings related to his research as well as attend seminars focusing on geriatrics medicine.