

Project Summary/Abstract

The underlying triggers that prompt patients to seek care in the emergency department (ED) are not well understood, particularly among patients in patient-centered medical homes (PCMHs). This proposal seeks to better understand the precipitants that result in ED use despite enrollment in a PCMH and will ultimately lead to better integration of the ED into chronic cardiovascular care by leveraging the ED's diagnostic and therapeutic capabilities.

This career development award develops criteria to reliably identify the most vulnerable, high-cost patients in the Vanderbilt MyHealthTeam (MHT) PCMH—those with uncontrolled BP and medication non-adherence—at the time of their presentation to the ED. The **Specific Aims** of the research are to: **1) Identify ED values of BP that correctly classify hypertension control status**, as defined by clinic BP, and that predict 6-month recidivism to the ED and hospital; **2) Determine optimal thresholds of a mass spectrometry assay that detects 34 cardiovascular medications, including 19 antihypertensive medications, to correctly classify patients with medication non-adherence**, and compare the assay's performance to other measures of adherence; and **3) Determine the hazard of 6-month recidivism to the ED and hospital associated with antihypertensive non-adherence. These aims test the hypotheses that 1) BP values in the ED correctly classify BP control and predict 6-month ED and hospital recidivism, and 2) Medication non-adherence, as measured by a mass spectrometry drug assay, predicts 6-month ED and hospital recidivism, despite enrollment in the MHT PCMH.**

Proposed **Career and Learning Objectives** are to: **1) Attain advanced skills in cardiovascular epidemiology study design, data management, measurement, and analytic methods, and 2) Attain the analytical skills needed to expertly evaluate the discriminatory capacity, criterion validity, and predictive validity of a mass spectrometry cardiovascular drug assay as an objective, novel measure of medication non-adherence. These objectives will be accomplished through: a) advanced, doctoral coursework in cardiovascular epidemiology, pharmacokinetics, and biostatistics, with completion of the Vanderbilt Doctoral Program in Epidemiology in Year 2 of the 4-year award; b) a multidisciplinary mentorship research experience, c) participation in national emergency and cardiovascular meetings to gain additional expertise in hypertension disease management and develop external collaborations.**

By identifying vulnerable, high-cost PCMH patients and determining the role of medication non-adherence as a trigger for ED visits among these patients, this proposal is a crucial first step in partnering emergency and primary care and developing interventions to better align healthcare resource utilization and improve BP control. It also provides the mentorship, skills, and experience for the candidate to develop a career focused on maximizing the ED's contribution to cardiovascular care.

Project Narrative

Patients with chronic cardiovascular disease are an important driving force in the rising demand for emergency department (ED) care, even though most of these patients have health insurance and primary care providers; to better serve these patients within a rapidly changing healthcare structure, contemporary solutions are required. I wish to begin building a career maximizing the ED's contribution to coordinated, high quality cardiovascular care by elucidating the causes of these emergency visits among patients with treated hypertension who are enrolled in a patient-centered medical home. I propose to leverage our institution's expertise in hypertension, medication adherence, and emergency services within the unique MyHealthTeam patient-centered medical home as an initial test bed for my early stage mentored research; developing this model will drive later translation into a other cardiovascular diseases and care settings.

Facilities and Resources

General Institutional Resources for Current Grant

THE INSTITUTION

Vanderbilt University (VU) (*Nicholas S. Zeppos, JD, Chancellor*)

Vanderbilt University is a private, non-sectarian university located in Nashville, Tennessee. Founded in 1873 on a gift from the shipping and rail magnate Cornelius Vanderbilt in the hope that it would “contribute to strengthening the ties that should exist between all sections of our common country.” Today, Vanderbilt University is an internationally recognized research university where scientists collaborate to solve complex problems affecting our health, culture and society. With more than 18,000 employees and strong partnerships with its neighboring institutions and the community, Vanderbilt is the largest private employer in Middle Tennessee and the second largest private employer in the state of Tennessee.

Vanderbilt University School of Medicine (*Jeffrey Balser, MD, PhD, Dean*)

In 1874, the School of Medicine was incorporated into Vanderbilt University. Biomedical research at the School of Medicine has long been recognized for its contributions to the advancement of medicine, producing two Nobel Laureates, Earl Sutherland Jr., and Stanley Cohen. Eight of the School of Medicine’s basic science departments – physiology, pharmacology, pediatrics, biochemistry, radiology, anesthesiology, medicine and cell and developmental biology – rank in the top 10 in the country in terms of competitive NIH funding. The School of Medicine currently has 1,753 faculty and more than 600 students. From 2000-2009, Vanderbilt University School of Medicine (VUSM) had the fastest growth in NIH funding among all academic medical centers (17.8%). Currently, it ranks 10th in NIH funding among U.S. Medical Schools, with 724 NIH awards exceeding \$368 million in 2010. With continued investment in new research space, including the recent completion of Medical Research Building IV and the Imaging Institute, total research space at VUMC is over 650,000 square feet. The work of the research enterprise now engages 1110 faculty investigators, with a significant portion of the 1833 total working faculty in the medical center. A collegial, multidisciplinary research environment at Vanderbilt is supported by 36 funded Cores and Centers.

The Department of Emergency Medicine (*Corey M. Slovis, MD, Chairman*)

The School of Medicine is committed to continued growth of the Department of Emergency Medicine and to continued growth in the research faculty through recruitment of new and established investigators and through the development of faculty from our own scholars. This growth enables the Department of Emergency Medicine to continue to enhance the training environment.

The Emergency Medicine Research Division is organized to provide administrative support to the academic activity of all research faculty. Research Division staff are distinct from those supporting clinical activity, allowing their activity to be focused on research support and not encumbered by the Hospital’s management. The academic mission of the Division of Research is supported by a \$2.0 million annual budget, which includes support for nineteen staff positions divided into three areas: financial/sponsored research, education, and administrative support. In addition, the Research Division receives nearly \$90,000 annually in gift and endowment income, which is used to support our various academic programs. In the brief time since Dr. Alan Storrow joined the Vanderbilt Department of Emergency Medicine, there has been remarkable growth in the number of IRB protocols, clinical studies, and clinical trials developed by our program.

Within the Department of Emergency Medicine, Faculty whose primary activity is research are provided a minimum of 75% of time protected for research and teaching. Some of this activity is supported by funds coming from the School of Medicine for extended teaching activity. Each research faculty has some percent of their time protected for program development and mentoring of Scholars. Gifts and endowment income to the Division are used entirely to support the development of the academic environment focused on the research and educational activity of our trainees.

The Alan B. Storrow Research Lab

In 2008, the Department of Emergency Medicine opened its first ED-based laboratory dedicated solely to research. Funded partially by the Vanderbilt University CTSA, this approximately 1500 square foot facility is located next to the Emergency Department and is fully equipped for biological specimen processing, testing, shipping, and long- term storage in a -80 degree Centigrade freezer. The lab has established a well-maintained electronic database and wide-range of bio-specimen collections from the emergency department. These include serum, plasma, DNA, urine, and cerebrospinal fluid. Barcoding and 24-hour freezer monitoring are in

use for specimen organization, retrieval, and protection.

The Vanderbilt MyHealthTeam

The Vanderbilt MyHealthTeam patient-centered medical home is designed to implement population-based care coordination and disease management across hospital and clinic-based settings using inter-professional health care teams and enhanced health information technology, including disease registries and evidence-based decision support that is integrated into clinical workflow. System-wide implementation across Vanderbilt University and its 3 affiliate hospitals is scheduled over the next 3 years. Between October 2012 and April 2013, 5,217 primary care patients among 58 primary care providers were enrolled, in addition to the 3,000 patient enrolled during the program's development. In order to qualify for enrollment in MHT, patients are required to have a minimum diagnosis of treated hypertension. Virtually all enrolled patients have health insurance, with 27% of encounters covered by Blue Cross/Blue Shield, 22% of covered by Medicare HMO, 2.5% designated self-pay, and the remainder split among other forms of health insurance. Over 8 months, 469 ED visits occurred among MHT patients resulting in 262 hospitalizations. ED visits per month ranged between 56 and 105, and hospitalizations per month ranged between 107 and 121. This data and the expected total MHT enrollment of 70,000 patients over the next 3 years are a more than ample source patient population for the proposed research.

Institute for Medicine and Public Health (IMPH): VUMC has made improving population-based health and health care systems research a strategic priority with a major deliberate investment in health services, T2 and T3 translational research, including dedicating a significant proportion of its NIH CTSA grant-funded resources and the creation of the campus-wide Institute for Medicine and Public Health (IMPH). Directed by Dr. Robert Dittus, the IMPH aims to improve personal and public health through discovery, training and service programs designed to protect against threats to health, promote healthier living, improve the quality of health services, and prepare leaders to advance health and health care. The Institute, consisting of more than 150 faculty, coordinates the activities of multiple Centers and over 25 programs including: Center for Health Services Research; Institute for Global Health; Center for Biomedical Ethics and Society; Center for Medicine, Health and Society; Center for Quality Aging; Center for Interdisciplinary Workforce Studies; Epidemiology Center; Center for Perioperative Research in Quality; the Institute for Community Health, the Center for Improving Patient Safety. The Institute also coordinates the activities of the Nashville VA's Center for Patient Healthcare Behavior; Geriatric Research, Education and Clinical Center (GRECC), and the VA Quality Scholars Program. IMPH faculty have collectively generated more than \$250 million in extramural funding. The Institute supports multiple pre-doctoral and post-doctoral training programs including an MPH and **Doctoral Program in Epidemiology**.

Doctoral Program in Epidemiology

This PhD is a graduate program of The Institute for Medicine and Public Health at Vanderbilt, home to more than 127 researchers who are raising the bar for large-scale collaborative research. Their work ranges from DNA databank studies in clinical populations to large population-based cohorts with data and biological samples from more than 250,000 participants. Vanderbilt Epidemiology Center faculty have more than 80 NIH awards totaling more than \$82 million in current funding. The breadth of researchers, richness of resources, and dedication to training young faculty will ensure Dr. McNaughton's adequate mentorship, resources, and inspiration for advances in research.

Center for Clinical Improvement (CCI)

Quality improvement involves systems thinking, a culture of leadership and teamwork, reducing variation, and using data to test change. The mission of the Center for Clinical Improvement is to systematically and continuously improve dimensions of care as defined by the Institute of Medicine. Over the past year, the Center for Clinical Improvement has supported over 45 projects, each documented with action plans and time-series data in the form of run and control charts. Some of these projects represent funded research studies including the evaluation of computerized nursing pathways; transplantation clinical process of care and outcomes; integrated primary and specialist care of diabetes; pediatric oncology chemotherapy. Dr. McNaughton has worked with members of the CCI on hospital-related quality improvement projects. They use clinical repository data frequently for quality improvement projects and will be able to offer assistance in navigating potential barriers and planning for future implementation projects.

Office of Career Advising and Outcomes Research

This office was established with the objectives of providing career counseling and longitudinal follow-up of all prior trainees. They offer detailed and extensive career planning advice in the form of written material, a comprehensive web presence (http://bret.mc.vanderbilt.edu/career_development/), career development workshops and symposia, and a weekly newsletter highlighting professional development articles and events, as well as postings for a range of academic and commercial career opportunities from around the nation. Confidential, one-on-one career development sessions are available to all graduate students and postdoctoral fellows in the basic biomedical and biological sciences. The Office is also working to survey alumni and establish a network of long-term contacts with former trainees who can serve as a resource for current students and postdoctoral fellows.

CLINICAL

Vanderbilt University Medical Center (VUMC) is a private, non-profit, tertiary care teaching institution located in Nashville, Tennessee. VUMC consists of the School of Medicine, the School of Nursing, the 832-bed Vanderbilt University Hospital and Clinic, the Monroe Carell Jr. Children's Hospital, and the Vanderbilt Psychiatric Hospital. VUMC is also affiliated with the 485-bed Veteran's Administration Medical Center and the 80-bed Stallworth Rehabilitation Hospital, located adjacent to the campus. The 350-bed Monroe Carell Jr. Children's Hospital opened in 2004 with state-of-the-art treatment facilities and has been named one of the top 10 children's hospitals in the nation. A number of VUMC programs are unique to the region, including a Level I Trauma Center, a comprehensive adult and pediatric Burn Center, LifeFlight emergency transport, a Level IV Neonatal Intensive Care Unit, and the state's only comprehensive organ transplant program. VUMC admits over 42,000 inpatients annually, and the adjacent free-standing children's hospital admits over 11,000 children annually. Vanderbilt provides more than \$119 million each year in uncompensated and charity care to members of the community unable to pay for their own care. It therefore serves a diverse population in terms of socioeconomic status and education level. The Vanderbilt Clinic registered 1.02 million outpatient visits in the last year. Patients come from a diverse range of geographic areas. It is estimated that 34% of the patients at VUMC reside in the Nashville area, and 92% of the patients live in the state of Tennessee. Approximately 8% of patients are from outside the state.

Emergency Department

The Department of Emergency Medicine includes a faculty of 55 Emergency Medicine attending physicians who have offices adjacent to the Emergency Department (ED). The educational activities include an emergency medicine residency and a pediatric emergency medicine fellowship program (39 residents/fellows). The entire ED staff includes more than 200 members who care for more than 110,000 patients annually. The ED is a trauma level 1 center; the pediatric ED is the only pediatric emergency facility in Middle Tennessee.

Vanderbilt University Hospital

Vanderbilt University Hospital (VUH) receives approximately 55,000 adult Emergency Department visits and 42,000 admissions per year. Medical patients who are admitted to inpatient medical wards at VUH are assigned to 1 of 12 possible teaching teams or to a non-teaching team. The 12 teaching teams include 4 for General Internal Medicine, 4 for Cardiology (including 1 heart failure team), and 4 for other subspecialties. Non-teaching teams include General Internal Medicine, Cardiology, and Geriatrics. Patients may also be admitted to the Cardiovascular Intensive Care Unit (ICU) or Medical ICU.

Vanderbilt Heart and Vascular Institute

Most patients admitted to the Cardiology, General Internal Medicine and Geriatrics services are followed in the Vanderbilt primary care and cardiology practices. About 70% of admitted patients receive follow-up care in the outpatient clinics. In fiscal year 2009, there were over 80,000 adult primary care visits and over 70,000 outpatient Cardiology visits to the Vanderbilt Heart and Vascular Institute (VHVI). VHVI inpatient units consist of a combined medical/surgical Cardiovascular Intensive Care Unit with 26 ICU beds and 56 stepdown beds. This Unit is directly adjacent to physician offices and the 40,000 square foot outpatient facility with dedicated noninvasive imaging. VHVI has its own dedicated Magnetic Resonance Imaging facility located immediately adjacent to the cardiac invasive laboratories, which include the combined surgical/interventional facility known as the hybrid cath lab/OR. Currently, VHVI includes over 70 full-time faculty, 7 of whom are cardiothoracic surgeons. In 2009, there were over 5000 admissions, 2500 procedures in the interventional laboratories, 5000 procedures in the electrophysiology laboratories, and 1200 adult open heart surgeries.

The VHVI/CV Medicine Clinical Research Enterprise is currently made up of 21 full time research related personnel that provide outstanding support for all clinical research within or in collaboration with the departments of CV Medicine and CV surgery. This includes direct collaboration with a multitude of departments and divisions within the Vanderbilt Medical Center and the VA Hospital in Nashville. The physical presence includes 3 research offices within VHVI and 1 core lab, as well as direct access to the VICTR/CRC inpatient unit for studies that require overnight or daily visits within the study protocol. There are more than 105 ongoing clinical cardiovascular studies. These studies range from prevention and risk factor modification to therapeutic trials, high risk intervention and CV surgical studies. Vanderbilt is one of only 5 clinical sites in the country for stem cell trials. The Clinical Research Enterprise also has a requirement for participation in some documentable aspect of clinical research for all fellows, and an established mechanism for mentorship from the faculty. All trainees are required to present information at a regional or national meeting, and actively participate in monthly meetings in which internal data is presented and critiqued. In addition, there is a monthly journal club research presentation, with statistical critique available, in our web-based curriculum. The Clinical Research Enterprise has a yearly budget that exceeds \$2 million/year.

RESEARCH SUPPORT

Department of Biostatistics

The Department of Biostatistics, occupying approximately 7500 square feet in Medical Center North, is directed by Frank Harrell, Jr., Ph.D. Centrally located on campus adjacent to the Eskind Biomedical Library, the department offers a full array of biostatistical support with an emphasis on establishing long-term collaborative relationships with investigators in accomplishing the research mission of the institution. The department has 22 Ph.D. faculty, 8 senior M.S.-level biostatistician faculty, 19 M.S. staff biostatisticians, 10 computer systems analysts, and 11 administrative staff members. The department operates four server computers: a custom-built system with two Intel Xeon processors, 3 GB of main memory, and 120 GB of mirrored disk storage; a custom-built system with two Intel Xeon processors, 3 GB of main memory, and 160 GB of mirrored disk storage; 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; and a custom built system with two 64-bit AMD Opteron 250 (2.0 GHz) processors, 4 GB main memory, and 200 GB of mirrored disk storage.

Dandan Liu, Ph.D and Cathy Jenkins, M.S. are the primary biostatisticians working with Dr. McNaughton. They have both worked extensively with Dr. Storrow and the Research Division in the Department of Emergency Medicine. In addition, as part of her training in the doctoral Epidemiology Program, Dr. McNaughton will work closely with Dr. Greavy and other biostatisticians as she develops her own expertise in biostatistical analysis and interpretation.

Biostatistics Collaboration Center (BCC)

The BCC is a university sponsored core resource whose goal is to provide for, enhance, and/or facilitate statistical collaborations involving the design, conduct, analysis or publication of biomedical research at the university. The BCC is comprised of biostatisticians from the Department of Biostatistics who are available to work with faculty on a variety of projects. They offer a wide range of highly trained experts with unique expertise for almost any collaboration. The BCC has considerable expertise in the design, conduct, and analysis of large scale clinical trials and research design for basic biomedical research. The core is available for additional statistical support if/when required.

Vanderbilt Informatics Center. The Department of Biomedical Informatics is the largest academic biomedical informatics department in the country with more than 50 faculty members, a graduate training program, and a portfolio of research and development projects that spans from computational biology and bioinformatics applied to understanding of biological molecules, through advanced clinical information systems that care for hundreds of thousands of patients, to regional health information projects that span many states. The Informatics Center has generated many very successful and nationally/internationally recognized tools. Examples include: StarChart, a comprehensive Electronic Health Record (EHR) with web-accessible intranet retrieval tools and currently has more than 31 million documents; WizOrder, a relational database of all orders entered on all inpatients at Vanderbilt since January 1998; StarPanel, an integrated app where clinicians can access electronic information from one screen; Pathworx, a care management and documentation system that electronically links clinical care pathways to patient flow sheets; and RxStar, an outpatient prescription writer generating 794,602 prescriptions in 2009. The resources developed by the Informatics center are central to the

database that will be developed for the research plan and future implementation procedures.

Vanderbilt Evidence Based Practice Center (EPC) In 1997 the Agency for Health Care Policy and Research (AHCPR), now known the Agency for Healthcare Research and Quality (AHRQ) the created a program to increase the use of evidence based practice in standard medical care by funding evidence based practice centers (EPCs). The objective of the EPC is to undertake systematic reviews of currently available evidence concerning various topics including clinical medicine, social and behavioral science, and economics. In 2007, AHRQ awarded Vanderbilt one of two EPCs that year. Vanderbilt's EPC offers resources and hands- on opportunities to learn the conduct of systematic reviews and meta-analyses. They have assisted fellows and faculty in the successful conduct of multiple systematic reviews and meta-analyses. This resource will assist Dr. McNaughton as she delves deeper into interventions designed to partner ED and primary care, preparing to design and test an intervention as part of future research based on the findings in the proposed research.

Annette and Irwin Eskind Biomedical Library (EBL) is a state-of-the-art library that will provide the with access to information worldwide through the very latest in informatics retrieval and management technology, traditional library services, book stacks and comfortable reading areas are also provided along with technology training and assistance. The Research Informatics Consult Service (RICS), available to Dr. McNaughton, provides proactive, targeted information services for Vanderbilt researchers delivered at the point of need. Services include training, grant assistance, electronic resources, database searching, bibliographic databases, full text resources, and molecular biology databases. Individual and group consultations are available with experienced information specialists. The library has a comprehensive, multidimensional Digital Library that offers fast, targeted access to online books, journals, databases and websites. EBL provides access to over 2,800 full-text electronic journal titles. EBL has developed proactive mechanisms to integrate evidence into clinical and research workflow through linkages of patient care guidelines within the electronic medical record. Polly Todd Alexander, a masters level librarian and a member of the Research Division in the Department of Emergency Medicine will be working with Dr. McNaughton in designing and implementation of search queries, and providing assistance with data management of library resources.

Vanderbilt Institute for Clinical and Translational Research (VICTR) and the Clinical and Translational Science Award (CTSA)

Vanderbilt University, in partnership with Meharry Medical College, was awarded a \$40 million Clinical and Translational Science Award (CTSA) funded by the National Center for Research Resources of the National Institutes of Health (NIH), its largest ever government research grant, to expedite the translation of laboratory discoveries to patients in the community. The CTSA consortium is comprised of 38 academic health centers in 23 states. The CTSA program provides support to the consortium to establish centers, departments, or institutes in clinical and translational science. VICTR leveraged the existing NIH-funded Clinical Research Center (CRC), which has been an established center generating clinical research for 50 years. The CRC provides space, hospitalization cost, laboratories, equipment, and supplies for clinical research. The Center serves as a resource for teaching students, for research in the methodology of patient care systems, and for apprenticeship for young clinical investigators. The CTSA also provides support for the newly developed Pediatric Clinical Research Center, housed in the Monroe Carell Jr. Children's Hospital at Vanderbilt, and the existing Clinical Research Center Assay Development and Services Laboratory. The VICTR Informatics Core is a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data (StarBRIGHT). The VICTR provides weekly training workshops on basic instruction and practical advice on commonly encountered clinical research topics, as well as grant writing and IRB process assistance for investigators. The funds will also be used to establish a Community Engagement and Research program, which leverages Vanderbilt's strong ties with the community. Also involved within Vanderbilt is the Institute for Medicine and Public Health, as well as the Schools of Medicine, Nursing, Law, Business, Engineering, Peabody College of Education and Human Development, the College of Arts and Sciences, and the Kennedy Center for Research on Human Development.

VICTR has been focused on and generous to junior investigators in providing funds for preliminary studies leading to NIH submissions. The "voucher" system has been particularly novel and frequently utilized. It is available to all Scholars and faculty on campus, whereby in a *single page application* one can apply for up to \$2000 for use in any Vanderbilt Core facility. VICTR also sponsors the popular research "studios," a series of structured, dynamic sessions bringing together relevant experts in a particular methodology, intended to

enhance research quality, foster advances in clinical practice, and generate new hypotheses. Gordon Bernard, MD, is PI for our CTSA and Director of VICTR, while Alan Storrow, MD, serves as a member of VICTR's Scientific Review Committee (SRC).

The SRC reviews all proposals seeking funding from VICTR. The Committee is composed of a diverse cross-section of experts who are investigators and understand the VICTR mission. Members of the Committee are selected exclusively based on their scientific credentials (spanning T1 through T2 expertise) and are responsible for judging scientific merit. The method of scoring scientific merit is similar to NIH study sections, although the criteria are supplemented specifically for translational and clinical research focus areas. A weekly VICTR Clinic is held each Monday in the Clinical Research Center Conference Room for all investigators and research teams. The VICTR Clinic is supported by personnel from VICTR administration who assist scientists with VICTR resource request applications, answer questions about VICTR resources, and guide them through the application process.

Clinical Trials Center (CTC)

The Clinical Trials Center was created to facilitate clinical research at the institution. The CTC provides investigators with a pool of research personnel who can be dedicated to specific projects. CTC research coordinators can assist in IRB preparation, regulatory documentation, subject recruitment, coordination of studies, and research procedures. CTC coordinators can be primarily responsible for assisting in all aspects of the study, or can be used by investigators temporarily to meet or exceed recruitment goals in intensive clinical projects. It eliminates the need to maintain a high level of personnel to accommodate periods of increased activity. CTC coordinators receive intense training in ethical conduct of research and their involvement ensures compliance with regulatory requirements.

VICTR Resources

VICTR/CTSA Resource Request Voucher Program

This program provides awards for \$2,000 or less with a short approval process time (2-3 days) for the generation of preliminary data and pilot work for clinical and translational studies, allowing for rapid acquisition of proof-of-principle data that may justify full-scale investigation. Expediently stimulating pilot work, the outcomes of which guide research programs in the most promising directions, is a mission of VICTR and the VICTR Scientific Review Committee, the body charged with overseeing and administering all VICTR funding requests. If criteria are met, the voucher is approved, triggering a bar-coded itemized label the investigator can redeem at Vanderbilt's core facilities for requested services or expert consultation, or specific instructions are generated for redeeming the voucher for study supplies or services provided outside the Vanderbilt core invoicing system. The pilot funding program allows investigators to request biostatistical consultation including study design, sample size estimation, statistical planning and analysis. Additional resources include research to measure and improve long-term retention of statistical skills by investigators and validation and simulation tools to detect and minimize bias in estimating the effect of treatments, risk factors and biomarkers of disease and outcomes. This program also provides ethical consultation to assist investigators in approaching and appropriately handling the ethical challenges that can arise throughout the research process. As appropriate, ethicists are invited to participate in consults and research studios. Investigators can also request assistance with developing posters for national scientific meetings for sharing their study results. The VICTR Clinical Research Center has reduced rate poster printing capabilities that can be requested through pilot funding.

VICTR StarBRITE Research Portal

This portal is an interactive web-based system that provides one stop shopping for research needs. Through a single portal, researchers and study personnel can identify resources, obtain regulatory support, access templates for research preparation and study conduct, obtain database development software, learn about educational requirements and opportunities, find research volunteers, and more. StarBRITE also provides institutional application and research approval process support. This system was launched in October, 2007 as part of the Vanderbilt CTSA initiative and contains traditional portal offerings (i.e., template language and links to support research strategies and implementation, integrated calendar of training events), as well as custom Institutional Environment applications to support the research enterprise (e.g., healthy volunteer registry, Customized Action Plan which is a turbo-tax-like concept project guiding researchers through regulatory process, funding support requests, web-based data resources for individual studies and more). The StarBRITE portal also provides CTSA leadership with real-time dashboards for use in project evaluation and future planning. My Research is a view that allows investigators to view research applications, and check their status

from departments such as the Institutional Review Board (IRB), Grants and Contracts Mgmt (GCM), etc.

VICTR Research Support Services (RSS)

Personnel supported by the VU Office and Research and CTSA provide investigators and research personnel with a broad range of services and resources designed to assist them in navigating the complex human research process at VU and to ultimately improve the quality of research; research compliance and the protection of human subjects. RSS provides a responsive “one-stop shopping” venue with easy (free) access to personnel experienced in responding to inquiries regarding bench and clinical research, study organization, IRB navigation, regulatory affairs, protocol development, preparation of study related documents, budgeting, billing, contract negotiations, conflict of interest, technology transfer, internal and external regulatory communication and documentation, advertising, recruitment, identification of financial resources, literature searches, and more. RSS personnel interact daily with other departments (i.e., IRB, GCM, technology transfer, etc.) and are proficient at answering research and administrative-related questions and are able to refer questions that require specific “context” expertise to an appropriate person or department. Information and tools are continually being developed and updated for access by the research community via the RSS Website and the StarBRITE research portal. RSS also provides research staff educational sessions including the Clinical Research Immersion Boot Camp that introduces new clinical research staff with fundamental information and introduces them to the resources and support services available to them. Boot Camp sessions are followed by a cycle of follow-up sessions designed to provide staff at all levels of experience with expanded information about critical topics only briefly presented in the introductory course. RSS personnel also offer a voluntary quality improvement program “IMPACTT”, designed to assist investigators and the research team in identifying strengths and weaknesses, to provide education related to a specific project or research program, and to support improvements in the research program. IMPACTT evaluations begin with a brief interview, followed by an on-site assessment of a research protocol using a comprehensive assessment tool developed to examine the necessary elements involved in effectively managing a research study. During a conclusion exit interview a final report, including findings and recommendation is provided and reviewed. Optional return visits may be conducted as needed.

VICTR Design, Biostatistics and Clinical Research Ethics

This program provides biostatistical and ethical supportive resources to investigators to improve research quality and rigor and is another important goal of VICTR and the NIH funded CTSA. Currently there are four biostatisticians and four ethicists who provide support, consultation, project review and training for VICTR research/researchers. These personnel support both the investigator and the VICTR Scientific Review Committee through individual consultation and pre-review of VICTR Resource Requests, providing proactive biostatistical input to minimize bias, improve study designs, assure recording of appropriate data and confounding factors, avoid common research obstacles, assure appropriate sample size, produce sound and safe study design and apply advanced methods of reproducible statistical analysis and reproducible reporting. Investigators may request biostatistical and ethical consultation services using a VICTR Resource Request. VICTR biostatisticians and ethicists also support investigators by participation in VICTR Studios.

VICTR Studio Program

The studio program strives to improve research quality and rigor by offering and broadly implementing a wide range of supportive research from study design and set-up to analysis and publication, available to new and experienced researchers. There are six different types of studios (hypothesis generation, design, implementation, analysis and interpretation, manuscript review and translation), each providing a different look at an investigator’s research study. A studio is scheduled to include the investigator, the investigator’s mentor/teacher (if applicable), an experienced moderator, and up to six content and process experts, and a biostatistician. Materials are distributed to the experts prior to the studio and discussed in detail during the studio. Studios offer an opportunity for experienced researchers to provide suggestions and critiques of a research strategy or the data generated by a study. It also provides an opportunity for investigators to meet and begin collaborations with other experts who share interest in their field of research. Investigators are provided with minutes of the studio for reference. Studios are proving to be a major asset to junior investigators, and Dr. McNaughton will utilize this resource throughout the award period.

The VICTR Informatics Core

The informatics core will be used as a central location for data processing and management. Vanderbilt

University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the VICTR Informatics Core. The iterative development and testing process results in a well-planned data collection strategy for individual studies. The newly released REDCap Survey is a powerful tool for building and managing online surveys, which Dr. McNaughton has already utilized to enroll the first 300 ED patients with treated hypertension in the prospective cohort study. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails and reporting for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

INFORMATION TECHNOLOGY AND INFORMATICS

University-wide Infrastructure

Dr. William W. Stead is Assistant to the Chancellor for Informatics and Chief Information Architect for the University. He is charged with overseeing University-wide planning and policy formulation for information technology. His responsibilities include working with the academic and administrative leadership in both University Central and the Medical Center to identify common standards for information technology, overseeing long-range planning and forecasting, creating University-industry strategic partnerships, and developing funding and service models. This position was created in 2000 and the choice of title reflects the decentralized structure of Vanderbilt, fostering diverse collaborations. This strategy avoids the rigidity of central models while achieving the benefits of interoperability and scale that are difficult in other decentralized models. Vanderbilt University Hospital has been selected as one of the "most wired" hospitals every year since 2005.

VUH and Department of Emergency Medicine Informatics

The ED information system is operational in the adult and pediatric EDs and is integrated into the hospital-wide enterprise network infrastructure. There are more than 100 clinical workstations and more than 20 administrative workstations. Two 60-inch large touch-screen plasma monitors act as the ED's central whiteboards for tracking patients and monitoring ED activity. The ED information system includes an interactive computerized whiteboard, an order tracker, and a computerized triage component. The ED information system is based on Oracle® relational databases (V 10g) and is integrated with the institutions electronic medical record system (StarChart) and the provider order entry system (WizOrder). It uses Java/JSP-based, JavaScript, Servlets, Cascading Style Sheets, and stateless session and message beans. It is based on a three-tiered client-server infrastructure with Internet Explorer as the browser-based client. A JMS interface provides connectivity to GenServices, the radiology information system, and the statistics collection module. Laptops mounted on mobile units are used for in-room registration purposes and respiratory therapy. PACS viewing stations, EKG station, and monitoring equipment are accessible in both ED's. A wireless CISCO network is installed in both ED's. User identification and authentication services are provided by a hospital-wide RACF ID-based application that manages access to different information resources and informatics applications. Two LAN managers support the adult and pediatric ED for daily operations. Space on shared drives is available for departmental information storage.

With few exceptions, the ED and VUH are paperless and rely on electronic information. An enterprise data warehouse contains clinical and administrative data, including information from the ED information system. This infrastructure has been used extensively for research, operational, and administrative initiatives, including student and fellowship projects. In close collaboration between the EM department and biomedical informatics, the ED information system infrastructure has been used to implement real-time decision support systems, such as prediction models, evidence-based medicine, guidelines, patient recruitment, clinical studies, etc. The ED information system continues to be a primary source for data analysis and research for emergency medicine and other clinical research operations throughout the hospital

Computers

Vanderbilt University has seen tremendous growth in both computer and network utilization over the last several years. As of August 2010, a typical day will see 16,824 unique computer connections at any given

time, with 2,582 of these being wireless connections. Internet utilization is at an all time high with peak capacity recently being increased to 1.5 Gbps (August 2010). Further, to assist the research community at Vanderbilt, Internet 2 is available and features a very high data capacity of 10 Gbps.

Vanderbilt operates two primary data centers on campus that feature tremendous capacity. One data center alone features 7,500 square feet of data center space. At the time of this writing, it provides hosting for 1,423 servers (1184 Physical and 239 Virtual). Both data centers provide a wide variety of services from enterprise email (1.68 billion emails Aug 09 – Jul 10) and web hosting (136.2 million web visits per month Sep 09 –Aug 10) to patient centric services, such as StarPanel (Patient EMR) and PACS (Radiology Image Storage and Access).

Due to the nature of the data stored by Vanderbilt, security is very important. Both data centers feature a Network Operations Center (NOC) that is staffed 24 hours a day. Physical access to a data center is only permitted to authorized employees. Access is granted via card key or biometric scanning device. Typically, server rack doors are locked and require NOC personal to take action before physical access to a server is available.

The Department of Emergency Medicine has its own extensive computer resources available to faculty, residents, and staff. The department operates 3 Apple X-Serves and 1 large V-Track Enterprise storage system with 16TB of RAID-5 storage. Two of these servers act as production and development servers. The third is specifically dedicated to the bedside emergency ultrasound program and acts as a PACS resource for this modality. The department features two full time employees dedicated to web, video, and application development. The primary web property is located at emergencymedicine.mc.vanderbilt.edu or www.vanderbiltem.com. The department's web presence has seen tremendous growth in the last year with 49,379 unique visitors, of which 65.11% are new visitors. The department features a large amount of video on its site. There have been 81,804 video loads from all over the globe, including Guyana and Afghanistan, where the US military has used the video for medical training.

To ensure that valuable data is not lost, fault-tolerant and redundant central file servers are available for file storage and are backed up multiple times per day to ensure data integrity. End users utilize Windows and Mac based workstations to connect to the network and are protected by various anti-virus and anti-spyware solutions, as well as both perimeter and data center specific firewalls. Employees also have the ability to connect through a Virtual Private Network (VPN) when off-site, providing a secure transmission pipeline for sensitive information while allowing users to work remotely when necessary.

Collaboration among faculty, residents, and researchers is facilitated by our high performance network and central file storage, which provides both physical and data security. Policies can be created that will only allow certain employees access to the contents of a given folder, all others are effectively forbidden. The department's IT personnel can provide access to any software that may be required and can often help translate incompatible file formats to help ensure a file is readable or playable.

Within the medical center, users can access OVID, the Vanderbilt University Medical Center library holding management system. With ACORN, users can perform keyword searches on journal articles held by the medical center's library or from other institutions. An increasing number of e-journals are becoming available. Authorized Division users can access MARS (Medical Archive and Record System) from their desktop. MARS is a comprehensive repository of clinical information collected at Vanderbilt Hospital. A medical center wide e-mail system based on Microsoft Outlook is available to all faculty and staff. This system includes an Internet gateway that allows e-mail distribution to all points on the Internet.

Access to computing resources outside the Vanderbilt University is facilitated by the World Wide Web. Users can access government supported resources around the country. The Internet has made collaboration between faculty at far-flung institutions feasible.

The Department of Biomedical Informatics

Over the past decade, Vanderbilt has built an international reputation in academic biomedical informatics. The institution is widely regarded as one of the premier informatics programs nationally and is viewed as a leader in informatics related to clinical practice and library innovation and research. The Department of Biomedical Informatics (DBMI) has grown to more than 50 faculty members and is an integral part of the Informatics Center, which unifies all service components of clinical and administrative informatics activities within Vanderbilt University Medical Center (VUMC). DBMI also enjoys a close relationship with the Eskind Biomedical Library, which is nationally recognized for its interdisciplinary training of new-generation biomedical librarians and its initiatives in evidence-based medicine. As data intensive molecular biology begins to inform decisions made for clinical care, and the volume and types of biomedical research data expand in the era of

genome-enabled life sciences, opportunities and demand for the skillful application of informatics principles is increasing in the areas of service, research and education. We expect the historical strength of the department in providing service to clinicians by development, deployment, and evaluation of clinical information systems will be matched and, perhaps, overtaken by emerging needs and opportunities in bioinformatics. The current emphasis on genomics and proteomics will be supplemented by new forms of “array science informatics”, which pose the general problem of detecting meaningful associations and patterns in n-dimensional arrays of data derived from thousands to millions of simultaneous measurements.

A major strength of Biomedical Informatics at Vanderbilt is the functional integration of informatics within the institution, aligned with institutional research, education, and clinical practice objectives. The Vanderbilt DBMI Training Program is uniquely positioned to simultaneously provide a strong foundation in the principles and theory of biomedical informatics and to take advantage of an advanced informatics applications environment. This unique setting includes readily accessible, large-scale operational clinical information systems created and maintained by DBMI faculty, in which new scientific hypotheses can be tested and new technologies can be deployed. DBMI faculty also manage the Vanderbilt gene expression microarray core facility, and assist with the management of the shotgun proteomics core, giving DBMI graduate students access to state of the art facilities and high volume/high dimensionality data sets created by more than 200 different research groups and laboratories. Vanderbilt’s creation of the Institute for Clinical and Translational Research (VICTR) provided a new 300,000 square foot research building, in which DBMI has 20,000 additional square feet of space. These resources are emblematic of the high value that the institution places on informatics and its positioning as one of the key growth areas for new faculty and programs

The Department of Biomedical Informatics’ research mission is developing and evaluating innovative technologies for the storage, retrieval, dissemination, and application of biomedical knowledge. Thirty-two faculty members have primary appointments in the Department. Major research focuses include: architectures to support large scale systems; interlinguas to support development of and interchange between ontologies; deductive heuristics; algorithm development; knowledge management strategies; data mining; man-machine interfaces; and organization development/change management techniques. Educational programs include a Masters and PhD program in Biomedical Informatics and a variety of non-degree tracks ranging from fellowships to short courses. The department is located next to the main hospital in the Eskind Biomedical Library (see below) which provides space to co-locate faculty, administrative and research staff and students. This area includes a computer laboratory for teaching and demonstration sessions for new and existing applications.

Informatics Center

The Informatics Center consists of the Department of Biomedical Informatics, the Eskind Biomedical Library, and the Department of Information Management. Information Management has responsibility for the information technology infrastructure of the medical center. The network has been described above under Vanderbilt University. Hardware platforms include: an OS390 based parallel sysplex with 2 CEC (240 MIPS) and 692 Gigabytes of disk storage; an AS400; a VAX 6510; 10 RS 6000s; 5 Sun Enterprise class servers; 60 Sun Ultra Class servers; 100 NT, Novelle and OS2 servers; and >3000 Pentium class desktops. Distributed monitoring products include HP OpenView, Optivity and Tivoli. A second redundant data center was started in 2004. Considering the reliance on information exchange within Vanderbilt University Medical Center and with investigators outside Vanderbilt University Medical Center, these high capacity resources are important assets. The Informatics Center has defined and implemented an Enterprise Information Architecture that separates the management of corporate information assets, such as data definitions, business rules and patient data, from the transaction processing systems that support operations. This permits vendor applications and locally developed role-specific user tools to interoperate as components supported by an integrated repository infrastructure. All applications have a single logical connection to a shared communication subsystem, and a repository infrastructure eliminated the n squared interface problem.

StarChart is the medical center’s electronic patient chart. It was developed by Dario Giuse, Associate Professor of Biomedical Informatics at Vanderbilt. StarChart is a distributed system that brings together all information about a patient to provide a complete electronic patient record. It currently receives data from over 50 sources/systems, and the earliest source is complete back to 1984. In its current implementation, it uses more than 60 servers located in two separate areas for maximum availability. StarChart is entirely written in the Perl programming language. In addition to interactive use through a Web browser, StarChart provides application programming interfaces for the medical centers decision support systems. Every word and every number is indexed, permitting full text data mining. Because StarChart is based upon a farm of workstations,

maintenance of this large-scale database is inexpensive and distribution of queries permits rapid response. WizOrder is the medical center's decision support and computerized provider order entry environment. It was developed by faculty in the Department of Biomedical Informatics working with both Informatics Center employees and clinicians from Vanderbilt University Medical Center. WizOrder brings together information about the patient with local and national protocols. Providers note decisions in clinical short hand and it translates those decisions into the administrative orders that are required to carry them out. WizOrder is implemented throughout the entire University Hospital, including the psychiatric hospital, the Children's Hospital and the ED's. Per day, more than 10,000 orders are generated, 70% through direct interaction by physicians, and >500 alters are issued. WizOrder has a light Java client with embedded HTML and with C/C++ on Linux servers. WizOrder was implemented in the ED in 2004, and ED physicians rank highest for physician-entered medication orders (>92%) in the entire hospital.

Research Electronic Data Capture (REDCap)

Data will be stored and managed using the REDCap electronic data capture tools hosted at the Vanderbilt University Medical Center. REDCap is a secure, web-based application designed to support data capture for research studies providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures of de-identified data for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. One of REDCap's features is the ability to readily export de-identified data directly into a variety of statistical software packages including SAS, STAT, R, and SPSS. Thus, we have the ability to tightly control who has access to patient identifying information and can track precisely who accesses the data, when it was done, and what was done (i.e. any data change, import or export). Because of this tight level of control, it will be possible to readily and expeditiously generate de-identified reports of patient accrual (expected vs. actual) and adverse events (number, severity, grade, attribution, expected/unexpected) as often as necessary.

RELEVANT FACULTY EXPERTISE

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

Mentors: Dr. McNaughton's Primary Mentor, Dr. Alan B. Storrow, and her Co-Mentors Drs. Sunil Kripalani and Christianne Roumie, are highly successful clinical investigators and health services researchers with strong track records of mentorship.

Mentor: Alan Storrow, MD is an Associate Professor of Emergency Medicine, the Vice-Chairman for Research and Academic Affairs, and Co-PI for the Vanderbilt Emergency Medicine Research Training Program (VEMRT) Institutional K12 Fellowship. He is passionate in his promotion of an environment that drives excellent clinical research, promotes advancement to independent funding, supports education in research methodology, and ultimately improves patient care. In his roles as the Vice-Chairman for Research and Academic Affairs and Program Director of the VEMRT Program, he has mentored and collaborated with Dr. McNaughton since her residency and has continued to provide career and education guidance, facilitate collaborations with other researchers, and collaborate on multiple manuscripts. Through his collaborations, Dr. McNaughton has gained experience with emergency cardiovascular cohorts and has designed, executed, and disseminated the findings of observational studies. As the primary mentor for Dr. McNaughton's career award application, Dr. Storrow has been involved in shaping her research and career goals and helping her develop necessary skills and maximize the potential for future impact. Her research plan will not only help move her career forward but it will produce vital data to develop interventions to improve hypertension management of high-cost patients and potentially reduce unnecessary use of the emergency department.

Dr. Storrow will continue to meet with Dr. McNaughton weekly during the duration of the award to address operational research details, ensure continued progress along expected timelines, address difficulties as they arise, and ensure timely dissemination of findings in the form of abstracts, presentations, posters, and manuscript. Dr. Storrow's office is located on the same floor as Dr. McNaughton's, separated by approximately 100 feet; this proximity also allows impromptu meetings to address operational or other issues as they arise. In addition to serving as the candidate's primary mentor, Dr. Storrow has committed operational support for Dr.

McNaughton's research project in the form of cost sharing, directing research personnel effort toward patient enrollment beyond that which can be budgeted into this funding mechanism.

Co-Mentor: Sunil Kripalani, MD MSc is an Associate Professor of Medicine in the Department of Internal Medicine and an NHIH-funded health services researcher with extensive experience in medication adherence, health communication, and transitions of care. Dr. Kripalani is conducting ongoing research investigating health literacy and medication adherence, as well as work evaluating interventions to improve transitions of care between the hospital and clinic, including work with the MyHealthTeam PCMH. Dr. Kripalani has mentored Dr. McNaughton over the past two years as she has gained experience with health literacy and medication adherence. With the help of his continued research mentorship and career guidance, Dr. McNaughton will accomplish the goals set out in this proposed research and progress to an independent researcher; she will identify driving factors for emergency department use within a PCMH, evaluating the role of uncontrolled hypertension and medication non-adherence in hospital and emergency department recidivism. Dr. Kripalani will also facilitate her collaborations with key stakeholders among emergency and primary care clinicians. Dr. McNaughton will meet monthly with Dr. Kripalani to focus on rigorous development of methods to use a mass spectrometry assay as a novel measure of medication adherence and evaluating its relationship with ED and hospital recidivism.

Co-Mentor: Christianne Roumie, MD MPH As a Co-Mentor, Dr. Roumie will meet with Dr. McNaughton weekly and participate in quarterly meetings with the Research and Academic Advisory Committee. Dr. Roumie is an Assistant Professor of Medicine and Pediatrics and is currently Dr. McNaughton Primary Mentor on her NHLBI-funded Vanderbilt Emergency Medicine Research Training (VEMRT) Mentorship committee. Dr. Roumie is a highly successful clinical investigator and health services researcher with a strong track record of mentorship. During the proposed career development award, she will provide Dr. McNaughton with mentorship in cardiovascular epidemiology, cardiovascular outcomes measurement, and in the future, collaboration in design and execution of comparative effectiveness research and quality improvement interventions. She has provided Dr. McNaughton with effective career, education, and research mentorship since her VA Quality Fellowship. Dr. Roumie continues to collaborate with Dr. McNaughton, including an ongoing analysis of a large retrospective cohort, exploring the relationship between health literacy and blood pressure control among outpatient and hospitalized patients. Throughout her training, Dr. McNaughton will continue to meet with Dr. Roumie weekly, as she has for the past three years.

Research Advisory Committee

Dr. McNaughton will benefit from the input of the Research Advisory Committee (RAC). This committee will meet quarterly and include the primary mentor and co-mentors: Dr. Alan Storrow (Emergency Research, Emergency Cardiovascular Diseases), Dr. Sunil Kripalani (Medication Adherence, Health Communication, Care Transitions), and Christianne Roumie (Hypertension, Cardiovascular Disease, Epidemiology, Quality, Primary Care); Drs. Robert S. Dittus (Vanderbilt MyHealthTeam, Care Coordination, Quality, Health Systems, Systems Engineering), Thomas Elasy (Health Behaviors, Primary Care), Kenneth A. Wallston (Psychometrics, Health Status Measurement, Quality of Life), and Dandan Liu (Biostatistics, Longitudinal Data). The following consultants will also provide additional support as indicated for specific periods during the research process: Richard Caprioli (Analytical Chemistry, Mass Spectrometry); and Drs. Stephan Russ (Bioinformatics, Clinical Operations). Each member has extensive experience in various aspects of clinical investigation and mentoring. Between meetings, the members of the committee will be easily accessible to the candidate in person and by e-mail.

Robert Dittus, MD MPH is the Albert and Bernard Werthan Professor of Medicine at Vanderbilt University Medical Center (VUMC). Dr. Dittus' positions include the Chief of the Division of General Internal Medicine and Public Health and Director of the VA Tennessee Valley Geriatric Research, Education and Clinical Center, and the Quality Scholars Program. He is also the project leader and PI for the Vanderbilt MyHealthTeam patient-centered medical home. Dr. Dittus has extensive experience in health services research and modeling methods. Dr. Dittus will provide the Dr. McNaughton with all the resources the Vanderbilt MyHealthTeam program can offer to support her initial career development, including access to a multidisciplinary group of researchers, research space, administrative and research support, and pilot funding as needed to ensure her success. Dr. Dittus has mentored Dr. McNaughton

since recruiting her to the VA Quality Scholar fellowship in 2010 and will help guide future grant writing, research dissemination, and impact study development. In addition, Dr. Dittus has mentored numerous research scientists from multiple clinical backgrounds in the fields of quality, safety, and informatics. Dr. Dittus will ensure streamlined, effective collaboration with the MyHealthTeam project leaders, programmers, implementation team, bioinformaticians, and clinicians, as appropriate for each stage of research.

Thomas A. Elasy, MD MPH is Director of the Division of General Internal Medicine and Public Health and Associate Professor of Medicine at Vanderbilt University Medical Center. Given his clinical research focused on longitudinal diabetes care, his mentorship will strengthen Dr. McNaughton's approach to evaluating cardiovascular health and outcomes among emergency patients over the long-term. He has extensive clinical research experience in health communication, health behaviors, and deterioration of chronic disease control. He has extensive independent research and mentorship experience and is a nationally known expert in diabetes and cardiovascular disease management. He has authored over 50 publications, and he directs the Social and Behavioral Science course for the Vanderbilt MPH program.

Kenneth A. Wallston, PhD is Professor of Psychology in Nursing. Dr. Wallston is a world-renown expert in psychosocial measures assessing beliefs about control over a person's health status, and he has developed and validated a number of measures of individual differences. Dr. Wallston has served as a mentor for Dr. McNaughton during her prior work validating measures of numeracy and health literacy in an ED population and later investigating the roles of numeracy and health literacy in outcomes in ED heart failure patients. His expertise in health communication behaviors will guide Dr. McNaughton as she achieves Aims 2 and 3.

Dandan Liu PhD Dr. Liu will serve as a member of the Research and Academic Advisory Committee and the lead biostatistician on the K23. Dr. Liu is an Assistant Professor in the Department of Biostatistics at Vanderbilt University, School of Medicine. Dr. Liu has significant experience carrying out statistical analysis in clinical and outcomes research, and more specifically in the field of survival analysis and event history data analysis, as well as risk prediction and assessment of biomarkers. As the primary statistician for the Research Division in the Department of Emergency Medicine, Dr. Liu has provided programming and statistical expertise in multiple studies in the field of emergency cardiovascular conditions including heart failure and atrial fibrillation. As a result, Dr. Liu is ideally suited to assist in statistical planning for the complex relationships between longitudinal measures of cardiovascular health such as blood pressure, analysis of the LC-MS assay, and survival analysis. In addition to overseeing biostatistical analysis performed by Dr. McNaughton, Dr. Liu will participate in the Research Advisory Committee and oversee Dr. McNaughton's continuing education in statistical modeling, execution, and application.

Additional Advisors / Faculty Expertise

Dr. McNaughton will benefit from the input of consultants with expertise in analytic chemistry and mass spectrometry, as well as bioinformatics, systems engineering and quality improvement. Each member has extensive experience in various aspects of clinical investigation and will be critical to completion of proposal and future projects

Richard M. Caprioli, PhD trained at Columbia University in New York in Pharmacy and Biochemistry and currently a Professor of Biochemistry, Chemistry, Pharmacology and Medicine at Vanderbilt University. Dr. Caprioli's role in the proposed research is to provide analytical chemistry expertise and support for the novel, high-throughput liquid chromatography mass spectrometry (LC-MS) assay that has been designed as a semi-quantitative measure of medication adherence to a broad range of the most commonly prescribed cardiovascular medications. In collaboration with Dr. Nancy J. Brown and Dr. McNaughton, Dr. Caprioli's lab developed and refined the cardiovascular drug LC-MS assay and will continue to collaborate with and support Dr. McNaughton's research as she deploys the assay in cardiovascular research studies.

Stephan Russ, MD MPH is an Associate Professor of the Department of Emergency Medicine and the Associate Chief of Staff and Vanderbilt University Hospital, acting as the primary liaison between the

Informatics Center and Vanderbilt's emergency department and clinics. As both a practicing Emergency Medicine physician and an expert in clinical informatics applications, Dr. Russ has advanced the integration of the electronic health record and clinical practice. His work focuses on operational optimization to maximize clinical safety and efficiency. He has been nationally recognized for his work in emergency department operations. Dr. Russ will support Dr. McNaughton in clinical informatics design and applications, assisting with the access and critical evaluation of necessary data elements from the extensive clinical data repository (CDR).

FACILITIES AND OTHER RESOURCES Clinical Resources

See Vanderbilt University Medical Center Description Above.

Computer Resources

Dr. McNaughton's office is supplied with a Microsoft Windows® desktop computer (Intel® Core™2 Duo), a Hewlett Packard Laser Jet P4014 printer, a 22-inch monitor, and access to the Vanderbilt network server and the Internet via a T1 connection. The Department of Emergency Medicine has also purchased a 15-inch Macintosh MacBook Pro (Intel® Core i7) with for Dr. McNaughton. Both desktop and laptop computers operate with high-level current security standards. Both also have the following software: Microsoft Office®, Internet Explorer®, Adobe Acrobat 9 Professional®, EndNote®, and STATA v11®.

Technical Support

The Informatics Center provides central computer support for all university faculties for e-mail, software access and clinical information systems. Specialized informatics support is also available through the Department of Biostatistics. The Vanderbilt Department of Emergency Medicine has its own technical support, and Dr. McNaughton has access to a full array of computer support technology and resource support throughout the medical center.

Office

Dr. McNaughton has adequate office support. She has a private office in the Department of Emergency Medicine. This office provides Dr. McNaughton with close proximity to her primary mentor, co-mentors, internal advisors, and support personnel. Dr. McNaughton has a Macintosh MacBook Pro with a 24-inch docking screen, as well as a Dell desktop computer (see above description), nine horizontal locked filing drawers, nine book shelves, and enough space to hold meetings of up to three persons.

Administrative Support. Dr. McNaughton has direct secretarial support from Tammy Jones, who provides 100% of her time to the Department of Emergency Medicine. In addition, Dr. McNaughton has access to all of the other administrative resources provided by the Department of Emergency Medicine, including a Department Administrator who manages hiring of research personnel.

Research Infrastructure

The candidate will also have access to several personnel whose salary support is provided by the Department of Emergency Medicine. These personnel include a full time grants manager, an IRB specialist, and a research nurse manager, each of whom provide 100% effort to the Research Division of the Department of Emergency Medicine. Each of these individuals will provide support for Dr. McNaughton's training and research by assisting with IRB, grant, and manuscript submissions.

Library Support: Eskind Biomedical Library

See Eskind Library description above.

EDUCATION AND OPPORTUNITIES FOR INTELLECTUAL INTERACTIONS

Vanderbilt University School of Medicine offers a wide variety of educational opportunities for Dr. McNaughton as she develops her expertise and expands her knowledge in hypertension, cardiovascular disease, advanced biostatistics, and informatics. A directed plan of attendance and participation in these opportunities is part of Dr. McNaughton's career development plan. Below is a description of the opportunities and resources at her disposal.

Epidemiology Doctoral Program

In order to attain the necessary depth and breadth of analytic skills, Dr. McNaughton's education plan incorporates completion of a doctoral degree in Epidemiology during Year 2 of the career development award. Dr. McNaughton will complete the majority of doctoral didactic coursework prior to initiation of the award period; remaining doctoral degree requirements will include personalized, one-on-one seminars with content

experts, addressing specific areas of the proposed research.

The Division of General Internal Medicine Works in Progress Workshop

A weekly Tuesday morning seminar is held by the Division of General Internal Medicine and Public Health that includes Master in Public Health students, faculty within the Center for Health Services Research, and fellows in the VA Quality Scholars Program. During these weekly sessions, fellows and faculty present results from recently completed research, hold work-in-progress sessions to discuss and refine designs for future research studies, and provide feedback regarding the methodologies and challenges of quality improvement, epidemiology, and health services research topics. Sessions are directed by Dr. Russell Rothman as well as Dr. Marie Griffin, both accomplished health services and epidemiology researchers with dedication toward advancing the science of young investigators.

Department of Emergency Medicine Journal Club

Monthly Emergency Medicine group meetings are multidisciplinary conferences during which the latest developments in emergency medicine are highlighted, providing a formal environment for the review of recently published research in emergency medicine and cardiovascular disease.

National Research Meetings

Dr. McNaughton will attend the Society for Academic Emergency Medicine's annual meetings and will alternate attending either the American Heart Association's High Blood Pressure Research scientific session or the Society for Epidemiological Research (SER) annual meeting. In addition to presenting her research, she will attend interest group meetings related to her research and will attend seminars focusing on hypertension, emergency evaluation of hypertension, and care coordination. These scientific meetings are crucial to her development as an emergency cardiovascular researcher, exposing her to advanced research methods. These meetings will also allow her to build collaborative relationships with researchers and establish potential sites for future multi-center trials.

Additional Opportunities

In addition to these conference and opportunities within the Epidemiology PhD Program, Department of Emergency Medicine, and the Division of General Internal Medicine, Dr. McNaughton will benefit from frequent educational workshops held by the Department of Biostatistics, which holds weekly biostatistics educational conferences, as well as the clinician scientist oriented Elliot Newman research society and the Women on Track society, which both host monthly educational seminars. Dr. McNaughton will attend these as they relate to the proposed current and future research plans.

INSTITUTIONAL COMMITMENT TO CANDIDATE'S RESEARCH CAREER DEVELOPMENT

Dr. Corey Slovis, Chair of the Department of Emergency Medicine at VUMC, has written a letter of support for Dr. McNaughton. In this letter, he states his commitment on behalf of the institution to support Dr. McNaughton's career development. This includes the commitment that no more than 25% of the Dr. McNaughton's effort will be spent on clinical, teaching and other institutional activities, and she will not have any administrative responsibilities. The Department of Emergency Medicine has provided Dr. McNaughton with the necessary resources and environment to foster a successful and productive career. This includes office space, on-going career guidance from the members of the Dr. McNaughton's mentor and advisory team, computer and technology resources, a wide array of educational resources and support through the Research Division of the Department of Emergency Medicine.

In summary, Vanderbilt University's environment is both extremely supportive of rising faculty and intellectually stimulating. In addition a supportive environment unique to Vanderbilt will provide Dr. McNaughton with all necessary support to ensure successful attainment of her career development goals and lead to growth into an independent investigator focused on emergency patients with cardiovascular disease.

BIOGRAPHICAL SKETCH

NAME McNaughton, Candace		POSITION TITLE Assistant Professor, Department of Emergency Medicine, Vanderbilt University	
eRA COMMONS USER NAME mcnaugc			
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
Brigham Young University	BS	1998-2001	Microbiology
Washington University in St. Louis	MD	2002-2006	Medicine
Vanderbilt University Medical Center	Internship	2006-2007	Anesthesiology
Vanderbilt University Medical Center	Residency	2007-2010	Emergency Medicine
Vanderbilt University	MPH	2010-2012	Public Health
Veterans Affairs, TN Valley Healthcare,	Fellowship	2010-2012	Quality Improvement
VEMRT K12 Fellow	Fellowship	2012-current	Research Fellowship
Vanderbilt University	PhD	2012-current	Epidemiology

A. Personal Statement

The majority of patients who seek care in the emergency department (ED) have health insurance and access to a primary care provider; how best to leverage emergency evaluations among these vulnerable patients to improve long term cardiovascular outcomes is not known. The overarching goal of the proposed research lays the groundwork for a further, future independent research integrating the ED into chronic management of cardiovascular diseases; the proposed research will maximize the value of ED encounters by utilizing a novel, objective measure of medication adherence and clinical information obtained during ED visits to improve long-term cardiovascular outcomes.

My background in Quality Improvement, patient safety and clinical research form a foundation upon which to build additional quantitative analysis skills, fully exploring the clinical importance of ED measures of blood pressure (BP) and adherence and their impact on long term cardiovascular health. The proposed career development and research plans, which include completion of an ongoing doctoral degree in epidemiology, will maximize and augment skills gained during the National Quality Scholar Fellowship and the Masters of Public Health. Using the mentorship, training, and skills gained in the process of this proposed research, future independent research will continue the rigorous exploration of methods to partner ED care with primary care in the long-term management of cardiovascular disease.

B. Positions and Honors.

Positions and Employment

2001-2002 Blood Banker, Massachusetts General Hospital, Boston, MA
 2002-2003 Blood Banker, St. Louis University Tenet Hospital, St. Louis, Missouri
 2010-2011 Clinical Instructor, Department of Emergency Medicine, Vanderbilt University, Nashville, TN
 2011-present Assistant Professor, Department of Emergency Medicine, Vanderbilt University, Nashville, TN

Professional Memberships

American College of Emergency Physicians, 7/2007-current
 Society of Academic Emergency Medicine, 4/2009-current
 Women on Track, Vanderbilt University Medical Center, 4/2009-current
 Academy for Healthcare Improvement, 7/2010-6/2012
 Elliot Newman Society, Vanderbilt University Medical Center, 7/2012-current

Honors

1999-2001 Abrelia Clarissa Seely Hinckley Scholarship
2000-2001 Office of Research and Creative Activities Grant, Brigham Young University
2001 Magna Cum Laude, Brigham Young University
2006-present Alpha Omega Alpha Medical Honor Society, Washington University in St. Louis
2009-2010 Vanderbilt Sepsis Protocol Development Committee
2010-present Resident Research Award, Vanderbilt University
2010-present Invited Reviewer, *Patient Preference and Adherence*
2010-present Invited Reviewer, *Patient Education and Counseling*
2010-present Invited Reviewer, *Medical Care*
2010-2012 Middle Tennessee Electronic Health Exchange Privacy and Security Committee
2010-2012 Middle Tennessee Electronic Health Exchange Clinical Work Committee
2010-2012 VA Geriatrics Scholar Coach
2011-present VA INSPIRE Stroke Care Improvement Query Committee
2013-present Vanderbilt MPH Advisory Committee Representative

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

1. Garbutt JM, DeFer TM, Highstein G, **McNaughton CD**, Milligan P, Fraser VF. Safe prescribing: an educational intervention for medical students. *Teach Learn Med.* 2006 Summer;18(3):244-50.
2. Garbutt J, Milligan PE, **McNaughton CD**, Highstein G, Waterman BM, Dunagan WC, Fraser VJ. Reducing medication prescribing errors in a teaching hospital. *Jt Comm J Qual Patient Saf.* 2008 Sep;34(9):528-36.
3. **McNaughton CD**, Zhou C, Robert L, Storrow A, Kennedy R. A randomized, crossover comparison of injected buffered lidocaine, lidocaine cream, and no analgesia for peripheral intravenous cannula insertion. *Ann Emerg Med.* 2009 Aug;54(2):214-20.
4. **McNaughton CD**, Wallston KA, Rothman RL, Marcovitz DE, Storrow AB. Short, subjective measures of numeracy and general health literacy in an adult emergency department. *Acad Emerg Med.* 2011 Nov;18(11):1148-55.
5. **McNaughton CD**, Self WH, Jones ID, Arbogast PG, Chen N, Dittus RS, Russ S. ED crowding and the use of nontraditional beds. *Am J Emerg Med.* 2012 Oct;30(8):1474-80. PMID: 22386355
6. Self WH, Speroff T, **McNaughton CD**, Wright PW, Miller G, Johnson JG, Daniels TL, Talbot TR. Blood culture collection through peripheral intravenous catheters increases the risk of specimen contamination among adult emergency department patients. *Infect Control Hosp Epidemiol.* 2012 May;33(5):524-6. PMID: 22476282[PubMed - indexed for MEDLINE]
7. Self WH, **McNaughton CD**, Grijalva CG, Zhu Y, Chappell J, Williams JV, Talbot HK, Shay DK, Edwards KM, Griffin MR. Diagnostic performance of the BinaxNow Influenza A&B rapid antigen test in emergency department patients. *Am J Emerg Med.* 2012 Nov;30(9):1955-61.
8. Self WH, Courtney DM, **McNaughton CD**, Wunderink RG, Kline JA. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *Am J Emerg Med.* 2013 Mar;31:401-405.
9. **McNaughton CD**, Collins S, Jenkins C, Arbogast P, Miller K, Kripalani S, Rothman R, Naftilan A, Storrow A. Lower numeracy is associated with increased odds of 30-day emergency department and hospital recidivism for patients with acute heart failure. *Circulation: Heart Failure.* 2013 Jan 1;6(1):40-6.
10. Barrett TW, Self WH, Wasserman BS, **McNaughton CD**, Darbar D. "Evaluating the HATCH score for predicting progression to sustained atrial fibrillation in ED patients with new atrial fibrillation." *Am J Emerg Med.* 2013 Mar 8. [Epub ahead of print] PMID:23478104
11. Self WH, Speroff T, Grijalva CG, **McNaughton CD**, Ashburn J, Liu D, Arbogast PG, Russ S, Storrow AB, Talbot TR. "Reducing blood culture contamination in the emergency department: an interrupted time series quality improvement study." *Acad Emerg Med.* 2013 Jan;20(1):89-97. PMID:PMC3623801 [Available on 2014/1/1]
12. Seger D, Barker K, McNaughton CD. "Misuse of the Naranjo Adverse Drug Reaction probability scale in toxicology." *Clinical Toxicology.* In Press, June 2013.

Book Chapters and Invited Review Articles

1. **McNaughton CD**, Self WH, Slovis C. Diabetes in the Emergency Department: Acute Care of Diabetes Patients. *Clinical Diabetes*. 2011;29:51-59.
2. **McNaughton CD**, Fick P, Storrow A., Heart Failure Research in the Observation Unit and Emergency Department, in: Short Stay Management of Heart Failure, 2nd ed., Lippincott Williams & Willkins. 2012.
3. **McNaughton CD**, Self WH. Hypoglycemia, in: Emergency Medicine, 2nd ed. 2012.
4. **McNaughton CD**, Self WH, Levy P, Barrett T. The high-risk patient with hypertension. *Clinical Medicine Reviews in Vascular Medicine*. 2012 Aug;4:65-71.
5. Ford D, Self WH, Slovis C, **McNaughton CD**. Diabetes in the Emergency Department and Hospital: Acute Care of Diabetes Patients. *Current Emergency and Hospital Medicine Reports*. Accepted February 2013.
6. Barker K, Seger D, **McNaughton CD**. Toxicology's misuse of the Naranjo Adverse Drug Reaction Probability Scale. *Submitted to Clinical Toxicology*. Under revision, February 2013.

Presentations

1. **McNaughton CD**, Collins S, Jenkins C, Kripalani S, Levy P, Miller K, Naftilan A, Rothman R, Storrow, A. Clinical Outcomes and Literacy and Numeracy in ED Patients with Suspected Heart Failure. SAEM Annual Meeting, presented June 1-5, 2011 as a lightning oral presentation, in Boston, MA, 2011.
2. **McNaughton CD**, Collins S, Jenkins C, Arbogast P, Miller K, Kripalani S, Rothman R, Naftilan A, Dittus RS, Storrow A. "The Associations Between Numeracy and Health Literacy and 30-Day Recidivism in Adult Emergency Department Patients Suspected of Having Acute Heart Failure" Presented as a Guided Oral Presentation at the SAEM Annual Meeting, Chicago, IL, May 9-11, 2012.
3. **McNaughton CD**, Self WH, Wrenn K, Russ S. "Hospital-Acquired Pressure Ulcers" Presented as a Lightning Oral Presentation at the SAEM Annual Meeting, Chicago, IL, May 9-11, 2012.
4. **McNaughton, CD**. "When to treat elevated blood pressure in the emergency department." Emergencies in Medicine Annual Conference, March 3-7, 2013.
5. Self WH, Grijalva CG, Zhu Y, **McNaughton CD**, Barrett TW, Collins SP, Storrow AB, Griffin MR. Incidence of Emergency Department Visits Due to Pneumonia in the United States, 2006-2009: Findings from the Nationwide Emergency Department Sample (NEDS). Society for Academic Emergency Medicine (SAEM) Annual Meeting. Atlanta, GA. May 17, 2013.
6. **McNaughton CD**, Korman R, Dettorre K, Mohamed-Rambaran P, Bovel T, Wright S. "The Prevalence of Suspected Undiagnosed Diabetes Mellitus and use of Random Blood Sugar to Detect Elevated A1c Among Emergency Department Patients in a Developing Country." Oral Presentation at the Society for Academic Emergency Medicine (SAEM) Annual Meeting, Atlanta, GA, May 18, 2013

D. Research Support (in chronological order)

1. Office of Research and Creative Activities Grant
Brigham Young University, Provo, UT (2000-2001)
2. Vanderbilt Institute for Clinical and Translational Research Grant
Vanderbilt University, Nashville, TN #VR1839 (2011)
3. Vanderbilt Institute for Clinical and Translational Research Grant
Vanderbilt University, Nashville, TN #VR2739 (2012)
4. Vanderbilt Institute for Clinical and Translational Research Grant,
Vanderbilt University, Nashville, TN #VR3269 (2012)
5. Vanderbilt Institute for Clinical and Translational Research Grant
Vanderbilt University, Nashville, TN #VR4310 (2012)

2003 – present	Coordinator, SGIM Health Literacy Interest Group
2005, 2011	Reviewer, NIH Special Emphasis Panel for Health Literacy Research (ZRG1 RPHB-B 50)
2006	Chair, NIH Special Emphasis Panels for Health Literacy Research (ZRG1 RPHB-B 50 & 51)
2006	Co-Editor, <i>Journal of General Internal Medicine</i> special issue on health literacy
2006	Planning Committee, AMA Foundation Conference on Health Literacy and Patient Safety
2006 – 2007	Chair, Health Literacy Series, SGIM annual meeting
2006 – 2008	Handoffs Task Force, SHM
2007 – 2010	Research Committee, SGIM
2007 – 2011	Deputy Editor, <i>Journal of Hospital Medicine</i>
2009	Reviewer, NIH Challenge Grants (ZRG1 RPHB-A (58) and ZRG1 RPHB-E (58))
2011 – present	Transition Management Steering Committee, Vanderbilt University Medical Center
2012 – present	Editorial Board, <i>Journal of Hospital Medicine</i>

C. Selected peer-reviewed publications or articles in press (selected from 70)

1. **Kripalani S**, Henderson LE, Chiu EY, Robertson R, Kolm P, Jacobson TA. Predictors of medication self-management skill in a low-literacy population. *J Gen Intern Med* 2006;21(8):852-856. PMID: PMC1831567.
2. **Kripalani S**, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA* 2007;297(8): 831-841. PMID: 17327525.
3. **Kripalani S**, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med* 2007;167:540-550. PMID: 17389285.
4. Gatti ME, Jacobson KL, Gazmararian JA, Schmotzer B, **Kripalani S**. Relationships between beliefs about medications and adherence. *Am J Health Syst Pharm* 2009;66(7):657-664. PMID: 19299373.
5. Gazmararian JA, Jacobson KL, Pan Y, Schmotzer B, **Kripalani S**. Effect of a pharmacy-based health literacy intervention and patient characteristics on medication refill adherence in an urban health system. *Ann Pharmacother* 2010;44(1):80-87. PMID: 20028960.
6. Blake SC, McMorris K, Jacobson KL, Gazmararian JA, **Kripalani S**. A qualitative evaluation of a health literacy intervention to improve medication adherence for underserved pharmacy patients. *J Health Care Poor Underserved* 2010;21:559-567. PMID: 20453356.
7. **Kripalani S**, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;81(2):177-181. PMID: 20684870.
8. Marvanova M, Roumie CL, Eden SK, Cawthon C, Schnipper JL, **Kripalani S**. Health literacy and medication understanding among hospitalized adults. *J Hosp Med* 2011;6(9):488-493. PMID: PMC3575735
9. Martin D, **Kripalani S**, DuRapau VJ Jr. Improving medication management among at-risk older adults. *J Gerontol Nurs* 2012;38(6):24-34. PMID: 22587641.
10. Kansagara D, Englander H, Salanitro AH, Kagen D, Theobald C, Freeman M, **Kripalani S**. Risk prediction models for hospital readmission: a systematic review. *JAMA* 2011;306(15):1688-1698. PMID: PMC3603349
11. Mueller SK, Sponsler KC, **Kripalani S**, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. *Arch Intern Med* 2012;172(14):1057-1069. PMID: PMC3603349
12. **Kripalani S**, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, Shintani A, Sponsler KC, Harris LJ, Theobald C, Huang RL, Scheurer D, Hunt S, Jacobson TA, Rask KJ, Vaccarino V, Gandhi TK, Bates DW, Williams MV, Schnipper JL, for the PILL-CVD study group. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized controlled trial. *Ann Intern Med* 2012;157:1-10. PMID: PMC3575734
13. **Kripalani S**, Schmotzer B, Jacobson TA. Improving Medication Adherence through Graphically Enhanced interventions in Coronary Heart Disease (IMAGE-CHD): a randomized controlled trial of two low-literacy interventions. *J Gen Intern Med* 2012;27(12):1609-17. PMID: PMC3509298 [Available on 2013/12/1
14. Mohan A, Riley MB, Boyington DR, **Kripalani S**. PictureRx: illustrated medication instructions for patients with limited health literacy. *J Am Pharm Assoc* 2012;52(5):e122-9. PMID: PMC3603360
15. Mohan A, Riley MB, Boyington DR, **Kripalani S**. Illustrated medication instructions as a strategy to improve medication management among Latinos: a qualitative analysis. *J Health Psychol* (e-pub ahead of print). PMID: 22453163.

D. Research Support**Ongoing**

R01 HL109388 Kripalani (PI) 8/17/11-4/30/16

NIH/NHLBI

Health Literacy, Hospital Discharge, and Cardiovascular Outcomes

The Vanderbilt Inpatient Cohort Study (VICS) seeks to better understand the association of health literacy, social support, and other sociobehavioral factors with the quality of patients' transition home from the hospital, medication management, health care utilization, quality of life, and mortality.

Role: Principal Investigator

R18 HS019598 Schnipper (PI) 10/1/10-9/29/13

AHRQ

Multi-Center Medication Reconciliation Quality Improvement Study – MARQUIS

MARQUIS is a mixed-methods study to develop and evaluate a multi-faceted medication reconciliation intervention at 6 hospitals.

Role: Co-Investigator

1C1CMS331006-01-02 Schnelle (PI) 7/1/12-6/30/15

Centers for Medicare & Medicaid Services

Reducing hospitalizations in Medicare beneficiaries; a collaboration between acute and post-acute care

This project seeks to reduce hospital admission and readmission for patients in skilled nursing facilities, through both hospital-based and post-acute care-based interventions.

Role: Co-Investigator

1C1CMS330979-01 Dittus (PI) 7/1/12-6/30/15

Centers for Medicare & Medicaid Services

My Health Team: regional team-based and closed-loop control innovation model for ambulatory care delivery

This large initiative will use innovative, inter-professional health care teams and enhanced information technology to improve chronic disease management and reduce excess health care utilization.

Role: Co-Investigator

R01 HD059794 Rothman (PI) 1/5/09-12/31/13

NIH/NICHD

Addressing Health Literacy and Numeracy to Prevent Childhood Obesity

This randomized controlled trial is assessing the efficacy of a low-literacy/numeracy-oriented intervention designed to promote healthy family lifestyles and to prevent early childhood obesity in predominately underserved populations.

Role: Co-Investigator

R18 DK083264 Rothman (PI) 7/5/10-6/30/15

NIH/NIDDK

Public-Private Partnership Addressing Literacy-Numeracy to Improve Diabetes Care

This study involves a partnership with the Tennessee Department of Health to improve care for vulnerable English and Spanish speaking patients with diabetes by improving health care providers' health communication skills, and providing a novel diabetes education toolkit that is sensitive to literacy and numeracy issues.

Role: Co-Investigator

UL1 000445 Bernard (PI) 6/27/12-5/31/17

NIH/NCATS

The Vanderbilt Institute for Clinical and Translational Research

The VICTR Clinical and Translational Science Award (CTSA) represents a major component of Vanderbilt's infrastructure for patient-oriented research.

Role: Co-Investigator; Director, Health Communication Research Core

R43 MD005805 Boyington (PI) 7/10/10-6/30/13

PlainLanguageRx: Improving Medication Labels to Reduce Health Disparities

This Phase I Small Business Innovation Research grant supports the development and evaluation of an illustrated, evidence-based prescription drug label in English and Spanish.

Role: Consultant (Director of Evaluation)

Completed (selected)

R43 MD004048 Boyington (PI) 9/30/09-7/31/12

PictureRx: An Intervention to Reduce Latino Health Disparities

This Phase I Small Business Innovation Research grant supported the development and evaluation of an internet-based, Spanish-language educational intervention to improve medication management among Latinos.

Role: Consultant (Director of Evaluation)

R21 HL096581 Kripalani (PI) 7/5/10-6/30/12

NIH/NHLBI

Brief Assessment of Health Literacy and Association with Cardiovascular Outcomes

This study established the feasibility of incorporating nurse-administered brief health literacy questions into an electronic health record upon hospital admission for use as a research tool, including a psychometric evaluation, and examination of the independent association of the brief health literacy questions with important clinical outcomes including blood pressure control and heart failure readmissions.

Role: Principal Investigator

HHS 290 2007 Hartmann (PI) 9/1/07-6/30/12

AHRQ

AHRQ Evidence Based Practice Centers III

The EPCs develop evidence reports and technology assessments on topics relevant to the clinical, social science/behavioral, economic, and health care organization and delivery arenas.

Role: Co-Investigator

R01 HL089755 Kripalani (PI) 9/1/07-5/31/11

NIH/NHLBI

Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD)

This randomized controlled trial tested the efficacy of a health literacy-sensitive, pharmacist-delivered intervention to reduce the incidence of clinically important medication errors after hospital discharge among patients hospitalized with acute coronary syndromes or heart failure exacerbation.

Role: Principal Investigator

D. W. Reynolds Foundation Powers (PI) 7/1/06-6/30/11

Vanderbilt-Reynolds Geriatric Education Center

The purpose of this grant was to develop, implement and evaluate new programs in geriatric education for physicians including approaches using informatics and simulation.

Role: Co-Investigator (7/09-6/11)

Pfizer Fellowship in Health Literacy/Clear Health Communication White (PI) 8/1/08-7/31/10

The Impact of Health Literacy and Numeracy on Diabetes Care among Latinos

This randomized trial studied the impact of a diabetes health literacy and numeracy toolkit on glycemic control among Latinos in a safety net clinic.

Role: Mentor

K23 HL077597 Kripalani (PI) 9/1/04-6/30/10

NIH/NHLBI

Training in Medication Compliance and Health Literacy

This mentored award included separate studies to evaluate: 1) the effect of health literacy on adherence among patients hospitalized with acute coronary syndromes, 2) a low-literacy intervention to improve adherence after hospital discharge, and 3) a medication counseling workshop for physicians.

Role: Principal Investigator

2. Candidate's Background

Increasing focus on population-level disease management mandates corresponding evolution of the role for the emergency department (ED). As an emergency medicine physician, I have been struck by the lack of evidence available to guide emergency and primary care providers as they grapple with system-level changes and increasingly limited resources. There is need for methods to **leverage ED visits to inform chronic cardiovascular care plans and flag patients at high risk for deterioration**. Currently, ED clinical information such as blood pressure (BP) is rarely integrated into care plans or systematically communicated with other providers. As a result, patients undergo repeated testing, wade through multiple non-value added clinical encounters, and experience delays to achieving control of chronic conditions, including hypertension.

Recognizing the important role that health systems play in safe and effective healthcare, particularly in the ED, I pursued the **VA Quality Scholars fellowship** after completing my Emergency Medicine residency. In this fellowship, I gained extensive skills and experience with patient safety and quality improvement and established critical career and research mentoring relationships with Drs. Roumie and Dittus. In the **Masters of Public Health (MPH)** program, I gained important fundamental skills in study design, analysis, and dissemination while working with Drs. Storrow, Kripalani, Dittus, Rothman, and Wallston to validate and then use subjective measures of numeracy and health literacy in the ED to determine their relationships with 30-day ED and hospital recidivism. I gained experience with factors associated with poor disease self-management, which may be an important cause of rising ED visits among patients with chronic diseases.

I continued research training to gain high-level study design and analytic skills. In 2012, with Dr. Storrow's support I was awarded an NHLBI-funded institutional K12 training position in the **Vanderbilt Emergency Medicine Research Training (VEMRT) program**. With Drs. Kripalani, Roumie, and Wallston, I am developing additional expertise in health literacy, medication adherence, and hypertension. I am gaining expertise in cardiovascular epidemiology through work with Dr. Storrow and Dr. Dittus, a key stakeholder and leader in the **MyHealthTeam (MHT) patient-centered medical home (PCMH)**. The MHT PCMH is a transformative model of health care delivery designed to coordinate chronic disease management across hospital and clinic settings, although the *ED care was not explicitly integrated*. Patients with a confirmed diagnosis of treated hypertension and participating primary care physicians are eligible for MHT PCMH enrollment. This innovative care model is one of Vanderbilt University's top priorities over the next decade; its implementation and evaluation are funded in part by an \$18.8 million CMS Innovation award (PI: Dittus).

Distinguishing uncontrolled BP due to medication non-adherence from that due to low therapeutic intensity or ineffective therapy is crucial to safely achieve blood pressure (BP) control. Currently available measures of adherence are impractical or have not been validated in the ED setting.¹⁵⁻²¹ To begin addressing the need for an objective, reliable measure of medication non-adherence in the ED setting, I collaborated with Drs. Caprioli and Brown on initial work to validate a liquid chromatography mass spectrometry (LC-MS) assay that detects 34 of the most commonly prescribed cardiovascular drugs, including 19 antihypertensive medications. Preliminary analysis among 294 hospitalized patients indicates the assay is accurate when results are dichotomized at analytic chemistry thresholds. Use of this **LC-MS assay as a novel, objective measure of medication non-adherence** has the potential to revolutionize clinical research in uncontrolled hypertension, making accurate measurement of medication non-adherence widely and easily available. Over the past 9 months we have already **enrolled 300 patients in a prospective cohort** of patients with treated hypertension to determine therapeutic assay thresholds to correctly classify patients with medication non-adherence and to determine the hazard of recidivism to the ED or hospital due to non-adherence (**Aims 2 & 3** of the proposed project).

I am pursuing a **doctoral degree in epidemiology** focused on advanced epidemiological methods and analysis, explicitly designed to achieve my research goals. While completing many of the first-year doctoral classes during the VEMRT fellowship, I recognized the need for training and mentoring in advanced analytic methods. I will matriculate as a formal student and complete comprehensive exams prior to beginning the K23 and defend my dissertation in May 2016. A PhD in epidemiology will provide me with essential training and expertise to ensure progression to scientific independence and will distinguish me from my peers.

My background in health services research, clinical epidemiology, health systems, and patient safety make me an ideal candidate for a career development award, which will allow my **transition from an institutional K12 to an individual K23 award**. This step from an institutional training award to a mentored individual award is critical for my successful progression to an independent investigator.

3. Career Goals and Objectives

Between 10-20% of Americans seek care in the emergency department (ED) annually,^{1,2} and the majority of these patients have health insurance and access to a primary care provider.^{1,22} The driving forces behind these ED visits are not well-understood, impeding efforts to partner primary care and emergency care and resulting in lost opportunities to improve cardiovascular health in these vulnerable patients. In the face of the worsening primary care provider shortage²³ and rising demand for ED care,²⁴⁻²⁶ my long term career goal is to address this fundamental question: **How can the ED best serve patients with chronic cardiovascular diseases?** There is controversy regarding the appropriate interpretation and utilization of ED assessments such as blood pressure (BP) as predictors of long-term cardiovascular health.²⁷⁻³¹ Reliable, objective measures of medication non-adherence in the ED setting are also needed to distinguish uncontrolled blood pressure (BP) due to medication non-adherence from that due to low therapeutic intensity or ineffective therapy. To address these evidence gaps, I will use hypertension as a model chronic cardiovascular condition and develop the skills to advance the science of emergency care for cardiovascular diseases and become a national expert on precipitants of ED visits such as medication non-adherence in primary care patients enrolled in a patient-centered medical home (PCMH). Building on my prior scientific work and skillset, the following rigorous learning objectives have been designed to accomplish these goals:

Career and Learning Objective 1: Attain advanced skills in cardiovascular epidemiology, study design, data management, measurement, and analytic methods to correctly classify hypertension control and medication non-adherence in the ED and evaluate their impact on recidivism to the ED and hospital.

Career and Learning Objective 2: Attain the analytical skills needed to expertly evaluate the discriminatory capacity, criterion validity, and predictive validity of a liquid chromatography mass spectrometry (LC-MS) assay as an objective, novel measure of medication non-adherence.

With these two learning objectives, I will gain advanced skills targeting the intersections of cardiovascular epidemiology, clinical research, and clinical practice. I will develop the professional and academic skills necessary for success as an independent investigator focused on maximizing the value of ED visits and partnering emergency and primary care to improve chronic cardiovascular disease care.

4. Career Development / Training Activities During Award Period

My career development plan reflects interdisciplinary learning objectives and goals. I propose building on my existing research, including: a) *mentorship* from experts in hypertension, epidemiology, biostatistics, clinical pharmacology, analytic chemistry, and informatics; b) *coursework* to develop expertise in these areas, as well as *grant writing*, c) *research conferences*; and d) *dissemination of findings* at professional meetings.

In **preparation** for my K23, I will complete *two years of doctoral didactics and doctoral comprehensive exams*, expand my *clinical expertise* through the American Heart Association's Hypertension Summer School and the Training in Hypertension Course, and continue *collaboration with key stakeholders in the Vanderbilt MyHealthTeam (MHT) patient-centered medical home (PCMH)*. My planned career development activities **during** the K23 period are multifaceted and tailored to maximize the personalized advanced training available through the epidemiology doctoral program (Advanced Methods in **Table 1: Doctoral Didactics, Years 1 and 2**; **Table 2: Mentored Research and Training, Years 1-4**, including personalized doctoral seminars tailored to the research aims).

Table 1: Doctoral Didactics, Years 1 and 2

Year 1 (Aims 1-3)	Year 2 (Aims 1-3)
<ul style="list-style-type: none"> ▪ Quantitative Measurement ▪ Drug Metabolism and Pharmacokinetics ▪ Research Ethics ▪ Proposal development ▪ Dissertation proposal defense 	<ul style="list-style-type: none"> ▪ Bioinformatics ▪ Advanced Predictive Modeling and Simulation ▪ Dissertation defense

I plan R01 preparation and submission in Years 2 and 3, respectively. Selected face-to-face, monthly conferences will include *journal club*, *bioinformatics seminars*, and seminars for the *Vanderbilt Elliot Newman Society*, which is designed to support early-stage investigators transition to scientific independence, and *Vanderbilt Women on Track*, which provides mentorship, support, and career education for junior faculty women to promote the retention and advancement of tenure track women faculty in medical science. I will also attend the Johns Hopkins Intensive Summer session on Leadership in Strategic Health Communication in Year 4 to gain additional skills for development and testing of an intervention focused on ED patients with uncontrolled hypertension and medication non-adherence as part of an R01 proposal.

Table 2: Mentored Research and Training Years 1-4

Year 1 (Aim 1&2)	Year 2 (Aims 1&2)	Year 3 (Aims 2&3)	Year 4 (Aim 3)
<ul style="list-style-type: none"> ▪ <u>Doctoral Seminars</u>: Cardiovascular disease epidemiology; Advanced quantitative analysis of ED BP; Advanced analysis of LC-MS assay ▪ Continued MHT PCMH collaboration 	<ul style="list-style-type: none"> ▪ Collaborate with care transitions experts 	<ul style="list-style-type: none"> ▪ Collaborate with key clinical policy stakeholders for guideline development and dissemination 	<ul style="list-style-type: none"> ▪ Johns Hopkins Intensive Summer session: Leadership in Strategic Health Communication ▪ Intervention development

4.1. Research, Career, and Educational Mentorship

I have assembled an outstanding mentorship team made up of nationally recognized content experts and experienced researchers crucial for success (**Table 3**). Dr. Alan B. Storrow will serve as the *Primary Mentor*. He, Dr. Sunil Kripalani, and Dr. Christianne Roumie comprise the *Co-mentorship Team*.

Table 3: Mentorship Team: Primary Mentor, Co-Mentors, Advisors, and Consultants

Member	Expertise Provided to K23	
Co-Mentorship Team	Alan B. Storrow, MD Weekly	Emergency cardiovascular research, professional success, grantsmanship
	Sunil Kripalani, MD MSc Monthly	Medication adherence, health literacy, health services research, care transitions
	Christianne Roumie, MD MPH Weekly	Professional success, cardiovascular research, grantsmanship
Research Advisory Committee (Quarterly)	Robert S. Dittus, MD MPH	MyHealthTeam leadership and data development; professional and research success
	Tom A. Elasy, MD MPH	Chronic disease management, health psychology, clinical interventions
	Kenneth A. Wallston, PhD	Behavioral health measures; psychometrics
	Dandan Liu, PhD	Biostatistical design and analysis
Consultants	Richard M. Caprioli, PhD	Analytical chemistry, mass spectrometry assay
	Stephan Russ, MD MPH	Bioinformatics, large data management, operations

Primary Mentor: Alan B. Storrow, MD is an Associate Professor of Emergency Medicine, Vice-Chairman for Research and Academic Affairs, and Co-PI for the Vanderbilt Emergency Medicine Research Training (VEMRT) Institutional K12, one of 6 NHLBI sponsored Emergency Medicine institutional research training programs. He is nationally recognized for emergency cardiovascular research, has an impressive mentoring track record, and has had continuous NHLBI PI funding for 7 years. He has authored over 120 peer-reviewed papers, including 3 of my first-author papers. Dr. Storrow and I will continue to meet weekly to address operational details and ensure timely progression of research and dissemination of findings in the form of abstracts, presentations, posters, and manuscripts. Our offices are located on the same floor, approximately 100 feet apart, allowing impromptu meetings to address issues as they arise. Dr. Storrow has committed operational support for my research in the form of cost sharing, directing research personnel effort to patient enrollment beyond that available via this funding mechanism.

Co-Mentor: Sunil Kripalani, MD MSc is an Associate Professor of Medicine, Department of Internal Medicine and will serve as a Co-mentors. Dr. Kripalani is an NIH and NHLBI-funded health services researcher with extensive experience investigating medication adherence, health communication, and care transitions, including collaboration with MyHealthTeam. Dr. Kripalani has provided crucial mentorship over the past two years as I gained expertise in health literacy and medication adherence. With the help of his continued research mentorship and career guidance, I will accomplish my research goals and progress to an independent researcher. Dr. Kripalani will facilitate collaborations with key stakeholders among emergency and MHT primary care clinicians. Dr. Kripalani and I will continue to meet monthly to focus on rigorous development of methods to use a mass spectrometry assay as a novel measure of medication adherence and evaluate its relationship with ED and hospital recidivism.

Co-Mentor: Christianne L. Roumie, MD MPH is an Assistant Professor of Medicine and Pediatrics and will serve as a Co-mentor. She has already provided effective career, education, and research mentorship since my VA Quality Fellowship, and she is currently the primary mentor on my NHLBI-funded VEMRT mentorship committee. Together we designed the protocol for enrollment of the first 300 ED patients of the prospective cohort of ED patients with treated hypertension (Aims 2&3). Dr. Roumie is a highly successful clinical investigator and health services researcher with a strong track record of mentorship. She will provide mentorship in cardiovascular epidemiology and outcomes measurement, as well as health communication behaviors. Throughout my training, Dr. Roumie and I will continue to meet weekly to address research study design, analysis plans and execution, and rapid dissemination of findings in the form of manuscripts.

Quarterly meetings will be held with my **Research Advisory Committee (RAC)** to evaluate and guide my overall progress toward scientific independence. Each member has been chosen to provide a complementary role in the proposed research and training plan, with important roles in advancing my research and career development goals. Members of the RAC include:

a) **Robert S. Dittus, MD MPH**, Director of the Institute for Medicine and Public Health, the Center for Health Services Research, and the Center for Improving Patient Safety. Dr. Dittus is also the project leader and PI of the Vanderbilt MHT PCMH, involved in its design and implementation since its inception. He will ensure effective collaboration with the MHT leadership and clinicians throughout the duration of the project. Dr. Dittus brings substantial expertise in population disease management and complex analytic methods. His mentorship and career guidance skills will be invaluable my academic growth; Dr. Dittus has provided mentorship to over 100 fellows; over 90% have remained in academic medicine.

b) **Tom A. Elasy, MD MPH**, Director of the Division of General Internal Medicine and Public Health and Associate Professor of Medicine. Dr. Elasy has extensive independent research experience investigating social factors in health and mentorship experience; he is a national expert in diabetes and cardiovascular disease management, with over 50 publications. His mentorship will substantially strengthen the approach to evaluating health behaviors and deterioration of chronic cardiovascular diseases.

c) **Kenneth A. Wallston, PhD**, Professor of Psychology in Nursing. Dr. Wallston is a well-known expert in psychosocial measures and their relationships with health status, having developed and validated a number of behavioral health measures. Dr. Wallston provided invaluable mentorship during my work validating measures of numeracy and health literacy in an ED population. He will continue to provide expertise in psychometric measurements of characteristics associated with ED and hospital recidivism.

d) **Dandan Liu, PhD**, Assistant Professor, Department of Biostatistics. Dr. Liu has extensive experience carrying out statistical analysis in clinical and outcomes research, particularly survival analysis, event history data analysis, risk prediction, and assessment of biomarkers. In the epidemiology doctoral program I will gain considerable statistical experience and expertise, which will be augmented by Dr. Liu's support.

The following **consultants** will provide their continued expertise and support:

Richard M. Caprioli, PhD, Professor of Biochemistry, Chemistry, Pharmacology and Medicine. Dr. Caprioli's lab developed, refined, and performed analytic chemistry validation of the cardiovascular drug liquid chromatography mass spectrometry (LC-MS) assay. He will continue to collaborate with and support my efforts to further develop the assay as measure of medication non-adherence.

Stephan Russ, MD MPH, Associate Professor, Department of Emergency Medicine, Associate Chief of Staff, Vanderbilt University Hospital, and primary liaison between the Informatics Center and Vanderbilt's ED and clinics. Dr. Russ will provide support for efficient and reliable data extraction and manipulation, assisting with the critical evaluation of necessary data elements from the extensive clinical data warehouse (CDW).

Candidate's Anticipated Teaching Load, Clinical Responsibilities, and Administrative Assignments

My research efforts will be protected, with **at least 75% effort devoted to mentored research endeavors** and the remaining 25% devoted to clinical duties in the form of ED shifts. I will not have any required teaching or administrative assignments during this award.

Candidate's Transition to Independence (Figure 1)

I will develop the characteristics and skills required to emerge as a leader in emergency cardiovascular research. Over the course of my career development, I will gradually function more independently, preparing for successful transition to scientific independence by the time the K23 is completed. As I gain advanced analytic skills, I will continue to draft and lead the revision of all manuscripts and will submit an R01 in Year 3, allowing seamless transition from K23 to R01 funding. The combination of didactic and close mentorship with increasing skills and independence will ensure this steady progression.

4.2. Training Activities

In Year 1, 75% of my effort will be devoted to the proposed research aims: 60% overall effort directed *exclusively* to the proposed research, including doctoral work, and 15% effort directed to didactics that *provide additional skills necessary to accomplish the research aims* but that may require use of unrelated datasets. Year 2 didactics are designed to produce publishable works and exclusively use my research datasets.

4.2.1 Epidemiology Doctoral Degree In order to attain the necessary depth and breadth of advanced skills, my education plan incorporates completion of a doctoral degree in epidemiology at the end of award Year 2 (May 2016). I will complete two years of doctoral coursework prior to initiation of the K23. Remaining doctoral requirements will be leveraged to accomplish the proposed research aims (Tables 1&2):

Doctoral Seminars One-on-one seminars with content experts, focused on specific areas of the proposed research (Table 2). **Advanced Analytics and Biostatistics** The research aims rely heavily on advanced analysis of longitudinal data and multivariable modeling; as part of the doctoral epidemiology degree, I will complete advanced biostatistics training in quantitative analysis and advanced predictive modeling and simulation, which are integral to the proposed research. **Clinical pharmacology and analytic chemistry** I will receive advanced training in clinical pharmacology and analytic chemistry to perform in-depth interpretation and use of the LC-MS assay within the context of variable administration and dosing. **Bioinformatics** To expand skills in the effective use of electronic health records as a complementary source of data, I will attend the Foundations of Biomedical Informatics and Evaluation Methods in Biomedical Informatics course. **Grant Writing Development** Additional instruction in effective grant writing and protocol development during the epidemiology doctoral program and regularly scheduled Elliot Newman Society and Women on Track career development seminars will bolster rapid dissemination of findings and future investigations and funding

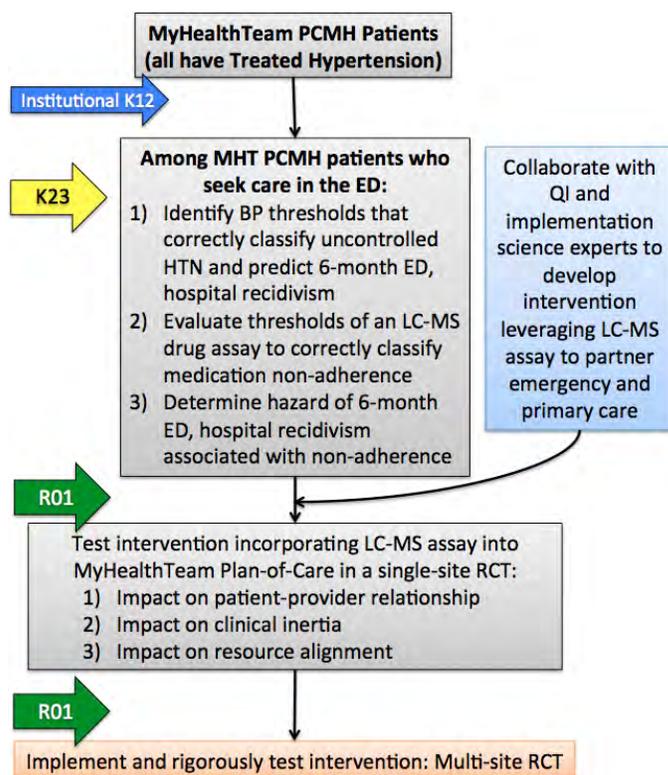


Figure 1: Candidate Research Career Pathway
[PCMH, patient-centered medical home; ED, emergency department; HTN, hypertension; LC-MS, liquid chromatography mass spectrometry; QI, quality improvement; RCT, randomized controlled trial]

applications. ***Training in the Responsible Conduct of Research*** Building on the RCR training received during the MPH and VMERT fellowship, I will complete a face-to-face, semester long course in ethics and human subject protection, as required for the epidemiology doctoral degree. I will also attend bimonthly, 1-hour Clinical Research Center Research Skills Workshops designed to provide cutting edge research conduct training. I will also present an Emergency Medicine grand rounds lecture on informed consent in the ED.

4.2.2 Research Seminars and Conferences I will broaden my knowledge base and opportunities for collaboration through directed reading and participation in the following seminars, journal clubs, and national meetings: Weekly: Department of General Internal Medicine Works in Progress; Emergency Medicine Research Division; Bi-monthly: Department of Biomedical Informatics and CRC; Monthly: Vanderbilt Emergency Medicine Journal Club, Elliot Newman Society, Women on Track; Annually: I will present research at two national scientific meetings per year: the Society for Academic Emergency Medicine and either the American Heart Association's High Blood Pressure Research Scientific Association or the Society for Epidemiological Research. I will also attend the Leadership in Strategic Health Communication session.

Training in the Responsible Conduct of Research

Building on my prior training and skills in the responsible conduct of research (RCR), I will receive additional, advanced RCR training through the following activities over the proposed 4-year award: 1) I will complete the formal Research Ethics course required by the epidemiology doctoral program; 2) I will attend a minimum of 8 hours of RCR content during each year of the proposed award, and 3) I will give an Emergency Medicine grand rounds talk addressing principles of informed consent, focusing on the unique aspects and pitfalls associated with the emergency setting.

In the course of my Masters of Public Health (MPH), I received formal RCR training, providing me with the skills and knowledge necessary to ethically and responsibly conduct the proposed research. The MPH required completion of a formal ethics course that provided training in the practice of scientific investigation with integrity. This included face-to-face discussion, guided readings, and the completion of online training modules required for IRB and NIH purposes. This course, completed in March 2011, required familiarity with the language and literature of research ethics and exploration of ethical dilemmas pertaining to the values, principles, rights, and beliefs that shape each person's concept of research and health care. The course also required discussion of the broader perspectives of research regulations, the role of research in society, the tools needed to conduct research, and the formation of public health policy. This provided me with skills necessary to apply these concepts to research and public health practice through a case-based approach that analyzed the relationships between ethics, policy, and culture. I was also required to assess my own research environment to analyze where principles of research ethics were and are being applied.

Through RCR training integrated into Elliot Newman Series (ENS) and Women on Track (WOT) seminars during my MPH and institutional K12 Vanderbilt Emergency Medicine Research Training fellowship, I have continued to augment my RCR training from 2010 to 2013, most recently including a 1-hour course on the ethics of authorship lead by Dr. Elizabeth Heitman in April 2013. ENS and WOT each hold 1-hour, monthly face-to-face seminars of varied didactic and small group discussions lead by research training faculty members, addressing topics relevant to early investigators. Reflecting the institutional priority placed on integrating RCR and research ethics into all career development programs, Vanderbilt has established a centralized system specifically to address responsible conduct of research, which also allows tracking of the participation of students, trainees, fellows/scholars, and faculty. StarBRITE and tools developed to support faculty compliance resources are used to preview the intended content of events such as lectures, seminars, workshops, and grand rounds, and approve those with clear RCR content for RCR credit. At the close of events approved for RCR credit, participants receive a unique identifier that they can use to log-on and enter their participation. This system will allow accurate summaries of my completed RCR participation.

The proposed research requires continued education and training in all RCR principles, with specific, focused attention to the following principles: data acquisition, management, sharing, and ownership; human subjects, including informed consent, confidentiality and privacy of data and patient records, risks and benefits, preparation of research protocols, institutional review boards, adherence to study protocols, proper study conduct, and special consideration of these factors within the emergency setting, particularly informed consent; and mentor/trainee responsibilities. Drs. Storrow, Roumie, and Kripalani will incorporate explicit discussion and instruction of these principles into their regularly scheduled mentor meetings (weekly or monthly, as described in the Career Development Section). These principles are explicitly incorporated into many of the activities in the Elliot Newman Series and Women on Track seminars, and other programs directed at early career faculty, which are scheduled regularly (at a minimum, monthly) and are easily available to all early career faculty. Over the 4-year award, I will attend a minimum of 8 hours per year of RCR training addressing these principles via these 1-hour long, face-to-face seminars.

I will also give a 1-hour Emergency Medicine grand rounds presentation addressing the unique aspects of informed consents in the emergency department setting, including the components of comprehension and assessment of risks and benefits, which are vital to the proposed research. Because it is unique to emergency research, I will also include discussion regarding the conditions and criteria required to conduct research without prior informed consent.

Description of Institutional Environment

Vanderbilt University has a strong, successful research and career development program that provides unique opportunities and support available only at Vanderbilt, including a high-quality research environment with key faculty members who will continue to collaborate with and support Dr. McNaughton.

1. Vanderbilt University School of Medicine and Medical Center (*Jeffrey Balser, MD, PhD, Dean*)

Vanderbilt University School of Medicine's mission is to perform research that will advance the science and practice of medicine. Through this commitment, 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 Dr. McNaughton's potential to succeed in her research and training goals.

2. Department of Emergency Medicine, Research Division (*Corey Slovis, MD, Chairman; Alan B. Storrow, MD, Vice-Chairman for Research and Academic Affairs and Program Director for the Vanderbilt Emergency Medicine Research Institutional K12 Training Program*)

Dr. Slovis is committed to continued growth of the department as a premier site for emergency medicine (EM) research. In 2006 he commissioned the Research Division, which ranks 6th in NIH funding among all EM departments. The Research Division has aggressively sought and obtained research and funding opportunities with the strong leadership provided by Dr. Alan Storrow, who is Dr. McNaughton's Primary Mentor. Dr. McNaughton will have continued access to shared departmental research resources, including a research nurse, six clinical trials associates, a grants manager, an IRB liaison, administrative support, and Ph.D. and Masters level biostatisticians. In addition to this substantial administrative support, Dr. McNaughton will continue to devote 75% of her effort to research and career development activities. The remaining 25% of her time will be devoted to clinical duties and teaching; she will have not required administrative duties.

3. The Vanderbilt MyHealthTeam patient-centered medical home (*Robert Dittus, MD MPH, Project Leader*)

MyHealthTeam (MHT) is designed to implement population-based care coordination across hospital and clinic-based settings via inter-professional teams and enhanced health information technology integrated into clinical workflow. All enrolled patients have treated hypertension and the vast majority have health insurance. System-wide implementation is ongoing among Vanderbilt University's 3 affiliates, potential sites for future study. As one of Vanderbilt's institutional priorities, MHT's implementation is also partially supported by a 3-year, \$18.8 million CMS innovation award. Drs. Dittus and Kripalani are key stakeholders in MHT and members of Dr. McNaughton's mentorship committee, ensuring effective collaboration during the proposed research.

4. Vanderbilt University Mass Spectrometry Research Center (*Richard M. Caprioli, Director*)

The mission of the Mass Spectrometry Research Center (MSRC) is to bring state-of-the-art mass spectrometry expertise, methodology, and instrumentation to the research and clinical infrastructure of the Vanderbilt University Medical Center. Directed by Dr. Caprioli, the MSRC will continue to collaborate with Dr. McNaughton to support refinement and deployment of the cardiovascular drug mass spectrometry assay in clinical research.

5. Epidemiology Doctoral Program (*Katherine Hartmann, MD PhD, Deputy Director*)

Home to more than 127 researchers, with more than 80 NIH awards and more than \$82 million in current funding, the Vanderbilt Epidemiology Center faculty will provide Dr. McNaughton with advanced analytic expertise and additional expert mentorship during completion of the doctoral program and as she performs the proposed research and develops and refines plans for future research.

6. Vanderbilt Institute for Clinical and Translational Research (*Gordon Bernard, MD, Director*)

In collaboration with the Office for Clinical and Translational Scientist Development, VICTR provides an integrated career development program for physician-scientists, with comprehensive services to assist faculty in their efforts to secure funding and conduct research of the highest quality and worldwide impact. Dr. McNaughton is a member of the Vanderbilt Elliott Newman society, which focuses on the transition from K to R funding, as well as the Vanderbilt Women on Track, which promotes the retention and advancement of tenure track women faculty and provides mentorship, support, and career education for junior faculty women. Both societies conduct monthly, 1-hour, face-to-face seminars targeted to early stage investigators.

7. Department of Biostatistics (*Frank Harrell, PhD, Chairman*)

With 22 Ph.D. faculty, 8 senior M.S.-level biostatistician faculty, 19 M.S. staff biostatisticians, 10 computer systems analysts, and 11 administrative staff members, this department provides unparalleled statistical expertise. Dr. McNaughton will have access to additional biostatisticians as needed for each stage of the proposed research via didactics, doctoral seminars, and consultations.

8. Vanderbilt Informatics Center (*William Stead, MD, Chief Strategy Officer and Director*)

The Department of Biomedical Informatics is the largest academic biomedical informatics department in the country and developed the Synthetic Derivative, a de-identified shadow of the electronic medical record.

1. Specific Aims

Patients with chronic cardiovascular diseases are an important driving force in the rising demand for emergency department (ED) care, even though most of these patients have health insurance and a primary care provider.¹⁻³ Contemporary solutions are required to better serve these patients within the rapidly changing healthcare structure. I will build a career *maximizing the ED's contribution to coordinated, high quality cardiovascular care* through innovative techniques for collecting, sharing, and integrating ED clinical information within patient-provider networks. I propose leveraging our institution's expertise in medication adherence, hypertension, and emergency services within the unique Vanderbilt MyHealthTeam patient-centered medical home (PCMH) as an initial test bed for my early mentored research. Developing this model will ultimately allow translation to other diseases and care settings.

“Current control rates for hypertension in the United States are clearly unacceptable.”⁴ Despite the well-known risks of uncontrolled blood pressure (BP)⁴⁻¹² two thirds of patients with hypertension do not meet Joint National Commission BP recommendations.^{10,13} The National Quality Forum and Centers for Medicare and Medicaid Services have declared hypertension control a marker of healthcare quality.¹⁴ **To achieve and maintain BP control, partnership among all treating clinicians is essential.**

The ED is an ideal location to identify vulnerable, high-cost patients with treated but uncontrolled hypertension. For the millions of patients who seek ED care despite health insurance and access to a primary provider,¹ ED visits should be leveraged as teachable moments or as signals to modify chronic care plans. Triggers for ED visits and hospitalizations, and the extent to which these are modifiable, are poorly understood. Improved measurement and understanding of medication non-adherence as a possible cause of ED visits is also vital to develop interventions to better align resource use and improve long-term cardiovascular outcomes.

This proposal leverages the well-defined and highly characterized **Vanderbilt MyHealthTeam (MHT) PCMH**. MHT seeks to provide high-quality, effective population disease management by coordinating care among patients across hospital and clinic settings; it is a top institutional priority for Vanderbilt and is partially funded by an \$18.8 million CMS Innovation Award. ED clinical information is not systematically integrated into long-term cardiovascular care plans within this otherwise highly coordinated medical home. We will also deploy a new liquid chromatography mass spectrometry (**LC-MS**) **assay as a novel tool to measure medication non-adherence**; preliminary evaluation suggests this semi-quantitative assay accurately detects 34 cardiovascular medications, including 19 of the most commonly prescribed antihypertensive drugs.

The potential roles for the ED in identification, risk stratification, and interventions for these vulnerable, high-cost patients have yet to be explored. To do so, I propose testing the following specific aims among ED patients with treated hypertension who are enrolled in the Vanderbilt MHT PCMH:

Specific Aim 1: **a)** Identify ED values of BP that correctly classify hypertension control status, as defined by clinic BP, and **b)** Determine the relationship between uncontrolled hypertension detected in the ED and 6-month ED and hospital recidivism.

Hypothesis 1: *BP values in the ED correctly classify BP control and predict 6-month ED and hospital recidivism.*

Specific Aim 2: **a)** Determine optimal thresholds of an LC-MS assay that detects 19 antihypertensive medications to correctly classify patients with medication non-adherence, using medication administration in the hospital as the gold standard, and **b)** Evaluate the LC-MS assay's validity by comparing its performance against other measures of medication adherence.

Specific Aim 3: Determine the hazards of 6-month ED and hospital recidivism associated with non-adherence to antihypertensive therapy.

Hypothesis 2: *Medication non-adherence, as measured by the LC-MS assay, predicts 6-month ED and hospital recidivism, despite enrollment in the MHT PCMH.*

By 1) correctly classifying patients with uncontrolled hypertension and medication non-adherence *in the ED* and 2) determining the relationship between medication non-adherence and recidivism, this proposal is a crucial first step in partnering emergency and primary care to develop interventions to better align healthcare resource utilization and improve BP control. It also provides the mentorship, skills, and experience for the candidate to develop a career focused on maximizing the ED's contribution to cardiovascular care.

11. Research Strategy

11.1 SIGNIFICANCE

Coordinated population-level disease management, such as that provided within Accountable Care Organizations, seeks to ensure patients get the best care at the right time while avoiding unnecessary duplication of services.³² The emergency department (ED) has often played an ancillary role in this and other population management strategies (Figure 2)³³ such as patient-centered medical homes (PCMHs),³⁴ despite evidence that the ED may provide cost effective care and eliminate the need for some hospitalizations.³⁵ In addition, between 10-20% of Americans seek emergency care annually,^{1,2} more than half of hospital admissions originate from the ED,³⁶ and the rising demand for ED care is largely due to patients with primary care providers and health insurance.¹ **The ED is a woefully underutilized location to identify high-risk patients with treated but uncontrolled hypertension, particularly among PCMH patients seeking ED care.** Moderately or significantly elevated BP is noted in 15-25% of ED visits,^{37,38} although the proportion with diagnosed hypertension is not known. Those vulnerable patients who seek ED care despite apparent access to primary care and healthcare resources represent an important target population likely to gain significant benefit from early, tailored interventions.

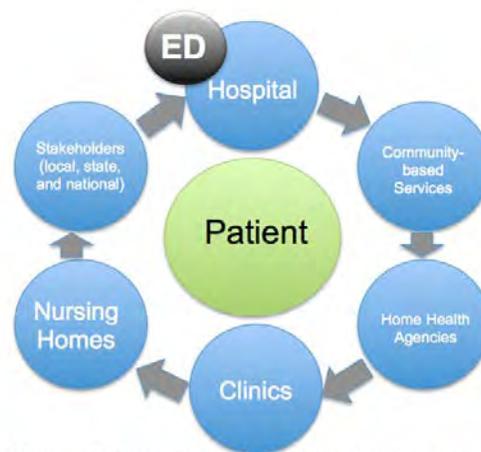


Figure 2: Interconnected Movement among healthcare sites, including the ED, for population management

“Current control rates for hypertension in the United States are clearly unacceptable.”⁴ Uncontrolled blood pressure (BP) is known to increase the risk of renal disease, stroke, heart attack, and heart failure,⁴⁻¹² yet two thirds of patients with hypertension do not meet the BP measurement recommendations set by the Joint National Commission.¹³ Recognizing this gap, **HealthyPeople 2020** set the following 10-year BP goals to improve the health of all Americans: 1) increase the proportion of adults with hypertension who are taking their prescribed BP medication to 69.5%; and 2) increase the proportion of adults with hypertension whose BP is under control from 43.7% to 61.2%.³⁹ Blood pressure control is already used as a quality indicator by the National Quality Forum and Centers for Medicare and Medicaid Services, and it is expected to be tied to incentives.¹⁴ **To achieve and maintain BP control, partnership among all treating clinicians is essential.**

Elevated BP in the ED should not simply be attributed to pain or anxiety^{40,41}; high BP during ED visits may predict chronically elevated BP,⁴²⁻⁴⁴ particularly among patients with diagnosed hypertension.^{44,45} The accuracy of ED measurement of BP may be of concern, however, due to measurement techniques,^{27,29} regression to the mean,^{28,30,31} and interventions such as administration of vasoactive medication. It is not known whether moderately or significantly elevated BP in the ED translates to poor long-term cardiovascular outcomes, as has been convincingly been shown for clinic BP.⁴ Such BP thresholds to identify uncontrolled hypertension in the ED are vital to advancing the science of hypertension management in the ED.

Primary goals of the PCMH are to provide timely, coordinated care, prevent decompensation of chronic conditions, and reduce cost, including ED visits and hospitalization.³⁴ However, triggers of acute decompensations of chronic diseases that result in ED visits or hospitalization, and the degree to which these triggers are modifiable, are poorly understood.⁴⁶ Within the Vanderbilt MyHealthTeam (MHT) PCMH, attempts have been made to determine whether ED visits were preventable or avoidable using time-intensive, manual chart review; this demonstrated the difficulty identifying triggers for ED visits using retrospective data. **To improve patient outcomes and reduce healthcare resource utilization, it is vital to identify and understand the triggers that precipitate ED visits among patients enrolled in a PCMH.** These findings will apply to a broad range of cardiovascular diseases.

To identify triggers of ED visits among MHT patients, we will fully develop a liquid chromatography mass spectrometry (LC-MS) assay as an **objective measure of medication non-adherence.** Medication non-adherence is associated with poor clinical outcomes and increased healthcare costs.⁴⁷⁻⁵⁰ Determining medication adherence is a key step in hypertension management (Figure 3); patients with elevated BP due to medication non-adherence should *not* undergo therapeutic intensification due to the risk of harm. Current measures of medication adherence rely on self-reported behaviors, pill counts, or pharmacy prescription data, which are either unreliable or not feasible in the ED.¹⁵⁻²¹

The LC-MS assay was designed to be semi-quantitative and provide easily interpretable, actionable information to researchers and clinicians; its ability to correctly classify patients with medication non-adherence, however, is not known. By 1) correctly classifying patients with uncontrolled hypertension and medication non-adherence in the ED, and 2) determining the relationship between medication non-adherence and recidivism, this proposal is a crucial first step to better integrating ED care into long-term patient care, better aligning healthcare resource utilization, and, ultimately, improving long-term BP control.

11.2 INNOVATION

This proposal combines two opportunities, **available only in combination at Vanderbilt**, to study patients with chronic cardiovascular conditions who seek emergency care:

- 1) The Vanderbilt MyHealthTeam PCMH, and
- 2) An LC-MS assay that detects 19 antihypertensive medications.

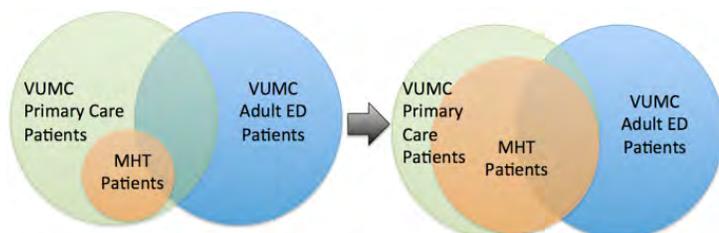
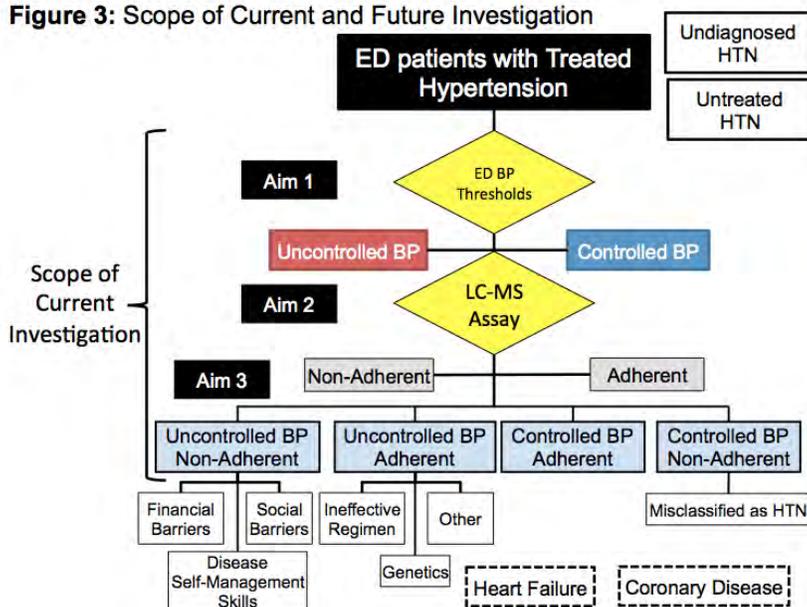


Figure 4: Increase in MHT Population over 3 years, anticipated total 70,000

1. Providers develop personalized, long-term patient care plans, including programmed intervals for follow-up and contact according to patient risk levels, defined by ED visits, hospitalization, and comorbidities.
 2. Care plans are meticulously integrated into clinical workflow using human factors engineering.
 3. Care coordinators confirm the diagnosis of treated hypertension at the time of enrollment.
 4. All MHT patients receive a calibrated home BP measurement machine at enrollment; they are taught machine use and are contacted at scheduled intervals for follow-up BP measurements.
 5. The treating physician is prompted to determine BP control status at each primary care encounter: *out-of-control*, *in-control*, and *in-control-with-exception* for patients with clinical circumstances that justify modified BP threshold goals (based on clinical judgment and using BP measurements over time).
 6. Patients seen in the ED or hospitalized are contacted in person or by phone 48 to 72 hours after discharge. This significantly reduces the risk of loss to follow-up and allows near-real-time tracking of care received at other healthcare facilities.
 7. Medication lists are manually reviewed in a standardized, systematic manner, and all prescriptions, including those for antihypertensives, are stored within the electronic medical record.
 8. Highly granular data, including home and clinic BPs, is maintained as part of quality improvement efforts.
- Patients are not eligible for enrollment in MHT if they are on hospice. *The MHT PCMH was not designed to explicitly incorporate ED care into long-term management.* By enrolling MHT patients who seek emergency care despite these resources, this project accomplishes two goals:

1. Identification of high-cost patients who seek care outside the core medical home; this will allow targeted use of MHT resources, focusing on patients most likely to benefit and potentially preventing deterioration of self-care behaviors to the point where emergency care is needed, and

Figure 3: Scope of Current and Future Investigation



The **Vanderbilt MHT PCMH** was designed to enhance chronic disease management, including blood pressure control. This program is a top institutional priority and is partially supported by an \$18.8 million CMS Innovation Award. System-wide implementation across Vanderbilt and its 3 affiliate hospitals began in 2012 and will enroll approximately 70,000 patients over the next 3 years (Figure 4). The MHT PCMH includes the following unique features:

2. Formally establishes collaboration between emergency and primary care, which in the future will lead to improved alignment of healthcare resources across a broad range of cardiovascular challenges.

Our proposal will evaluate a novel **LC-MS assay's function** as a semi-quantitative, objective measure of medication non-adherence. When dichotomized, the assay accurately identifies the 34 cardiovascular drugs, but its ability to correctly classify medication non-adherence has not been established. Used judiciously, the assay will distinguish uncontrolled hypertension due to medication non-adherence from low therapeutic intensity or true treatment resistance; ultimately it will improve BP control, in addition to other future research and clinical uses.

11.2.3 PRELIMINARY DATA

A. Vanderbilt MyHealthTeam patient-centered medical home

In the first 8 months of MHT implementation, 5,217 patients among 58 primary care providers were enrolled. Enrollment will increase exponentially as MHT is implemented across Vanderbilt and its affiliate institutions. Virtually all enrollees have health insurance (27% Blue Cross/Blue Shield, 22% Medicare HMO, 2.5% self-pay). Over the **8 months, 469 Vanderbilt University Medical Center (VUMC) Adult ED visits occurred among MHT patients**, resulting in 262 hospitalizations. Per month, VUMC ED visits ranged from 56 to 105, and VUH hospitalizations ranged from 107 to 121. This and planned enrollment of 70,000 patients over the next 3 years will provide an *adequate source population, even accounting for repeat ED visits (which are excluded) and potential reduction in ED visits due to care coordination.*

B. LC-MS cardiovascular drug assay

With serum from 294 hospitalized patients, we conducted a preliminary evaluation of the assay's ability to detect drugs using clinical samples, with variable dose, frequency, and duration (Table 4). Expected drug presence was defined by the recorded administration during medical care. Dichotomized, the assay is sensitive (≥ 0.97) for all 19 antihypertensives except captopril (0.25) and specific (≥ 0.98). **These compelling, preliminary findings** require further work to establish thresholds to classify medication non-adherence.

C. Initial Enrollment in ED Cohort Study

We have enrolled 300 ED patients over 9 months, or 25% of the enrollment goal for Aims 2B&3. Average age is 58.8 years (sd 11.3), 149 (54%) are female, 113 (41%) are on Medicare, and 104 (38%) have low medication adherence based on self-reported refill behavior. Mean systolic BP (SPB) is 150 (sd 29), diastolic BP (DBP) is 85 (sd 17), pain score is 4.8 (sd 3.6), and 157 (56%) were hospitalized. LC-MS assay performance and data cleaning are ongoing.

These preliminary findings indicate that:

- 1) An important proportion of MHT patients seek emergency care despite enrollment in a PCMH,
- 2) The LC-MS assay shows promise as a method for measuring medication non-adherence,
- 3) The MHT source population is large enough to support the proposed research aims, and
- 4) Enrollment targets are feasible, with 24% of enrollment for Aims 1&2 achieved in 9 months.

11.3 APPROACH

In the following complementary but independent specific aims, we rigorously evaluate the roles of uncontrolled BP and medication non-adherence as a potential trigger for ED visits among MHT PCMH patients, who are *all >21 years of age and have treated hypertension* (Tables 5, 6, and 7). **Three study populations** will be used: 1) a *retrospective cohort* of MHT patients seen in the VUMC Adult ED, 2) a *cross sectional study* of patients administered antihypertensive medication during their hospitalization at VUMC, and 3) a *prospective cohort* of MHT patients seen in the VUMC Adult ED. *Anticipated difficulties and proposed alternatives* are discussed in 11.4.

Table 4: Test characteristics of LC-MS assay for 19 antihypertensive medications

Drug Name	TN	TP	FN	FP	Sensitivity	Specificity	Accuracy
1 Amlodipine	241	49	1	3	0.98	0.99	0.99
2 Atenolol	264	30	0	0	1.00	1.00	1.00
3 Spironolactone	232	60	0	2	1.00	0.99	0.99
4 Captopril	290	1	3	0	0.25	1.00	0.99
5 Carvedilol	225	69	0	0	1.00	1.00	1.00
6 Clonidine	266	25	0	3	1.00	0.99	0.99
7 Diltiazem	261	30	0	3	1.00	0.99	0.99
8 Enalapril	279	15	0	0	1.00	1.00	1.00
9 HCTZ	247	46	0	1	1.00	1.00	1.00
9 Hydralazine	259	34	1	0	0.97	1.00	1.00
10 Lisinopril	203	88	0	3	1.00	0.99	0.99
11 Losartan	262	32	0	0	1.00	1.00	1.00
12 Metoprolol	182	111	1	0	0.99	1.00	1.00
13 Nifedipine	270	24	0	0	1.00	1.00	1.00
14 Propranolol	287	7	0	0	1.00	1.00	1.00
15 Ramipril	286	8	0	0	1.00	1.00	1.00
16 Triamterene	287	7	0	0	1.00	1.00	1.00
17 Telmisartan	292	2	0	0	1.00	1.00	1.00
18 Valsartan	255	35	0	4	1.00	0.98	0.99
19 Verapamil	275	17	0	2	1.00	0.99	0.99

Abbreviations: TN, true negative; TP, true positive; FN, false negative (drug not detected, drug reported in patient records); FP, false positive (drug detected, drug not reported in patient records); HCTZ, hydrochlorothiazide

11.3.1 Specific Aim 1: a) Identify ED values of BP that correctly classify hypertension control status, as defined by clinic BP, and b) Determine the relationship between uncontrolled hypertension detected in the ED and 6-month ED and hospital recidivism.

Hypothesis 1: BP values in the ED correctly classify BP control and predict 6-month ED and hospital recidivism.

11.3.1 Aim 1A&B

Aim 1 will be accomplished using a retrospective cohort of MHT patients treated in the VUMC Adult ED during the initial 18 months of the MHT program (Table 5). Data will be extracted from the MHT clinical data warehouse (CDW), which was designed with Dr. McNaughton's input to ensure accurate and reliable retrieval of variables pertinent to this analysis.

Table 5: Summary of Study Designs for Specific Aims

	Aim 1A&B	Aim 2A	Aim 2B and Aim 3
Study Design	Retrospective cohort	Cross sectional study	Prospective cohort
MHT patients	Yes	Not required	Yes
Enrollment	CDW data extraction	Completed (n=294)	300/1,255 enrolled
Inclusion	VUMC Adult ED visit, >2 ED BPs*, >2 clinic BPs <1 yr. before ED visit	Admitted to VUMC, Given >1 drug on LC-MS assay (except negative controls)	VUMC Adult ED visit, On >1 drug on LC-MS assay, Consent w/in 12hrs
Exclusion	ED visit for acute illness that alters BP**	Unable to provide informed consent, Unable to provide ~5ml of blood	Prior enrollment, Unable to provide ~5ml of blood, ED visit for acute illness that alters BP**

* Excluding BP measured after vasoactive medications; BP is measured every 2 hrs. in the ED

** Pregnancy related, alcohol withdrawal, acute stroke, hypotension due to blood loss or shock, level I trauma, sepsis, shock, and toxic ingestion

11.3.1 Aim 1 Study Procedures and Analyses

Extracted data will include ED and clinic vital signs; patient characteristics (age, gender, race, ethnicity, insurance status, highest level of education, health literacy as measured by clinical staff, comorbid conditions, and prescriptions); ED evaluation, treatment, and diagnoses; health communication details (barriers to care, documented by MHT care coordinators); determination of BP controls status by the MHT physician at the last clinic visit; laboratory values (creatinine, hematocrit); and the dates of clinic visits, ED visits, hospitalizations, death, and loss-to-MHT-follow-up

(defined as inability of MHT care coordinators to achieve contact over 6 months despite 8 attempts, by phone, email, or mail). This dataset will be stored in the secure, web-based application REDCap.⁵¹ We will obtain waiver of consent given the minimal risk and

because it is not feasible to request consent from every MHT patient seen in the VUMC Adult ED over an 18-month time period. **Data Quality:** Dr. McNaughton's mentors Drs. Kripalani and Roumie have extensive experience extracting and using data from the CDW and specifically the variables in this retrospective cohort. Data quality and accuracy will be verified prior to use.

Aim 1A Analysis: Mean ED systolic BP (SBP) is used as the primary classification variable (Table 6) because on a population level it has been shown to be a stronger predictor of cardiovascular outcomes than diastolic BP (DBP).⁵²⁻⁵⁶ However, given the prevalence of isolated diastolic hypertension in younger patients,⁴ we will identify separate thresholds for ED SBP and DBP to correctly classify uncontrolled hypertension. For mean ED

Table 6: Thresholds of ED BP to classify uncontrolled BP and the LC-MS assay to classify medication non-adherence

	Aim 1A	Aim 2A	Aim 2B
Classification variable	Mean ED SBP, continuous* Secondary: Mean ED DBP*	LC-MS assay results (continuous)	LC-MS (3-levels, from Aim 2A): non-adherent, equivocal, adherent
Reference variable	BP control – mean of 2 clinic BPs, 3-levels**: in-control; moderately-out-of-control; severely-out-of-control	Gold standard: Drug administration by healthcare provider	Alloy standard: Cumulative medication gap, from MHT prescription records
Alternative reference variable	BP control – physician label 3-levels: out-of-control, in-control, in-control-with-exception	None	Other adherence measures: ARMS, PAML, patient report, Adjudicated medication list
Analysis	ROC curves for each level of uncontrolled BP	ROC curve for each of 19 drugs	Correlations, kappa, linear, and logistic regression, as appropriate

* Excluding BP measured after vasoactive medications

**in-control: <140/90; moderately-out-of-control: 140-159/86-99; severely-out-of-control: >160/100, or if history of diabetes or renal disease⁴: <130/80; 130-149/86-89; >150/90, respectively

SBP, we will use 2 ROC curves, one for each of the 2 levels of uncontrolled BP (moderately and severely uncontrolled).

A similar approach will be applied to mean ED DBP. These analyses will be repeated using the alternative reference variables of BP control defined by an MHT physician, with an ROC curve for each level of uncontrolled BP (uncontrolled, controlled with exception).

Aim 1B Analysis: To determine the impact of BP control status *identified in the ED* on recidivism, we will use **6-month recidivism to the ED and hospital** as the primary outcome (Table 7); an important proportion of readmissions occur between 30 and 90 days among patients with severe hypertension.⁵⁷ Given incomplete

Table 7: Hazards of ED and hospital recidivism, analyses for Aim 1B and Aim 3

	Aim 1B	Aim 3
Exposure	BP control status <i>identified in the ED</i> , based on the results of Aim 1A (dichotomous)	Medication non-adherence, by LC-MS assay (based on Aim 2B)
Outcome	Time-to-recidivism within 6 months of being discharge from the index ED visit (ED and hospital in separate models)	Same
Adjusting variables	Age, gender, race, insurance status, education level, health literacy level, disease severity	Same
Censoring events	Death, hospice, loss to follow-up, completion of 6-month follow-up	Same
Analysis	Kaplan Meier curve Adjusted Cox proportional hazards model*	Same
Sample size	1,000 patients Conservatively anticipate 50% non-adherence (alpha 0.05, power 0.90)	1,255 patients (300 enrolled) Conservatively anticipate 50% non-adherence (alpha 0.05, power 0.90)
Detectable hazard of recidivism	0.81 or 1.24	0.83 or 1.20

* Verifying the proportional hazard assumption

conducted for hospital recidivism.

Aim 1: Sample size justification: There were 129.8 million ED visits in 2011,⁵⁸ and a 1-5% reduction in recidivism has been shown to be clinically important.^{59,60} The proportion of MHT patients who are non-adherent is not known. Based on preliminary MHT data and accounting for anticipated reductions in ED visits and hospitalizations among MHT patients, we conservatively anticipate that a minimum of 1,000 MHT patients will seek care in the VUMC Adult ED visits over 18 months. With a two-sided test, an alpha level of 0.05, power of 0.9, and conservatively estimating 50% medication non-adherence,^{48,61-63} the minimum detectable hazard ratio is 0.81 or 1.24.⁶⁴

11.3.2 Specific Aim 2: a) Determine optimal thresholds of an LC-MS assay that detects 19 antihypertensive medications to correctly classify patients with medication non-adherence, using medication administration in the hospital as the gold standard, and b) Evaluate the LC-MS assay's validity by comparing its performance against other measures of medication adherence.

11.3.2 Overview of Study Design

Two populations will be used in Aim 2: **a)** 294 hospitalized patients already enrolled and for whom the gold standard of medication adherence, drug administration by healthcare providers, is available; preliminary validation of the LC-MS assay by analytic chemistry criteria was performed in this population (Table 4); and **b)** ED patients with treated hypertension, comparing the LC-MS assay against other measures of medication adherence and using the cumulative medication gap (CMG) as the reference, alloy standard. Because determination of LC-MS assay thresholds and performance does not test a hypothesis, sample size calculations for Aim 2 were not performed.

11.3.2A Study Procedures and Analysis

A cross sectional study of 294 adult patients hospitalized at VUMC will be used to determine optimal thresholds for each of the 19 drugs on the LC-MS assay to correctly classify medication non-adherence (Table 6), compared the **gold standard**, defined as documentation of drug administration in the nursing administration record, pre-admission medication list, outpatient pharmacy records, daily notes written by physicians, transfer notes from other institutions, or procedure notes. Patients provided written consent to provide ~5ml of blood and de-identified drug administration records; enrollment ended August 2012. This de-identified dataset includes the dose, route, and frequency of drug administration, quantitative analytic

chemistry assay results (continuous), and expected drug presence for each drug for all 294 enrolled subjects. For each of the 19 antihypertensive medications, we will use an ROC curve to identify the **optimal threshold** of the LC-MS assay to define medication non-adherence.

11.3.2B Study Procedures and Analysis: Prospective cohort of MHT ED patients

Aim 2B will be completed using a **cross sectional study within in a prospective cohort study**, comparing multiple measures of adherence to evaluate the validity of the LC-MS assay as a measure of medication non-adherence. VUMC ED patients will be electronically screened to identify MHT patients as they register. Eligible MHT patients will be approached by the PI or a clinical trial associate (CTA) for written consent; CTAs staff the ED 16 hours a day, 7 days a week, ensuring enrollment during peak hours and minimizing risk of introducing bias by time-of-day. Enrolled patients will undergo **standardized, repeated measures of BP using the BpTRU®**, which measures BP using the oscillatory method and calculates an average of 6 BP measurements taken at 1-minute intervals; this average has been shown to be equivalent to ambulatory BP measurement.⁶⁵ The following will be collected in the ED or extracted from the MHT CDW (**Appendix A: Data collection sheet**):

1. Patients will provide demographic information and last date/time of medication ingestion; they will complete measures of self-reported medication adherence,¹⁹ health literacy,⁶⁶⁻⁶⁸ numeracy,⁶⁸⁻⁷⁰ quality of life,⁷¹ perceived expectancy,⁷²⁻⁷⁴ and an assessment of their emergency and primary care providers.⁷⁵
2. Standardized interview to **identify precipitant(s) of the ED visit** (referred by MHT provider, referred by other provider, self-referral; development of new symptoms, exacerbation of chronic symptoms; description of symptoms and their duration) and generate a **reference medication list** and calculate **therapeutic intensity** (current medication dose/maximum medication dose). The **pre-admission medication list** (PAML), which is systematically updated at each clinical encounter for every MHT patient, will be recorded
3. MHT prescribing data will be used to calculate the **CMG**.²⁰ All prescriptions for MHT patients are stored in the MHT CDW.
4. **Details of the clinical encounter** including laboratory and imaging, consultations, treatment, and ED and hospital diagnoses and dispositions.

Approximately **1 week after hospital discharge**, patients will be contacted by email, phone, or mail according to their preference to obtain an out-of-hospital BP measurement. Per established protocol, MHT care coordinators contact patients within 48-72 hours of ED or hospital discharge; **recidivism to the ED or hospital** within 6 months of the index ED visit will be obtained via MHT care coordinator report and verified by electronic health record review. With informed consent and authorization, we will also request information regarding ED visits or hospitalizations at other facilities. Patients enrolled in this study will continue to undergo electronic surveillance via the electronic medical record as long as they remain in the Vanderbilt University medical system.

Aim 2B Analysis

Convergent criterion validity of the LS-MS assay (Table 6) will be evaluated against the following alternative measures of medication adherence with correlation coefficients, kappa, ROC curves, and linear and logistic regression, as appropriate.⁷⁶ *The cumulative medication gap will be the primary reference (alloy) standard.*

1. Cumulative medication gap,²⁰ calculated from prescriptions extracted from the MHT CDW
2. Adherence to Refills and Medications Scale (ARMS)¹⁹
3. Adjudicated medication list at the time of the index ED visit
4. PAML recorded by clinical staff at the time of arrival to the ED
5. Patient report of last date and time of medication ingestion

Sample size justification for Aim 3 drives the enrollment goal for this study (**see 11.3.3 and Table 7**).

11.3.3 Specific Aim 3: Determine the hazards of 6-month ED and hospital recidivism associated with non-adherence to antihypertensive therapy.

Hypothesis 2: *Medication non-adherence, as measured by the LC-MS assay, predicts 6-month ED and hospital recidivism, despite enrollment in the MHT PCMH.*

11.3.3 Aim 3 Overview of Study Design and Analysis

Aim 3 will be accomplished using the prospective cohort assembled for Aim 2B (**11.3.2B and Table 5**). Predictive validity of the LC-MS assay will be evaluated by determining the 6-month⁵⁷ hazard of ED or hospital recidivism due to medication non-adherence. ED and hospital recidivism will be analyzed in separate models.³⁶ We will compare the influence of uncontrolled (vs. controlled) BP *identified in the ED* on recidivism using a Kaplan-Meier curve. We will use a Cox proportional hazards model, with the above adjusting covariates, to

determine the relationship between uncontrolled BP in the ED with recidivism after verifying the proportional hazard assumption. The same approach will be conducted for recidivism to the hospital.

Aim 3 Sample size justification: Based on preliminary MTH data and accounting for anticipated reductions in ED visits and hospitalizations among MHT patients, we conservatively estimate 50% medication non-adherence.^{48,61-63} In a two-sided test, to detect a minimum hazard ratio of 0.83 or 1.20^{59,60} with 0.90 power at an alpha level of 0.05,⁶⁴ we will **recruit 955 patients during the 4-year award** to accrue a total of 1,255 patients.

11.4 Anticipated Difficulties and Alternative Plans

A. Identification of uncontrolled BP in the ED: If thresholds of ED BP that correctly classify uncontrolled hypertension result in a sample size of patients with uncontrolled hypertension that has insufficient power to accomplish Aim 1B, we will perform a sensitivity analysis using BP control status defined by clinic BP (Table 6) as the exposure for Aim 1B.

B. LC-MS assay: Preliminary work suggests the LC-MS assay may out-perform the CMG, ARMS, PAML, and patient report in correctly classifying medication non-adherence, thus we expect imperfect correlation and agreement among these measures. These analyses are vital to more effectively interpret work done using other measures of adherence and inform future studies.

C. Enrollment: Over 9 months, we successfully enrolled 300 patients, or 24% of the overall enrollment goal for Aims 2B&3. To achieve the enrollment goal over 4 years, we will recruit ~238 patients/year. MHT is undergoing system-wide expansion, with an overall expected population base of 70,000 patients; accounting for patients with repeated ED visits (an exclusion criteria) and reduction in ED visits due to care coordination, the MHT population is large enough to support sample size requirements. If despite this we are unable to meet enrollment goals, we will expand inclusion criteria to include non-MHT patients whose primary care provider are within the Vanderbilt Medical System.

D. Loss to Follow-up: In the MHT PCMH, ED visits and hospitalizations trigger care coordinators to contact patients via phone or in person within 48-72 hours. At each encounter, care coordinators systematically inquire regarding care obtained outside the Vanderbilt system, and they continue to follow patients at regular interval until they no longer need acute care according to risk levels. As part of consent for this study, we will obtain permission to review healthcare provided at other institutions, and we will obtain permission to discuss health care provision with caregivers and family members to minimize the risk of missing ED or hospital recidivism.

E. Single site: As the project progresses, we will develop plans for multi-site evaluation to confirm our findings.

11.5 Future directions

The proposed research will serve as preliminary data for Dr. McNaughton's future investigations, including the following potential R01 proposals:

1. Develop an intervention leveraging the LC-MS assay and the ED visit as a "teachable moment,"⁷⁷ testing the impact on the a) patient-provider relationship, b) clinical inertia/therapeutic intensity, and c) resource alignment (i.e., appropriate use of the clinic and ED).
2. Deploy this intervention in a multi-site RCT, across VUMC and its 3 affiliate hospitals.
3. Refine methods to reliably identify patients *prior to deterioration* of BP control using the LC-MS assay; develop and test an intervention to *prevent* BP control deterioration.
4. Use the LC-MS assay to identify patients with refractory, resistant hypertension; evaluate the impact on total time spent with controlled BP and resource use.

Completion of these proposed aims is a crucial first step towards maximizing the value of ED visits, partnering emergency and primary care, and developing interventions to better align healthcare resource utilization while improving BP control.