Overall Aims
By virtue of its scope and complexity, the clinical care of vascular disease, defined as disorders of the veins, arteries, lymphatics and microcirculation, has frequently been fragmented, often segregated among a number of medical subspecialties. Until recently, the only graduate medical education dedicated to vascular disease recognized by the American Board of Medical Specialists was the residency in Vascular Surgery. However, a distinct discipline of Vascular Medicine devoted to the comprehensive evaluation and the longitudinal care of vascular disease is required because:

- Vascular disease is the most frequent cause of morbidity and mortality in our society.
- Discoveries in the pathobiology of vascular disease pertaining to new patient management have proceeded at an unprecedented rate.
- The Vascular Medicine specialist with comprehensive clinical training, combined with formal training in clinical research will best translate these discoveries to the most effective, evidence-based therapy for vascular disease.

Collectively, these issues support the view that the specialty of Vascular Medicine should be considered a strategic imperative for the future care of vascular disease. This proposal meets this health care necessity by coupling clinical vascular care and didactic research training at Wake Forest University Health Sciences (WFUHS) to create a unique competence unmet by other specialties. This proposed three-year mentored training program devotes the first year to comprehensive clinical training in vascular disease. The second year is devoted to didactic training in clinical research, culminating in a Masters of Science degree in Health Sciences Research. In the third year, the Candidate will complete their thesis project, which will serve as a basis for a “mock” K23 proposal. This third year will allow time for presentation and publication of results related to the Candidates’ research.

The clinical and research curricula will be constructed within the framework of a mentoring team. Each Candidate will select a mentoring team that will consist of a clinical mentor (a clinical scientist with ongoing clinical research in vascular disease) and a research mentor (a faculty member of the Division of Public Health Sciences active in the Masters Program in Health Sciences Research). During the first year of the training program, Candidates will participate in a comprehensive, multi-disciplinary clinical core curriculum in vascular disease that will include inpatient and outpatient evaluation and management, exposure to open surgical and endovascular management, non-invasive vascular testing and vascular imaging. This clinical training experience will be enriched by formal rotations in Neurology (stroke risk reduction and stroke management), Dermatology (wound management), Hematology (coagulation and thrombosis), and Cardiology (atherosclerotic risk assessment and risk reduction). In the second year of training, the one-year research core curriculum will provide the Candidate with didactic training to independently design and conduct clinical research. This experience will culminate in a Masters in Science degree in Health Sciences Research. Mentoring teams consisting of one member from both the clinical core and the research core will ensure the successful synthesis of clinical vascular training, mentored research and institutional resources related to that research. Candidate will select members of the mentoring team based on shared research interests; this will maximize the Candidate’s future professional career options.

Internal Advisory Committee
The Internal Advisory Committee (IAC) will advise the Program Director on issues pertaining to the development, implementation, and overall success of this career development program. In combination with the Program Director, the IAC will develop selection criteria for highly qualified Candidates. Twice yearly, the IAC will review the core research and core clinical curricula to consider new initiatives or alterations. In combination with the Program Director and mentoring team, the IAC will monitor the evaluation of the
Candidate’s progress in both the didactic research and clinical curricula. The Internal Advisory Committee consists of the following members:

**Gregory L. Burke, M.D., M.S.**
Professor and Chair of the Division of Public Health Sciences, will Chair the Internal Advisory Committee. His extensive research portfolio seeks better strategies for clinical and population-based disease prevention, with special focus on cardiac and vascular disease. Dr. Burke is currently co-PI of several NIH funded observational studies and clinical trials. These include the Soy Estrogen Alternative Study (SEA), the Cardiovascular Health Study (CHS), the Multiethnic Study of Atherosclerosis (MESA), and the Ginkgo Enhancing Memory Study (GEMS). At the national level, he is Chair of the Council on Epidemiology and Prevention for the American Heart Association, and a member of the NHLBI Board of extramural advisors. Dr. Burke’s experience with development and oversight of research development is extensive. He led the research and development core for the WFU Claude D. Pepper Older Americans Independence Center. Dr. Burke is an esteemed faculty mentor. His letter of commitment as Chair of the IAC is found in Appendix C.

**David M. Herrington, M.D., M.H.S.**
Professor of Internal Medicine (Cardiology) is the Program Director for a T32 Cardiovascular Disease Research Training Program that serves as training for physician scientists to translate advances in molecular biology to clinical and population research concerning cardiac and vascular disease. Dr. Herrington has served as a participating faculty member on the Pathobiology of Vascular Disease Training Grant and is on the internal advisory committee of the laboratory animal and comparative medicine training grant, which is the longest continuously funded NIH training grant in the nation. His educational activities include co-director of the annual Internal Medicine Board Review Course and he serves as a regular lecturer in the WFUSM Molecular Medicine and Molecular and Cellular Pathology graduate programs. Dr. Herrington is active at the national level within the AHA, and currently serves on its Leadership Committee, chairs the Fall program committee for the AHA’s Council on Epidemiology and Prevention, and serves on the national Committees for Scientific Sessions and Continuing Education. Directly relevant to this proposal, Dr. Herrington has reviewed numerous NIH-sponsored training programs, including both K23 and K24 awards. Most recently, he served as a reviewer for NIH solicitation for K08 awards in genetic epidemiology. He has been actively involved in clinical trials in cardiac epidemiology with focus on heart disease in women, the cardiovascular effects of estrogen and the pharmacogenetics of estrogen action, and holds several R01 awards from the NIH to fund investigations in these areas. His letter of commitment as a member of the IAC is found in Appendix C.

**Charles E. McCall, M.D.**
Professor of Medicine, Microbiology, and Immunology, Deputy Associate Dean for Research, and Director of the General Clinical Research Center. Dr. McCall’s career in translational patient oriented research has been consistently NIH funded for 35 years, with a focus of investigation in the molecular mechanisms of innate immunity as they apply to human sepsis. After five years of postgraduate training at Harvard Medical School and two years at the Centers for Disease Control, Dr. McCall joined the faculty at WFUSM in 1968. In 1972, he received a Fellowship to the Royal Society of Medicine where he performed disease related translational research at the Royal Postgraduate Medical School in London. Dr. McCall was the first member of the faculty of WFUSM elected to the American Society of Clinical Investigation and the first to be elected to the Association of American Physicians. In 1997, Dr. McCall received the first Established Investigator Award in Clinical Research. He is the recipient of the Distinguished Faculty Alumnus Award and Distinguished Service Award of WFUSM. He is the Founder and Co-Director of the Section of Molecular Medicine. He is Director of the Research Development Core of the NIH funded Pepper Center, and has mentored over 50 MD, postdoctoral PhD, PhD students, and Master’s degree students. His letter of commitment as a member of the IAC is found in Appendix C.

Each of these members of the Internal Advisory Committee has an extensive track record of NIH-funded research in cardiac and vascular disease and epidemiologic investigation. Each member demonstrates a substantial and ongoing commitment to teaching, mentoring, and administration.
Each Candidate will select the mentoring team in the first three months of year 01 based on his or her special interest(s) to maximize future professional/career options. The mentoring team will provide guidance and instruction concerning ongoing clinical research and the development of new research projects related to the Candidate’s interest. The team will advise and assist in the development and successful completion of a thesis project in the Masters of Science in Health Sciences Research program. The mentoring team will provide guidance and instruction concerning the development of a “mock” K23 application. The mentors will provide access to or the means to collect the clinical research data required for the Candidate’s research projects. The mentors will assist in the formulation of the research question and the development of research plans. Moreover, the mentors will be responsible for the support and training of career development skills necessary to ensure successful transition of the Candidate to a fully independent, funded investigator. These responsibilities will include counseling regarding the ethical conduct of research, exposure to opportunities for networking with other investigators, development in public presentation and speaking, scientific writing and publication, and grant preparation. The mentors will act as Candidate advocates, both locally and nationally.

Collectively, the potential mentors reflect a multi-disciplinary group of senior clinical scientists with successful track records in both research and mentoring. A brief synopsis of each mentor appears below.

**Clinical Mentors**

**Anthony Atala, M.D.** is the Director of the Wake Forest Institute for Regenerative Medicine and Professor and Chair of the Department of Urology at the Wake Forest University School of Medicine. He is a surgeon, researcher and expert on regenerative medicine and tissue engineering. His current work focuses on bioengineering of human tissues and organs, including vascular grafts. Dr. Atala currently serves as a member of the Board of Directors and Vice-President of the Society of Regenerative Medicine, a member of the Board of Governors of the Tissue Engineering Society, a member of the Scientific Advisory Board of the Engineering Tissue Growth International Conference, and as Chairman of the Board of Directors of the National Bladder Foundation. He has received numerous awards and honors, including the US Congress funded Christopher Columbus Foundation Award, bestowed on a living American who is currently working on a discovery that will significantly affect society and was named by *Scientific American* as a Medical Treatments Leader of the Year, for his contributions to the fields of cell, tissue and organ regeneration. Dr. Atala has led or served several national professional and government committees, including the National Institutes of Health working group on Cells and Developmental Biology, and the National Institutes of Health Bioengineering Consortium. He heads a team of 60 physicians and researchers.

**Alan Fleischer, M.D.** and his colleagues at WFUSM have published extensively in Health Services Research in Dermatology. His research group has investigated quality of care, quantity of care, and demographic determinants of care using extant data sources. Additionally, he has developed tools including the Self-Administered Psoriasis Area Severity Index, which has been validated and translated into at least four languages. Members of his Department have also developed and validated measures of atopic dermatitis and dermatomyositis. His group has pioneered novel methods of assessing compliance among dermatology patients, and currently has a series of ongoing projects assessing determinants of compliance in atopic dermatitis. Dr. Fleischer is currently principal investigator in numerous funded clinical trials involving therapeutic agents. His research group currently includes five full-time research fellows that spend one or more years in the Department and numerous medical students that spend one or more months of dedicated investigation time in the Department of Dermatology. Dr. Fleischer will provide oversight for the Dermatology Clinical Rotation.

**Barry Freedman, M.D.** Dr. Freedman’s basic research program evaluates genetic susceptibility to type 2 diabetes mellitus, hypertension, diabetic and non-diabetic nephropathy, and vascular disease. Through his extensive collaborations with the Center for Human Genomics, the Department of Biochemistry and the Division of Public Health Sciences, Dr. Freedman has recruited and phenotyped the largest existing group of African American families with multiple members having type 2 diabetes mellitus and diabetic and non-diabetic end-stage renal disease (ESRD). Dr. Freedman also leads recruitment for the Diabetes Heart Study which now contains more than 1,200 individuals in 500 families who are concordant for type 2 diabetes mellitus and...
who lack serious kidney failure. Participating families are evaluated for the presence of cardiovascular disease phenotypes including carotid intima-medial thickness using B-mode ultrasound and coronary artery calcified plaque using helical computed tomography. The overall objectives of his research program are to identify genomic regions that harbor susceptibility genes for type 2 diabetes mellitus and its vascular and kidney complications. He is also evaluating the role of circulating endothelial progenitor cells in the pathogenesis of diabetic vascular disease through his interactions with the Wake Forest Institute of Regenerative Medicine. Dr. Freedman chairs the NIDDK-sponsored Family Investigation in Nephropathy and Diabetes (FIND) study and he oversees the Wake Forest University Health Sciences-owned and operated dialysis program. This dialysis program contains more than 1,300 prevalent ESRD patients in 13 treatment facilities. In his role as Chief of the Section on Nephrology and the John H. Felts III, M.D. Professor of Internal Medicine and Nephrology, Dr. Freedman has mentored six graduate students and numerous residents/fellows.

Randolph Geary, M.D. As a member of the Vascular Teaching Unit, Dr. Geary's basic research examines events within the arterial wall after injury and arterial reconstruction. Through his collaboration with the Department of Comparative Medicine, Dr. Geary’s basic science projects characterize arterial remodeling in an atherosclerotic non-human primate model of angioplasty injury. His research characterizes gene expression responsible for smooth muscle cell proliferation and extracellular matrix production. Related studies examine vectors as means of introducing recombinant genetic material into the arterial wall. The overall objective of this basic investigation is to define the mechanisms of restenosis and gene therapy approaches for its prevention. In addition, through his appointment with the Wake Forest Institute of Regenerative Medicine Dr. Geary’s research encompasses bioengineering of vascular grafts. A current study protocol examines the GRAFTcath Vascular Access System as an alternative to the traditional vascular access for hemodialysis. Dr. Geary was the institution’s principal investigator for the recently completed PREVENT III trial that examined an E2F decoy to prevent stenosis within infrainguinal vein grafts placed for critical limb ischemia. In basic and clinical research, Dr. Geary has mentored 7 post-doctoral fellows and 14 Vascular Surgery Fellows.

Andrew Koman, M.D. Dr. Koman's clinical and basic research examines the microvascular physiology associated with chronic occlusive and vasospastic disease. Specific areas of interest include evaluation of vascular adrenergic supersensitivity following digital sympathectomy and peripheral microvascular control mechanisms. To extend this research to clinical applications, Dr. Koman has built a Clinical Microangiography Laboratory to quantitate the extremity microcirculation in patients. Laser Doppler fluximetry, laser Doppler perfusion imaging, and nailfold capillaroscopy are used to assess the impact of clinical interventions on the pathophysiology of extremity microvascular dysfunction. He has determined the physiologic outcomes of revascularization, nerve repair and palliative treatments on the microcirculation of the hands and feet. Ongoing basic research studies examine microvascular control mechanisms in the acral microcirculation of rabbits and the genetic expression of microvascular control agents in the adventitia from patients with vasospastic disease and secondary Raynaud’s. The overall objectives of basic and clinical investigations are to define the mechanisms associated with vasospastic responses in microcirculatory beds, including molecular events. Dr. Koman currently has an appointment with the Wake Forest Institute of Regenerative Medicine in which he is evaluating bioengineering of vascular grafts. Dr. Koman has received the Kappa Delta research award from the Orthopaedic Research and Education Foundation and the Huene research award from the Pediatric Orthopaedic Society of North America.

In education, Dr. Koman established the 7-year Physician Scientist Orthopaedic Residency program in the Department of Orthopaedic Surgery at WFUSM. This innovative program is the first of its kind in the United States and serves as a benchmark for post-graduate training for a career in Academic Orthopaedic Surgery. He also established the Hand Fellowship for post-residency training in Hand and Upper Extremity Surgery at WFUSM. Dr. Koman has mentored 2 Doctoral degree students, 5 Physician Scientists, and 13 Hand and Microvascular fellows.

Pavel J. Levy, M.D. heads the Vascular Medicine component of the Vascular Teaching Unit at WFUHS, which was established in collaboration with the Section on Vascular and Endovascular Surgery. Over the past 10 years, Dr. Levy's clinical research effort has focused on premature lower extremity atherosclerosis (PLEA) in
John Owen, M.D. directs the Special Hematology Laboratory that focuses on problems as presented both by individual patients and by patient populations. The underlying force behind his approach is to study a few individuals in great detail to better understand a problem. This information is then applied to the broader issues of day-to-day management of patients with hematologic disease. Recently, Dr. Owen has directed efforts to the development of a facile test for the circulating level of enzyme ADAMTS13. An assay for ADAMTS13 will help to recognize patients at risk for thrombotic thrombocytopenic purpura in whom an early escalation in therapy would lead to a better outcome. A second function of the laboratory is to act as a crucible for the development of critical thinking skills for fellows in training. By doing so, the laboratory experience develops the next generation of practitioners in the field. The Special Hematology Laboratory is the focus of a wide range of studies by his mentees. Recent work has included apolipoprotein-E genotypes in chemotherapy-induced cognitive failure, warfarin resistance and mutations in the VKORC1 gene, the genetic basis of alpha-2-plasmin inhibitor deficiency, mutation in the erythropoietin gene, and the development of a highly sensitive assay for ADAMTS13 activity in plasma noted above. Dr. Owen will guide the Hematology Clinical Rotation.

Michael Rocco, M.D. Dr. Rocco’s clinical research has focused on end-stage renal disease (ESRD) patients and epidemiologic research in ESRD patients. He is the principal investigator for the NIH sponsored Frequent Hemodialysis Network Nocturnal Hemodialysis study and is the clinical center principal investigator for the NIH sponsored Dialysis Access Consortium trial and the Acute Renal Failure Trial Network (ATN Study). He had served as the clinical center principal investigator for the recently completed NIH sponsored HEMO Study and was the Nutrition chair for that study. He has been a workgroup member of the Centers for Medicare and Medicaid (CMS) Clinical Performance Measures project and serves on the Executive Committee and is chair of the peritoneal subgroup. He is also the vice-chair for the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) and serves as the vice-chair for the NKF K/DOQI hypertension guidelines. Dr. Rocco is currently coordinating the updates for the Hemodialysis, Peritoneal Dialysis and Vascular Access K/DOQI guidelines. He has published extensively in the fields of ESRD clinical trials and epidemiology.

Charles Tegeler, M.D. Dr. Charles Tegeler’s research deals with the use of ultrasound in the prevention and treatment of stroke, cerebrovascular disorders, and concussion, as well as the use of such methods for assessment of cerebrovascular physiology, performance, and function in a variety of other clinical settings. Many of these projects utilize Dynamic Vascular Analysis (DVA), a new method for analyzing transcranial Doppler ultrasound data. Specific activities with DVA include the use of this method in the settings of sports-related concussion, vasospasm following subarachnoid hemorrhage, obstructive sleep apnea, carotid artery stenting, sickle cell disease, shunt-responsive hydrocephalus, hyperbaric oxygen therapy, treatment with a variety of compounds, and implementation of a DVA Core Reading Center. His group also studies peripheral arterial disease in stroke patients, and the use of an electronic stethoscope and neural network to better identify patients with carotid stenosis. He participates in a variety of clinical stroke prevention and treatment trials, and Phase II of the ongoing North Carolina Stroke Registry. Dr. Tegeler holds the McKinney-Avant Chair in Neurosonology, serves as Medical Director for the Neuroultrasound Laboratory, and is Head of the
Section on Stroke, Cerebrovascular Disease, and Neurosonology. He also is Director of the Neurovascular Ultrasound Courses in the Center for Medical Ultrasound, the Fellowship in Stoke, Cerebrovascular Disease, and Neurosonology, and the Neurosonology Mini-Fellowship Program. He has served as Fellowship Director/Mentor for 15 Fellows in Stroke, Cerebrovascular Disease, and Neurosonology. Dr. Tegeler will provide oversight to the Neurology Clinical Rotation.

David C. Sane, M.D. oversees a laboratory devoted to studies of thrombosis and vascular biology. He has studied the function and structure of extracellular matrix proteins, especially vitronectin. Dr. Sane has described the effect of transglutaminases on vitronectin and other substrates, and the role that transglutaminases may have in plaque stability and progression. He has recently reported that nicotine upregulates P2Y12 (ADP receptor) expression, providing a potential mechanism for smoking-induced hyperaggregability and thienopyridine resistance. His laboratory was the first to demonstrate that anti-platelet factor 4/heparin antibodies carry prognostic significance in acute coronary syndromes, even in the absence of thrombocytopenia. Dr. Sane also demonstrated that angiotatin is an inhibitor of C-met, blocking the angiogenic and mitogenic effects of hepatocyte growth factor. He has further characterized the vascular properties of hepatocyte growth factor, hepatocyte growth factor activator and inhibitors of this system. Dr. Sane has directly mentored three PhD students (2 in Physiology/Pharmacology, 1 in Cancer Biology) and has participated in the training of 18 additional graduate students, as well as directing research studies for more than 15 medical students, residents, and cardiology fellows. Dr. Sane is an attending cardiologist at North Carolina Baptist Hospital, where he treats patients with acute coronary syndromes. He will assist Dr. Wells in the Cardiology clinical rotation.

Gretchen Wells, M.D., Ph.D. Dr. Gretchen Wells' research relates cardiac parameters determined by echocardiography to adverse cardiac events and patient survival. She is a co-investigator for the STICH Trial, which examines the effects of surgical intervention to improve congestive heart failure. Her other active research interest is peripartum cardiomyopathy, a rare but potentially lethal complication of pregnancy. Through her collaboration with the Department of Obstetrics and Gynecology, she is coordinating a database of women with the disorder in North Carolina. A recently submitted American Heart Association grant will apply her extensive experience in medical genetics to identify genetic variants in women with peripartum cardiomyopathy. She is involved in several industry-sponsored heart failure drug trials. In clinical research, she has mentored 3 cardiology fellows and 1 internal medicine resident. Dr. Wells will coordinate the Cardiology Clinical Rotation.

Research Mentors

Ralph D’Agostino, Jr., Ph.D. is currently a Professor in the Department of Biostatistical Sciences and the Director of the Biostatistics Core of the Comprehensive Cancer Center. His research areas include developing methods for handling missing data in epidemiological studies, developing models for longitudinal data that incorporate measurement error, and developing techniques for reducing bias in observational studies using propensity score methods. He has been the Principal Investigator of several RO1 grants and subcontracts, including projects to develop statistical methodology as well as coordinate large scale epidemiologic studies.

In addition to statistical research, Dr. D’Agostino has also been actively involved in medical research in the areas of cancer, cardiac and vascular disease, and diabetes. He currently has over 100 journal articles and book chapters in these areas.

In addition to his applied and methodological work, Dr. D’Agostino has served as an Associate Editor for the American Journal of Epidemiology, the Journal of Cardiac Failure, and Current Controlled Trials in Cardiovascular Medicine. He has been the Program Chair for the Statistics in Epidemiology Section (1998) of the American Statistical Association (ASA), the Health Policy Statistics Section (2000) of the ASA, and the Secretary/Treasurer for the Biometrics Section of the ASA (2003-2005). He has served as a member of the NIH Skeletal Biology Development and Disease Study Section (SBDD) from 2002-2005. He has also served on the thesis committee for nine graduate students in the Clinical Epidemiology and Health Services Research program.
Ronny Bell, Ph.D. is an Associate Professor in the Division of Public Health Sciences, Department on Epidemiology, WFUSM, with training in nutrition and epidemiology. Dr. Bell’s primary interests are chronic disease prevalence and risk factors, with particular emphasis on ethnic minority populations. Dr. Bell was Principal Investigator of the HEARTQUEST project, one of 6 Enhanced Dissemination and Utilization Centers (EDUCs) funded by the NHLBI. The project targeted African Americans, Native Americans and whites in Robeson and Columbus Counties, North Carolina, to address the increased cardiac and vascular disease burden observed in these communities. Dr. Bell also serves as the Coordinating Center director for the SEARCH for Diabetes in Youth Study, a multi-center study funded by the Centers for Disease Control and Prevention with support from the NIDDK. The SEARCH study is designed to estimate the population prevalence and incidence of diabetes in youth by type, age, gender and ethnicity, and to develop practical approaches to diabetes classification. Dr. Bell received a minority investigator R03 from the NIDDK to estimate the prevalence of self-reported chronic health behaviors and chronic conditions among Lumbee Indians, and a minority investigator supplement to the Strong Heart Study to examine dietary factors related to diabetes and insulin resistance in the Strong Heart cohort. He was the recipient of the WFUSM New Investigator in Clinical Sciences Award in 2002.

Alain Bertoni, M.D., M.P.H., Assistant Professor in Public Health Sciences (Epidemiology and Prevention) with a joint appointment in Internal Medicine, is a general internist and epidemiologist with research interests in diabetes and its complications, cardiac and vascular disease, quality improvement in chronic disease, and ethnic disparities in health and healthcare. He is currently a co-investigator in the MESA cohort study and its ancillary study MESA-Family, a study of the genetics of atherosclerosis in minority populations; the multicenter clinical trial Action for Health in Diabetes (Look AHEAD), testing weight loss in adults with diabetes to prevent cardiovascular morbidity; the ACCORD trial; the Personal Digital Assistants for Guideline Adherence (PDA GLAD), a novel practice-based trial to improve utilization of the ATP cholesterol guidelines; and NC ACE, a quality improvement project for heart failure patients in NC managed care plans. Additionally, Dr. Bertoni has received an intramural grant to continue investigations of morbidity, mortality, and the impact of primary care on outcomes among Medicare beneficiaries with diabetes. He precepts Internal Medicine residents in clinic, and teaches in the Population Epidemiology and Evidence Based Medicine course for medical students.

Robert Byington, Ph.D. conducts research focused on cardiac and vascular diseases, with special emphasis on risk factors and prevention. Dr. Byington has taught Principles of Clinical Trials I/II at WFUSM. Currently, Dr. Byington is Principal Investigator of the Coordinating Center for the NHLBI’s Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. ACCORD is designed to test the effects of glycemia, blood pressure and lipid control on major cardiac and vascular disease events in patients with Type 2 Diabetes.

Mark A. Espeland, Ph.D., is chairman of the Department of Biostatistical Sciences. His primary research interest has been the analysis of data from clinical trials and epidemiologic cohort studies. This has led him to examine research questions in such diverse fields as women's health, aging, diabetes, cardiac and vascular disease, sickle cell disease, cognition, and obesity. His methodological interests are in developing models from incomplete data and error-prone data. As applications of this methodology, he has explored relationships involving ultrasonographic measurements, diet intake measures, and measures of maturation and growth. Dr. Espeland has been involved in leadership roles of coordinating and administrative centers for many major multi-center studies including the Action for Health in Diabetes (Look AHEAD), the Trial of Nonpharmacologic Interventions in the Elderly (TONE), the Women's Health Initiative Memory Study (WHIMS), the Type 1 Diabetes Genetics Consortium, the Postmenopausal Estrogen/Progestins Intervention (PEPI), the Asymptomatic Carotid Artery Progression Study (ACAPS), and the Cooperative Study of Sickle Cell Disease (CSSCD). Dr. Espeland is a frequent consultant to the National Institutes of Health and has served on over two dozen Data and Safety Monitoring Boards / Advisory Panels for major studies. He currently serves on the Board of Directors for the Society for Clinical Trials Research.

David C. Goff, Jr., M.D., Ph.D., Professor of Public Health Sciences (Epidemiology) and Internal Medicine and Co-Director of the Center for Healthcare Research and Quality at WFUSM. He is Chair of the Center for...
Disease Control and Prevention's Working Group for the National Action Plan to Prevent Heart Disease and Stroke, a member of the North Carolina Heart Disease and Stroke Prevention Task Force and Past Chair of the Tri-State Stroke Network (Georgia, North Carolina and South Carolina). He directs the Ten-Day Seminar on the Epidemiology and Prevention of Cardiovascular Disease sponsored by the Center for Disease Control and Prevention and the American Heart Association. He is active in the American Heart Association as Vice Chair of the Steering Committee for the Quality of Care and Outcomes Research Interdisciplinary Working Group and member of the Leadership Committee for the Council on Epidemiology and Prevention, the Get With the Guidelines Science Advisory Subcommittee, and the Committee on Statistics. His research interests include the epidemiology and prevention of heart disease and stroke with a focus on issues related to diabetes and dyslipidemia.

Beth A. Reboussin, Ph.D., Associate Professor of Public Health Sciences (Biostatistical Sciences) received her degree in Biostatistics from Johns Hopkins University School of Hygiene and Public Health. Her research interests are focused on the analysis of data from psychiatric epidemiologic studies. Dr. Reboussin has been actively involved in longitudinal research in the areas of adolescent suicide, dementia, depression, substance abuse, and youth violence prevention. Dr. Reboussin is an NIMH trained Psychiatric Epidemiology fellow. She holds a Mentored Research Award (KO7 DA016279) funded by the NIDA entitled “Drug Involvement in Context: Quantitative Perspectives”. The project is designed to provide training in the field of drug use and enable her to develop innovative biostatistical methods for understanding the processes underlying the transitions across stages of drug involvement. At the national level, Dr. Reboussin serves as a statistical editor for *Bipolar Disorders* and is a member of the Behavioral Genetics and Epidemiology Study Section for the National Institutes of Health.

David M. Reboussin, Ph.D., Associate Professor in the Division of Public Health Sciences (Biostatistical Sciences) He is the current Co-PI and Chair of the Coordinating Center Biostatistics and Computing Committee for Look AHEAD (NIDDK), and Co-leader for the Data and Systems group of the Type 1 Diabetes Genetics Consortium (NIDDK). Dr. Reboussin was a co-Investigator for ACCORD during protocol development and initiation of the Vanguard phase. He was Co-Investigator and Director of the Data Core for ERA (NHLBI) from 1995 to 2003. He was Co-PI and Senior Statistician for CONTROL, an industry-sponsored multi-center study. He was Principal Investigator for the Iron Overload and Hereditary Hemochromatosis Study (HEIRS) Coordinating Center from 2000-2005. Dr. Reboussin is currently a member of five DSMBs, including four NHLBI-sponsored trials, two of which are cooperative agreements. He serves as a permanent member of the NHLBI Clinical Trials Review Committee and serves on the Editorial Board of the Journal of ECT. He is a member of the WFUHS IRB.

Beverly Mellen Snively, Ph.D. Dr. Snively’s research activity is focused on analysis of data from genetic and epidemiologic studies. Her methodologic interests are in the development of statistical models for inference using profile likelihood functions with data from multiple sources. Dr. Snively was Co-Principal Investigator of the HEIRS Coordinating Center. She is Co-Investigator on several other projects, including the Search for Diabetes in Youth Study (SEARCH; Ronny Bell, Director, Coordinating Center), Type I Diabetes Genetics Consortium (T1DGC; Stephen Rich, PI, Coordinating Center), ¡La Familia! Reducing Farmworker Pesticide Exposure Study (Thomas Arcury, PI), and Rural Elders’ Diabetes Self-Management Study (Sara Quandt, PI).

Lynne E. Wagenknecht, Dr.P.H. is a chronic disease epidemiologist with an extensive research portfolio in cardiovascular disease and diabetes. Dr. Wagenknecht has been the PI of the ARIC Forsyth County field center for five years, working in collaboration with Dr. Gerardo Heiss at UNC-CH. She also directs the local field center for FHS-SCAN, a family study of coronary and aortic calcification. She is the PI of two NHLBI-funded observational study coordinating centers: the Insulin Resistance Atherosclerosis Study (IRAS), an epidemiologic study of diabetes, insulin resistance and carotid wall thickness; and the IRAS Family Study, a study of the genetics of insulin resistance and visceral adiposity. Dr. Wagenknecht is also Deputy Director of the Look AHEAD Coordinating Center funded by the NIDDK. She is a co-investigator on the Diabetes Heart Study being conducted at WFU, which is examining the genetics of coronary calcification in siblings with type 2 DM. Dr. Wagenknecht has published extensively in the area of the epidemiology of type 2 DM and
atherosclerosis, including work from her RO1 exploring novel mechanisms explaining the increased risk of cardiac and vascular disease in type 2 DM including glycated and oxidizedipoproteins. Dr. Wagenknecht has just completed a two-year term on the Scientific Sessions Committee of the American Diabetes Association and is now serving as Chair of the Council on Epidemiology and Biostatistics.

Overall Organization and Mentors of the Proposed Career Development Program

**Program Director**
Kimberley J. Hansen, MD

**Internal Advisory Committee**
- Greg Burke, MD (PHS)
- Charles McCall, MD (GCRC)
- David Herrington, MD (IM/Card)

**External Advisory Committee**
Career Development Program Directors

**Clinical Mentors**
- Anthony Atala, MD (Regenerative Med)
- Alan Fleischer, MD (Dermatology)
- Barry Freedman, MD (IM/Neph)
- L. Andrew Koman, MD (OrthoSurg)
- Randolph Geary, MD (Vascular Surg)
- Pavel Levy, MD (Vascular Med)
- John Owen, MD (Hematology)
- Michael Rocco, MD (IM/Neph)
- David C. Sane, M.D. (IM/Card)
- Charles Tegler, MD (Neurology)
- Gretchen Wells, MD, PhD (IM/Card)

**Research Mentors**
- Ronny Bell, PhD (EPI)
- Alain Bertoni, PhD (EPI)
- Ralph D’Agostino, Jr. PhD (Biostatistics)
- Mark Espeland, PhD (Biostatistics)
- David C. Goff, Jr, MD, PhD (EPI)
- Beth Reboisson, PhD (Biostatistics)
- David Reboisson, PhD (Biostatistics)
- Beverly Snively, PhD (Women’s Health)
- Lynne Wagenknecht, DrPH (EPI)

PHS=Public Health Science; GCRC=General Clinical Research Center; IM=Internal Medicine; Card=Cardiology; Neph=Nephrology; OrthoSurg=Orthopaedic Surgery; EPI=Epidemiology

**Mentors’ Clinical Research**
These program mentors were selected in part because of their extensive ongoing funded research in vascular disease. The preexisting clinical research and collaborations within the mentoring group will help to ensure effective communication as they work as teams in support of this training program. Moreover, these collaborations provide an extensive resource of ongoing funded research that may serve as a basis for secondary analysis and ancillary projects. Successful synthesis of these research resources will be achieved by the Candidate’s selection of a mentoring team with ongoing research in the area(s) of the Candidate’s interest. The list below is a brief description of the NIH-funded research projects and responsible mentors available for the Candidate’s future clinical research.

**Hypertension-Associated End-Stage Renal Disease** (H-ESRD-Freedman, Rocco). This study includes a comprehensive genome screen for more than 370 African-American sib-pairs with H-ESRD members and includes the detailed evaluation of selected genes demonstrating association and linkage to H-ESRD. Chromosome regions showing evidence of linkage to H-ESRD in the genome screens are evaluated by high density linkage mapping, disequilibrium mapping, and positional cloning of H-ESRD susceptibility genes. Allelic variations that are associated with H-ESRD will be identified to allow functional analysis of these mutations. The identification of hypertension-associated renal failure genes will form the genetic basis for detection of high risk individuals and allow for the development of treatment strategies to prevent H-ESRD.
The Family Investigation in Nephropathy and Diabetes Study (FIND-Freedman, Rocco). The FIND Study is a large multicenter study begun in September of 1999 conducted at eight participating investigative centers, with a single genetic analysis and data coordinating center. Fourteen thousand different families have been enrolled to provide blood and urine samples. Genetic material (DNA) is evaluated to identify genes that predispose to diabetic kidney failure and diabetic eye disease. During the next two years, WFUSM will evaluate 250 diabetic subjects for the presence of diabetic eye disease. These results will describe genes that cause diabetic complication. Findings may suggest treatments that have the potential to retard or prevent the development of vascular complications in diabetes mellitus.

Embolic Protection During Renal Artery Stenting (Edwards, Hansen, Levy, Rocco). This prospective, randomized clinical trial will examine the use of distal embolic protection during the performance of renal artery angioplasty and stenting of atherosclerotic renovascular disease. The specific aims of the project are to identify the safety and efficacy of distal embolic protection to improve renal function and blood pressure response after percutaneous intervention. Evidence that distal embolic protection improves outcome after renal artery angioplasty and stenting has the potential to alter contemporary medical practice and favorably impact dialysis-free survival for patients undergoing percutaneous intervention.

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST-Hansen, Geary, Levy, Tegeler). This large, prospective, randomized, multicenter trial compares carotid endarterectomy with carotid artery angioplasty and stenting to prevent stroke and adverse cardiovascular events in patients with atherosclerotic cerebrovascular disease. As one of only two NIH-funded studies examining the role of percutaneous intervention for cerebral vascular disease, the study will establish the safety and efficacy of carotid stenting as compared to open operative management.

Carotid Occlusion Surgery Study (COSS-Tegeler, Levy). This prospective clinical trial tests the hypothesis that the best medical therapy combined with surgical anastomosis of the superficial temporal artery to the middle cerebral artery can reduce ipsilateral ischemic stroke at two years in patients with symptomatic internal carotid artery occlusion. Patients included in the study have experienced a recent ICA occlusion and demonstrate ipsilateral increased oxygen extraction fraction measured by PET. This multicenter trial is powered to detect a 40% reduction in subsequent ipsilateral ischemic stroke at two years.

Peripheral Arterial Disease and Biomarkers for Cerebral Vascular Disease in Patients with Ischemic Stroke and Transient Ischemic Attack (Tegeler, Levy). The goals of this project are to study the prevalence of peripheral arterial disease among patients with stroke and transient ischemic attack. The relationship of excessive vascular disease, as defined by non-invasive measures, is related to atherosclerotic risk factors. The relationship of biologic and genetic markers within the study cohort and vascular disease are examined.

Hyperglycemia and Vascular Health (Sane, Geary): This study examines the effect of elevated glucose on basic vascular cell function including mitogenesis, angiogenesis and apoptosis. We are specifically examining the ways that elevated glucose affects components of the Hepatocyte Growth Factor system including HGF, its receptor C-met, the activator HGFA and the inhibitor HAI-1. We have found a marked downregulation of HAI-1 with hyperglycemia and are studying the role of the ubiquitin-proteasome system in HAI-1 degradation. Enhanced HGF activity with hyperglycemia could promote intimal hyperplasia, angiogenesis and tumorigenesis.

Vascular Disease and Platelet Function (Sane, Geary) examines the role of platelets as important inhibitors of thrombosis and contributors to inflammation. Platelet activity states in various CV risk conditions including smoking and hypertension are studied. Nicotine upregulates P2Y12, an important platelet receptor and ADP. The study examines upregulation of P2Y12 on baseline platelet function in smokers and on their response to thienopyridines. The effect of the reported transglutaminase-mediated AT1 dimerization in hypertensive patients on platelet and vascular function are also studied. A variety of measures of platelet function and molecular techniques are utilized.
The Atherosclerosis Risk in Communities (ARIC—Burke, Wagenknecht). This is cohort study of atherosclerosis, cardiac and vascular disease in four US communities: Forsyth County, North Carolina; the city of Jackson, Mississippi; eight northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. African-American residents were recruited exclusively in Jackson and over sampled in the Forsyth County cohort, whereas participants from the other two communities were predominantly white. The ARIC study, with 10-year follow-up and 725 adverse coronary artery events, has demonstrated strong associations between total cholesterol, LDL-C, and triglycerides, with increase adverse coronary artery disease risk and HDL-C with decreased risk.

Cardiovascular Health Study (CHS—Burke, Hansen, Herrington). CHS is a population-based longitudinal study of 5201 adults age 65 years of age and older. Participants were recruited from Forsyth County, North Carolina; Washington County, Maryland; Sacramento, California; and Pittsburgh, Pennsylvania. The CHS is an observational cohort study of cardiac and vascular disease risk factors, morbidity, and mortality. Detailed baseline examination and examination of subclinical cardiac and vascular disease permits the exploration of vascular disease defined by non-invasive measures and its association with adverse clinical events.

Insulin Resistance Atherosclerosis Study (IRAS—D’Agostino, Wagenknecht). IRAS is the first epidemiologic study designed to assess relationships between insulin resistance, insulinemia, glycemia, and other components of insulin resistance syndrome with prevalent cardiovascular disease in a large multiethnic cohort. Over 1600 men and women were recruited from four geographic areas to represent a range of glucose tolerance and ethnicity. Insulin resistance was assessed directly using frequently sampled intravenous glucose tolerance test, animal medial carotid artery wall thickness, an indicator of atherosclerosis, was measured using B-mode ultrasonography. Prevalent cardiac disease was assessed by questionnaire and resting electrocardiography. Forthcoming cross-sectional analyses will help to define the association between insulin resistance and cardiac disease apart from the concomitant hyperinsulinemia and related atherosclerotic risk factors.

Multiethnic Study of Atherosclerosis (MESA—Burke, Bertoni, D’Agostino, Goff, Herrington). MESA is an observational study of subclinical cardiac and vascular disease as progression to clinical disease in a diverse sample of men and women ranging in age from 35-84 years. The specific aims of the study are: 1) To determine individual characteristics related to the progression of subclinical to clinical cardiac and vascular disease; 2) To identify factors related to newer measures of subclinical disease having examined the relationship of new to establish measures; and 3) To develop population-based methods suitable for application to future screening and intervention studies to identify asymptomatic patients at highest risk of adverse clinical events.

The Heart and Estrogen/Progestin Replacement Study (HERS—Byington, Herrington). HERS was a randomized double-blind placebo-controlled trial designed to examine the efficacy and safety of estrogen plus progestin therapy for prevention of recurrent coronary heart disease events in women. HERS tested whether estrogen plus progestin would prevent a second adverse coronary event. The study involved 2763 postmenopausal women (average age 67) who had had previous heart disease. Women received either estrogen plus progestin or placebo for approximately four years. Findings reported in 1998 demonstrated that those on hormone therapy did not have fewer fatal or nonfatal coronary events. This study demonstrated that women’s risk for heart attack increased during the first year of hormone use and declined thereafter. HERS also demonstrated that hormone therapy caused an increase in blood clots in the legs and lungs. More recently, the “HERS follow up study” which provided three additional years of study found no decrease in heart disease from the use of estrogen plus progestin. Dr. Herrington received RO1 funding to conduct genetic analyses of this cohort, which is ongoing.

Estrogen Replacement and Atherosclerosis Study (ERA—Herrington, Reboussin). The ERA trial evaluated the effect of hormonal therapy on the progression of atherosclerosis assessed by quantitative coronary angiography in 309 women with coronary artery disease. No differences were observed in the change or minimal lumen diameter of major coronary segments among the three treatment groups. Subsequently, the
American Heart Association recommendation of hormonal therapy for primary and secondary coronary prevention was withdrawn.

**Action to Control Cardiovascular Risk and Diabetes** (ACCORD-Byington, Goff). The ACCORD trial tests three complementary medical treatment strategies for type 2 diabetes to attempt to reduce the high rate of major cardiac and vascular morbidity and mortality in this disease. The design is a randomized multicenter double two x two factorial design in 10,000 patients with type 2 diabetes mellitus. The trial is designed to test the effects of intensive glycemic control, treatment to increase HDL cholesterol and lower triglycerides, and intensive blood pressure control on major cardiac and vascular events.

**The Women’s Health Initiative** (WHI-Burke, Herrington). The WHI focuses on defining the risks and benefits of strategies to reduce incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. In an observational study at 40 clinical centers in the U.S., women aged 50 to 79 years were recruited between 1993 and 1998. Follow-up analysis demonstrated that women taking estrogen plus progestin demonstrated increased overall risk of breast cancer, heart attacks, stroke, and blood clots while fewer fractures and colon cancers were noted. Based on these findings, new guidelines for the use of estrogen plus progestin were published. Further analyses of the cohort continues.

**The NHLBI Family Heart Study** (FHS-Wagenknecht). The NHLBI Family Heart Study is a multicenter population-based study of genetic and nongenetic determinants of coronary heart disease, atherosclerosis, and cardiac and vascular disease risk factors. Two thousand randomly selected participants and 2000 with family histories of coronary heart disease were identified among 14,592 middle-aged participants in epidemiologic studies. Medical histories from these individuals, their parents and siblings, were used to calculate family risk scores. Additional biochemical and genetics studies are being done on selected participants. Contribution of genes, shared and individual environments and behaviors to variation and risk factors, preclinical atherosclerosis and coronary heart disease will be estimated.

**The Diabetes Heart Study** (DHS-Freedman, Herrington, Wagenknecht). The DHS uses a family study design and quantitative measure of coronary artery disease phenotypes to locate and identify genes contributing to subclinical atherosclerosis in sibling pairs concordant for type 2 diabetes.

**Project Action for Health in Diabetes** (Look AHEAD-Espeland, Wagenknecht): Look AHEAD is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. Look AHEAD focuses on the disease most affected by obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease.

**Search for Diabetes in Youth** (SEARCH-Bell, Snively): SEARCH is a 5-year multi-center study funded by the Center for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases. The study goals are to (1) identify the number of children and youth under age 20 who have diabetes, (2) study how type 1 diabetes and type 2 diabetes differ, including how they differ by age and race/ethnicity, (3) learn more about the complications of diabetes in children and youth, (4) investigate the different types of care and medical treatment that these children and youth receive, and (5) learn more about how diabetes affects the everyday lives of children and youth who have diabetes.

**Clinical Core Curriculum**
In the first year of training, each Candidate will participate in a comprehensive, multidisciplinary clinical core curriculum in Vascular Disease. The Vascular Teaching Unit will provide the backbone of the clinical core curriculum. This Teaching Unit exists within a distinct clinical Section within the Division of Surgical Sciences. It combines inpatient and outpatient Vascular Surgery and Vascular Medicine services. The Vascular Teaching staff consists of five, full-time board certified Vascular Surgery teaching staff, a fellowship trained Vascular Medicine specialist, two Vascular Surgery fellows, one General Surgery chief resident, one PGY III surgery
resident, three PGY I surgery residents, and 1-3 medical students. Additional clinical support is provided by two vascular nurse practitioners.

In the 2005 academic year the Vascular Teaching Unit provided over 10,000 outpatient vascular evaluations. Around the clock, inpatient vascular consultation provided over 1000 inpatient vascular consultations during this same period.

All outpatient vascular consultation and longitudinal outpatient follow up is performed within the Vascular Clinic in the Clinical Sciences Building 5th floor. All open surgical, angiographic and endovascular procedures pertaining to vascular disease for patients on the Vascular Teaching Unit are performed by the Vascular Teaching staff who provide all preoperative, postoperative, and follow-up care. Within this framework of evaluation and care, particular attention is given to assessment and modification of atherosclerotic risk, cardiac risk, stroke risk, and evaluation of thrombophilia. In the 2005 academic year the Teaching Unit performed over 1350 open vascular procedures, over 450 angiographic and over 500 endovascular procedures. These outpatient/inpatient resources support the following components of the clinical core curriculum:

**Outpatient Vascular Medicine Consultation**
Outpatient vascular consultation and longitudinal follow-up evaluation are provided each day Monday through Friday in the Vascular Clinic. On each day both a Vascular Surgery teaching faculty and a Vascular Medicine specialist jointly conduct outpatient vascular clinics. These clinics are supported by a vascular nurse practitioner. In the 2005 academic year this activity accounted for over 10,000 outpatient visits. In addition, the Dr. Hansen oversees an outpatient vascular clinic for indigent patients conducted in combination with the Vascular Surgery Fellows. The Vascular Medicine Applicant would dedicate one day per week for the first six months of clinical training to the outpatient Vascular Clinic.

**In-Patient Vascular Medicine Consultation**
Inpatient vascular consultation is provided around the clock, seven days a week. Over 1000 inpatient vascular consults were provided during the 2005 academic year. In each case consults are seen in conjunction with both PGY III residents and the responsible member of the Vascular Teaching Unit. The Vascular Medicine Candidate would be responsible for in-patient hospital consultation three months out of the first six months of the clinical core training.

**Peripheral Angiography and Catheter Based Endovascular Intervention**
The Vascular Teaching Unit performed over 450 cases of peripheral angiography (including CO₂ and gadolinium angiography) and over 500 catheter-based endovascular interventions in the 2005 academic year. A state-of-the-art endovascular suite dedicated to these procedures includes an observation area with digital telemedicine capability. The Candidate will devote one month of core clinical training to these procedures with emphasis on evidence-based selection of endovascular intervention versus open surgical repair versus medical management. Anticipated results from endovascular intervention, potential complications and methods of longitudinal follow-up and care will be emphasized.

**Vascular Surgery**
The Candidate will spend a two-month clinical rotation on the Vascular Surgery inpatient service. The Candidate will participate in preoperative assessment, morning rounds, inpatient surgical care and postoperative management. Preoperative outpatient evaluation, longitudinal follow-up, and appropriate methods of post-operative surveillance will be the focus of this clinical rotation.

**Non-Invasive Vascular Testing**
The Candidate will receive extensive experience with noninvasive vascular diagnostics within the Clinical Vascular Laboratory. This facility is a state-of-the-art noninvasive vascular laboratory directed by Dr. Hansen. The laboratory exists within the Vascular Teaching Unit and is accredited in all noninvasive vascular testing by the Intersocietal Commission of the Accreditation of Vascular Laboratories (ICAVAL). The Clinical Vascular Laboratory staff includes six full-time Registered Vascular Technologists, a secretary and data coordinator. In
the 2005 academic year over 12,000 noninvasive vascular studies were performed. The laboratory enjoys a national/international reputation in the development and application of deep abdominal Doppler evaluation of branch aortic disease. As a consequence, the laboratory has conducted over 50 tutorials for both physicians and technicians during the past ten years.

The Candidate will rotate into the Clinical Vascular Laboratory full-time for a 12-week period. The Candidate will receive in-depth exposure to the study of vascular hemodynamics and pathophysiology as they relate to noninvasive vascular testing, and will be trained in the performance, interpretation, and quality assurance/quality control of all non-invasive testing. Quality improvement is ensured by comparing all non-invasive imaging in the Clinical Vascular Laboratory with results from other in-hospital imaging modalities. The volume and variety of noninvasive vascular testing ensures that the Candidate will exceed the minimum laboratory case number for each procedure in adherence to ICAVL guidelines. This experience, combined with the other components of the clinical core curriculum, will prepare the Candidate to establish and direct an ICAVL accredited non-invasive vascular laboratory. At the completion of this training experience, the Candidate will sit for the ARDMS Physician Interpretation Examination.

The Clinical Vascular Laboratory training module will include the following areas:

- Upper and lower extremity arterial evaluation at rest with exercise stress and with position stress utilizing pulse volume recordings and Doppler waveform spectral analysis.
- Duplex evaluation for:
  - Aortic and peripheral artery aneurysms.
  - Congenital, acquired, and surgical arteriovenous fistulae.
  - Preoperative vein mapping.
  - Preoperative arterial mapping.
  - Venous thrombosis and deep venous valvular insufficiency.
  - Occlusive arterial disease.
  - Surveillance of endovascular and open surgical arterial and venous intervention.
  - Pseudoaneurysm evaluation with emphasis on compression and thrombin injection therapies.
  - Evaluation of renal artery stenosis and occlusion, mesenteric artery stenosis and occlusion, and aortoiliac aneurysm.
  - Carotid artery and vertebral artery disease.
  - Evaluation of neurocompressive thoracic outlet syndromes with both physiologic testing and direct duplex imaging.

The Clinical Vascular Laboratory training module will receive support from the Center for Medical Ultrasound under the direction of Fredrick W. Kremkau, Ph.D. This Center offers didactic course work three times a year as eight hour per day, four-day didactic courses. The Candidate will attend the peripheral vascular and neurovascular courses within the Center for Medical Ultrasound. Faculty from the Vascular Teaching Unit and sonographers from the Clinical Vascular Lab lecture in these courses.

Conferences
Throughout the three-year training period, the Candidate will attend each of the scheduled conferences conducted by the Vascular Teaching Unit. Conferences are held Wednesday morning at 7:00 and at 8:00 am, Tuesday afternoon at 1:00 pm, and Thursday afternoon at 1:00 pm in a dedicated conference room on the inpatient Vascular Unit floor with specific oversight from a member of the Vascular Teaching Unit. A brief description of each conference follows.
• **Vascular Indication Conference.** This one-hour, weekly conference is conducted by Dr. Hansen on Wednesday at 8:00 am. Vascular intervention planned for the upcoming week and unplanned emergent/urgent intervention from the prior week are presented. All relevant imaging (i.e. angiograms, MRA/CTA, noninvasive vascular studies, etc.) relevant to patient management are reviewed. Evidence-based treatment options for open surgical repair versus endovascular intervention versus medical management are reviewed. Discussion culminates in a management recommendation. This conference emphasizes the evidence-based choice of therapies, the methods of management, the interpretation of vascular imaging, interpretation of noninvasive vascular imaging and represents a synthesis of decision-making in each area.

• **Vascular Disease Conference.** This one-hour, bi-weekly conference is organized by Dr. M. Edwards. Material chosen for didactic presentation reflects uncommon, infrequently encountered topics in vascular disease.

• **Vascular Morbidity/Mortality Conference.** This one-hour monthly conference is conducted by Dr. R. Geary. All inpatient morbidities extending hospital stay or re-intervention are reviewed. All deaths are reviewed. When autopsy materials are available, the responsible pathologist is present to correlate clinical and pathologic findings. Ultimately the findings from this conference are used to create quality improvements and quality assurance of clinical care.

• **Vascular Journal Club Conference.** This one-hour monthly conference is conducted by Dr. M. Edwards. Literature pertaining to basic science findings relevant to vascular disease and clinical trials are reviewed. Study methodology, statistical analysis and translation to clinical care are emphasized.

• **Vascular Forum.** This forum is conducted twice a year by Dr. Hansen. Academic leaders in Vascular Surgery spend two days at the WFUHS where they participate in a Grand Rounds presentation and attend a resident case conference. Afterwards, there is an evening conference where vascular specialists from a hundred and fifty mile radius are in attendance. The conference is sponsored by WL Gore and Associates and provides case management commentary with case presentation by the guest speaker, outside vascular specialists, and residents in training.

• **Basic Science Research Meeting.** Dr. Geary's Vascular Biology Research Laboratory holds a weekly two-hour basic science conference each Tuesday afternoon at 1:00 pm to review ongoing research protocols and related vascular biology. The pre and post doctoral fellows in the laboratory present current literature and unpublished results pertaining to their specific projects and review experimental design and rationale of ongoing research. Data are reviewed and alternate explanations for results are explored. Invited outside speakers are regularly included in the discussions and presentations.

• **Clinical Science Research Meeting.** This two-hour conference is conducted by Dr. Hansen each Thursday afternoon at 1:00 pm. In attendance are Vascular Research Fellows, residents, a clinical research coordinator, a data coordinator, and two statisticians. The progress of current clinical research projects are discussed with emphasis on clinical research design, data analysis and interpretation.

The core clinical experience provided by the Vascular Teaching Unit and required related conferences will provide an extensive, in-depth experience regarding the evaluation, management, and longitudinal follow-up of vascular disease. To complement this exceptional experience, each Candidate will receive supplemental clinical training in 3-week rotations through the departments of Neurology, Dermatology, Hematology and Cardiology. Each of these supplemental rotations will receive oversight from a member of the mentoring group. A brief description of these rotations follows.

**Supplemental Clinical Training**

**Neurology Clinical Rotation**

The Neurology clinical rotation will be coordinated by Dr. C. Tegeler, Director of the Section on Stroke and Cerebral Vascular Disease. The overall goals of the rotation coincide with the major missions of the Center to: 1) Identify appropriate diagnosis and management of transient ischemic attack and cerebral vascular accident as well as other cerebral vascular disorders, 2) Understand the basic mechanisms of disease and intervention that affect the cerebral vascular circulation. The rotation will be organized as a mini-fellowship in Stroke and Cerebral Vascular Disease and Neuroimaging. The mini-fellowship in Stroke will emphasize stroke prevention by risk reduction, recognition of impending stroke, and acute management and rehabilitation. The Candidate
will participate on the inpatient Stroke service, attending the daily Multidisciplinary Stroke Team meeting and all clinical conferences regarding stroke and rehabilitation. Evaluation of new stroke for tPA and other interventions will be emphasized. The mini-fellowship in Neuroimaging will emphasize intracranial neurosonology, magnetic resonance imaging and angiography, cranial computerized tomography and angiography, and positron emission tomography.

**Dermatology Clinical Rotation**
The Dermatology clinical rotation will receive oversight from Dr. Alan Fleischer, Professor and Chair of the Department of Dermatology. The Candidate will participate daily in the Dermatology clinic, gaining experience in surgical, rheumatologic and skin diseases of aging; identification, differential diagnosis and treatment of wounds and other lesions of the skin; and will develop differential diagnosis and treatment plans for chronic venous stasis disease, chronic arterial insufficiency and ischemic ulceration, bacterial and viral infections, benign and malignant skin neoplasia, and drug hypersensitivity. This rotation will also include an in-depth exposure to dermatologic therapeutics, including percutaneous drug delivery, antimicrobials, immunosuppressants, and antipsoriatrics. The Candidate will participate in weekly didactic conferences that include a journal club, Clinical Pathology Conference, Grand Rounds, visual diagnosis sessions, and core curriculum lectures.

**Hematology Clinical Rotation**
A rotation in Hematology will be guided by Dr. John Owen, Professor of Internal Medicine Hematology/Oncology. This rotation will emphasize disorders of thrombosis and hemostasis. Issues of thrombogenesis and control of procoagulant proteins will be reviewed in depth. The structure and functional relationship of abnormal proteins and assays reflecting in vivo activation of coagulation will be a focus of this rotation. Inpatient and outpatient clinical assessment will consider disorders of hemostasis, with particular emphasis on thrombophilia and hypercoagulable states.

**Cardiology Clinical Rotation**
A rotation in Preventive Cardiology will receive oversight from Dr. Gretchen Wells, Assistant Professor of Internal Medicine/Cardiology. This rotation will examine cardiovascular risk factors and their modification. Identification and treatment strategies for dyslipidemia, hypertension, metabolic syndrome, and tobacco cessation will be emphasized. The Candidate will participate one day each week in the Cardiovascular Rehabilitation Program and the Smoking Cessation Clinic during this rotation. Non-invasive cardiac assessment will emphasize stress and resting, transthoracic and transesophageal echocardiography, magnetic resonance cardiography and cardiac scintigraphy.

**Didactic Clinical Research Core Curriculum - Year 2**
In the second year of training, the Candidate will complete didactic training in a Masters of Science Degree in Health Sciences Research. Faculty members in the Division of Public Health Sciences provide expertise and conduct vascular research in areas of health promotion and disease prevention, epidemiology, clinical trials methodology, biostatics, health services research, health policy and community interventions.

The philosophy behind this didactic curriculum is that the goals of clinical vascular research are the prevention, detection, and treatment of the vascular disease and consequently the delivery, financing, and quality of vascular health care related services. Epidemiology and Health Services research are distinct, but complementary fields of study. In epidemiology, the Candidate will examine the distribution and morbidity in populations as well as their determinants. In Health Services Research, Candidates will consider both the health care consumer and the service delivery system. Vascular research in these areas will address the biomedical, psychological and social factors that may contribute to the health outcome or may result from a specific intervention. Research into the service delivery system will consider an analysis of impact of the organization, financing, and delivery of vascular care services on cost access and quality of care. The combination of Epidemiology and Health Services Research will provide the Candidate with the tools for successful independent clinical research. Moreover, the program will provide a comprehensive overview of health care states ranging from etiology through the provision of health care services.
The major objectives of this didactic clinical research curriculum are:

- To provide Candidates with didactic training in conceptual/theoretical frameworks, research methodology, and statistical methods essential to the design and conduct of clinical research in vascular disease.
- To provide training in measurement of outcomes, health related quality of life, medical treatment/intervention effectiveness and health economics.
- To provide training in grant and manuscript preparation leading to a “mock” K23 grant and culminating in a thesis project.
- To present and publish the results of the Candidate’s research.

With oversight of the Program Director and members of the IAC, each Candidate will select a mentoring team that will include one research mentor and one clinical mentor. The members of the mentoring team will be selected by the Candidate in the first three months of Year 01. The breadth and variety of ongoing clinical research represented by the potential mentoring teams ensures early successful involvement in active projects. All Candidates will be required to define and design a thesis project of publishable quality that is closely aligned with the Candidate’s interest and career objectives. The mentoring team will assist the Candidate to create and complete “mock” K23 related to the thesis project.

The Candidate’s plan of didactic study will be designed in consultation with the mentoring team and the Program Director. The plan of study will include a minimum of thirty semester hours of graduate credit. This minimum requirement will include six hours of research credits. The didactic research curriculum will be adapted to fit the Candidate’s level of experience and prior training.

At the end of the second year, a thesis committee will be selected. The thesis committee will consist of the mentoring team and at least two other graduate faculty members. All thesis committees will include a statistician. This committee will convene to consider and formally approve the Candidate’s thesis proposal by May 1 of year 02 of the training program. An approved copy of the thesis proposal will be submitted to the Program Director and the IAC no later than July 1 of year 03 to ensure adequate progress and completion of the program.

To ensure satisfactory progress in the clinical research curriculum the Candidate’s performance will be reviewed every six months by the members of the mentoring team, the Program Director and the IAC. In didactic course work, satisfactory progress will require the Candidate maintain a “B” average or higher. Candidates unable to meet this academic requirement will devise a written plan with the mentoring team to outline strategies to meet the requirements of the program.

Successful completion of the clinical research curriculum will provide the Candidate with the knowledge and skills to create and execute a hypothesis driven clinical research project and to compete successfully for research funding.

**Didactic Course Sequence**

In this revised application, the didactic course sequence has been modified. The program is re-designed so that course work is completed in one year plus the summer semester. Year 03 of training is devoted to completing the Candidate’s thesis, creating a “mock” K23 grant application, and presentation/publication of research. A typical didactic course sequence and brief description of each course within the didactic research core curriculum appears below. This curriculum can be modified to account for the Candidate’s prior experience and education.

**Fall Semester (11 credits)- Year Two**

**HSRP 710 – Introduction to Health Services Research and Healthcare System (3 credits)** This course provides the Candidate with an introduction to health services research and an overview of the changing health care delivery system. Candidates will be provided with information regarding the organization and delivery of health care services in the United States including health care policies enacted to promote public health.
HSRP 720 – Introduction to Epidemiology (4 credits)
This course is an introduction to the basic concepts and methods of epidemiology. Topics include measurement of disease prevalence, incidence, effect, sensitivity/specificity analyses, prospective, case comparison, cross sectional, and clinical trials study design.

HSRP 730 – Introduction to Statistics (4 credits)
This course provides an introduction to statistical concepts and basic methodologies pertinent to clinical research. Descriptive statistics, probability, sampling distribution, hypothesis testing, simple linear regression, correlation, one way analysis of variance, categorical data analysis, and nonparametric methods are presented.

HSRP 763 - Topics in Public Health Science (1 credit)
This course considers a range of topics which include design of field and community studies, behavioral and social factors in health, quality of life issues, health policy and analysis, and health services research.

Spring Semester (12 credits)-Year Two
HSRP 732 – Applied Linear Models (4 credits)
The topics of this course will include simple and multiple linear regressions, experimental design, analysis of variance, and co-variance, and repeated measures analysis. Particular emphasis is given to the proper application and interpretation of statistical methods and results.

HSRP 740 – Research Design and Methodology (4 credits)
This course will provide Candidates with in depth knowledge of research design methodology used in clinical research. Topics include an overview of scientific method, ethical issues in research, quasi-experimental designs, surveys, qualitative methodologies, data collection, and instrument design.

HSRP 711 – Medical Outcomes (2 credits)
This course will introduce Candidate to theories and methodologies used to evaluate the health care outcomes. The assessment of morbidity and mortality, adverse affects, quality of care, compliance, health related quality of life, and patient satisfaction will be emphasized.

HSRP 763 - Topics in Public Health Science (1 credit hour)
This course considers a range of topics which include design of field and community studies, behavioral and social factors in health, quality of life issues, health policy and analysis, and health services research.

HSRP 750 – Thesis research (1 credit hour)
In conjunction with the mentoring team the Candidate will refine his thesis project within the framework of a "mock" K23 grant application.

Summer Semester (6 credits)-Year Two
HSRP 741 – Research Grant Preparation (3 credits)
This course will provide the Candidate with the knowledge and skills to develop grant proposals to pursue funding in their areas of interest. The preparation of a "mock" K23 grant proposal will be emphasized in parallel the Candidate’s thesis project. Course topics also will include the role of external funding in biomedical research, identification of public and private sources of funding, required components of grant submission, human subjects and budgeting considerations. During the course, Candidates will present their thesis proposal for peer review and critical discussion.

HSRP 734 - Applied Statistical Methods (3 credits)
This course will provide instruction in advanced statistical technique to analyze health outcomes data. Topics include categorical data and survival analysis with detailed overview of logistic regression and Cox’s
proportional hazards regression. Selected topics of particular relevance to the Candidate’s thesis project will be presented. The proper application and interpretation of statistical methods and results are emphasized.

**Year 03**

Devoted to completion of the thesis project, the development of a “mock” K23 grant proposal, and the presentation/publication of research. At the end of year 02, the Candidate will complete a final examination that concerns the thesis project and knowledge content in related areas. The examination committee will consist of the thesis committee to include the mentoring team and at least two members of the Wake Forest University Graduate Faculty, who will serve as a Chair of the examining committee. Dr. Hansen will serve as an ex officio member. The Candidate will submit a written copy of the thesis project four weeks prior to the date of final examination. The examination committee will poll committee members at least two weeks before the examination date to determine the acceptability of the thesis project for defense. After successful defense of the Candidate’s thesis, five copies of the thesis will be printed and bound. Successful completion of the didactic course work and thesis defense will result in awarding the Masters in Science Degree in Health Sciences Research.

**Supplemental Didactic Training**

In addition to the didactic course work, the Candidate will attend a 10 day seminar on Epidemiology of Cardiovascular Disease. Held in July of the second year of training, this seminar is directed by Dr. David Goff, a member of the research mentoring team. The primary goal of the seminar is to provide an intensive introduction to epidemiology. The prevention of major cardiac and vascular diseases for health professionals planning careers in clinical research are emphasized. Faculty in Epidemiology, Preventive Medicine, and Biostatistics, present a series of lectures. Laboratory and tutorial sessions are designed to illustrate the basic principles and their application to clinical research.

### Timeline for Career Development Training

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S = Semester; Q = Quarter; S1 = Fall; S2 = Spring; S3 = Summer