Vision and Creation of the American Heart Association Pharmaceutical Roundtable Outcomes Research Centers

Eric D. Peterson, MD, MPH; John A. Spertus, MD, MPH; David J. Cohen, MD, MSc; Mark A. Hlatky, MD; Alan S. Go, MD; Barbara G. Vickrey, MD, MPH; Jeffrey L. Saver, MD; Patricia C. Hinton, MA, MS

Background—The field of outcomes research seeks to define optimal treatment in practice and to promote the rapid full adoption of efficacious therapies into routine clinical care. The American Heart Association (AHA) formed the AHA Pharmaceutical Roundtable (PRT) Outcomes Research Centers Network to accelerate attainment of these goals. Participating centers were intended to carry out state-of-the-art outcomes research in cardiovascular disease and stroke, to train the next generation of investigators, and to support the formation of a collaborative research network.

Program—After a competitive application process, 4 AHA PRT Outcomes Research Centers were selected: Duke Clinical Research Institute; Saint Luke’s Mid America Heart Institute; Stanford University–Kaiser Permanente of Northern California; and University of California, Los Angeles. Each center proposed between 1 and 3 projects organized around a single theme in cardiovascular disease or stroke. Additionally, each center will select and train up to 6 postdoctoral fellows over the next 4 years, and will participate in cross-collaborative activities among the centers.

Conclusions—The AHA PRT Outcomes Research Centers Network is designed to further strengthen the field of cardiovascular disease and stroke outcomes research by fostering innovative research, supporting high quality training, and encouraging center-to-center collaborations. (Circ Cardiovasc Qual Outcomes. 2009;2:663-670.)

Key Words: coronary disease ■ stroke ■ statistics ■ mortality

Cardiovascular disease (CVD) and stroke remain the first and third leading causes of death and disability in the United States.1,2 The mission of the American Heart Association (AHA) is to reduce this burden of disease by supporting efforts “to build healthier lives, free of cardiovascular disease and stroke.”3 Attaining this goal will require continued scientific discoveries and therapy, as well as improving the translation of these discoveries into clinical practice. Outcomes research supports the innovation and science required to fulfill this latter need. Outcomes research draws on multiple scientific disciplines—including epidemiology, biostatistics, behavioral science, decision analysis, health economics, health policy, organizational theory, and implementation research—whose integration can accelerate the pace and application of evidence into practice.4,5

Given the field’s potential to reshape medical care delivery, and recognizing the current paucity of well-trained outcomes researchers, the AHA proposed the creation of an Outcomes Research Centers Network. The Network was to comprise select centers of outcomes excellence that could (1) carry out state-of-the-art outcomes research in CVD and stroke; and (2) serve as incubators for the next generation of investigators. The AHA launched this program in 2008, with the support of its Pharmaceutical Roundtable (PRT) (Appendix 1) and a generous gift from AHA Board member David Spina and his wife, Stevie. Although funding was a key component of the program’s formation, the sponsors played no role in the selection of the centers, nor did they influence subsequent research.

Structure of the Network
The AHA PRT Outcomes Research Centers Network (hereafter “the Network”) funded 4 US research centers, each led by a Director or Co-Directors, who are responsible for coordinating their individual research and training activities, as well as communicating and collaborating with the other centers. Each center proposed to carry out 1 to 3 outcomes research projects, organized around a common theme, and train 5 to 6 outcomes fellows over 4 years. Please refer to the Table for a summary of each of the 4 center’s leadership, themes, and associated research projects.

Center Selection
The Network’s Request for Application was announced in November 2007 and produced many competitive applications.
Each application was reviewed and scored by a panel of outcomes experts. Investigators from 6 applicant institutions with the highest scores participated in a reverse site visit. The 4 selected centers were:

1. Duke Outcomes Research Center, Duke University School of Medicine, Durham, NC (Director: Eric D. Peterson, MD, MPH)

2. Saint Luke’s Mid America Heart Institute and the University of Missouri–Kansas City Outcomes Research Center, Kansas City, Mo (Co-Directors: John A. Spertus, MD, MPH and David J. Cohen, MD, MSc)

3. Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center, Stanford University School of Medicine, Stanford, Calif and Division of Research, Kaiser Permanente of Northern California,
Positive impact on statewide STEMI mortality rates.11 This project will also prospectively study RACE ER (an ongoing extension of the RACE initiative) which is designed to better understand the role of emergency medical personnel in timely diagnosis and transfer of STEMI patients. Combining these 2 goals may result in many important insights for the AHA’s recently launched Mission Lifeline Initiative.12

**Project 3: “Preventing Recurrent Heart Failure”**
Heart failure (HF) is a condition that is characterized by high-rate downstream death or need for rehospitalization.13,14 Led by Adrian Hernandez, MD, Duke’s third project examines whether these “failure” rates are modifiable by improved transition of HF patients from hospital to home. Specific project components will include: (1) examining the degree to which rates of death or HF readmission vary among the >250 AHA Get with the Guidelines (GWTG) US hospitals; (2) using qualitative and quantitative methods, identify how hospitals with exemplary low readmission rates successfully transition their patients home; and (3) working with AHA GWTG leadership to disseminate these successful strategies for reducing recurrent events to other GWTG participants.

**Saint Luke’s Mid America Heart Institute**

**Center Theme: Improving the Translation of Evidence-Based Risk-Prediction Models to Create Patient-Centered Medical Decision-Making in Clinical Care**
The Institute of Medicine has challenged the medical profession to move toward a healthcare system that is evidence-based, efficient, safe, and patient-centered.15 Outcomes researchers have embraced this challenge, working to predict patient outcomes through the development of risk-prediction models that integrate numerous patient characteristics. To date, however, these models have rarely been used at the time of medical decision-making. The failure to incorporate quantitative prognostic estimates has led to a risk-treatment paradox, namely, patients with the most potential to benefit from treatment are very often denied therapy.16–20

An ideal opportunity to apply evidence-based risk-stratification tools is at the time of informed consent. As part of this process, the clinician should explain to the patient the nature and purpose of the procedure, along with attendant risks and benefits. Unfortunately, current informed consent processes often fail to accomplish these aims of educating and engaging patients in their own medical decision-making.21–23 In the setting of PCI, not only must the interventionalist explain the nature of the procedure, but also discuss and decide whether or not to place a drug-eluting stent. This later decision must balance a patient’s risk of restenosis and repeat revascularization (which can be reduced with a drug-eluting stent).24 with the higher risk of late stent thrombosis and consequent requirement for prolonged dual antiplatelet therapy. This risk-benefit calculation accentuates the need for careful patient selection (so as to identify those individuals at highest risk for restenosis), as well as the need to clearly communicate to patients their responsibility to adhere to prolonged dual antiplatelet therapy.24,25
Project: “Transforming Informed Consent for PCI into an Evidence-Based Educational Experience”

Over the past 5 years, Mid America Heart Institute (MAHI) researchers have developed Personalized Risk Information Services Manager (PRISM)—a web-based tool used to execute individualized risk projections into an easily-interpretable graphical output that can be used in patient care. Using Microsoft’s .NET platform, with interfaces for linking to existing health systems, PRISM can execute complex risk-prediction models to produce individualized estimates of peri-procedural risks and outcomes.26–28 Led by Carole Decker, PhD, RN, and John Spertus, MD, MPH, MAHI’s project will evaluate whether the PCI informed consent process can be improved, using PRISM, to provide patients and physicians with easily understood risk estimates. Customized informed consent documents will be implemented at 3 centers to provide patients and their practitioners with each individual’s estimated risks of peri-procedural mortality, bleeding, and target vessel revascularization (for both bare-metal and drug-eluting stents), within 1 year of treatment.

MAHI’s project aims to (1) identify institutional barriers in the implementation of a new consent process; (2) describe patients’ satisfaction and understanding of an individualized, evidence-based, informed consent process; (3) describe the effect of presenting preprocedural risks of target vessel revascularization on the use of drug-eluting versus bare-metal stents as a function of patients’ pre-procedural risk for restenosis; (4) determine whether patients who are informed about the risks and benefits of drug-eluting stents will be more compliant with dual antiplatelet therapy 6 months post-treatment; and (5) estimate the impact of this new paradigm of informed consent on the cost-effectiveness of PCI.

Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center

Center Theme: Defining Optimal Care for Coronary Heart Disease and Chronic Heart Failure in Clinical Practice

The goal of the Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center is to assess the longitudinal effectiveness and safety of cardiovascular pharmacological and device therapies used in routine clinical care. The Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center will build on the extensive computerized databases of Kaiser Permanente of Northern California to examine the use and outcomes of therapies within a large, well-defined, representative, and diverse patient population. The Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center will link multiple internal and external clinical and administrative databases to create a comprehensive record of incident coronary heart disease (CHD) and chronic heart failure patient care and outcomes. Linking external health plan clinical and administrative databases will create a wealth of clinical detail, including a comprehensive longitudinal picture of individual patient care and outcomes.

The Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center proposed 2 primary projects that will use the detailed clinical registry of patients to examine the use, outcomes, and costs of various therapeutic options for CHD and chronic heart failure. Both projects will (1) use similar methods and data sources to increase efficiency and standardization; and (2) assess the variation in the use and outcomes of therapies based on patient and system factors. Both projects will benefit from efforts to improve outcomes research methodology, particularly in efforts made to create state-of-the-art approaches to observational treatment comparisons. Assorted alternative analytic approaches, such as various propensity score methods,29 instrumental variables,30 marginal structural models,31 and new designs,32 will be tested on the same datasets. Results will be compared internally, as well as externally, to results from published RCTs. Alternative approaches will also be assessed using simulation methods to investigate which approach is best suited to compare nonrandomized alternative treatments.

Project 1: “Defining Optimal Care for Coronary Heart Disease”

Led by Mark A. Hlatky, MD, the first project will address several specific questions about the use and outcomes of treatment for incident CHD in routine clinical care. More specifically, the project will (1) examine the use of evidence-based drug therapies for CHD in practice, with a particular emphasis on exploring whether either initial prescription or subsequent medication adherence varies according to patient characteristics or health care delivery system factors33,34; (2) explore the effect of these therapies on outcomes and the extent to which these outcomes vary according to patient characteristics; and (3) assess the effectiveness of PCI versus medical therapy for symptomatic CHD in typical clinical practice (RCTs comparing these therapies typically enroll a small number of patients,35,36 so there is a chance that the outcomes observed in clinical trials may differ from the results in routine practice).

The potential for novel risk markers to identify higher risk patients and to “personalize” care has generated great interest, but the methods to assess the value of novel markers have not been adequately established. This project will examine a prototype novel risk marker, namely, kidney function based on estimated glomerular filtration rate (GFR), which is available on almost all patients and has evidence of prognostic value.37,38 The investigators will assess whether a patient’s level of GFR modifies the effectiveness and safety of various therapies and (after accounting for other patient characteristics), whether or not GFR levels provide useful information in selection of therapies.

Imaging modalities offer another tool for identifying and quantifying patient risk. Coronary computed tomography angiography (CCTA) is an emerging diagnostic technology that has the potential to revolutionize the evaluation of patients with either known or suspect coronary artery disease. Because CCTA has only been used in relatively small studies, little data are available regarding its effect on subsequent management or clinical outcomes.39 To rectify this gap, the Stanford University–Kaiser Permanente Cardiovascular Outcomes Research Center will develop a clinical database that will document the use and results of CCTA. The database will allow for outcomes comparison of CCTA patients with other
patients that are managed using alternative evaluation approaches.

Project 2: “Defining Optimal Care for Chronic Heart Failure”

The effectiveness of cardiac procedures and devices in patients with HF has been studied only in relatively small clinical trials,40–42 which may not be generalizable to more infrequently selected patients and care settings. Led by Alan S. Go, MD, this second project will examine the use of coronary artery bypass surgery (with or without preoperative myocardial viability testing) and cardiac resynchronization therapy (with or without implantable cardioverter-defibrillators) in a large clinical registry of patients with HF and reduced left ventricular systolic function. The overall safety and effectiveness of these therapies in practice will be tested, as well as the potential for variation in targeted patient subgroups.

This project will also examine whether or not the effectiveness of several specific drugs used to treat HF (eg, aldosterone receptor antagonists, β-blockers, digoxin, and the combination of isosorbide dinitrate and hydralazine) are as effective and safe in everyday practice as randomized trials have suggested.43–46 In addition, this project will test the effectiveness and safety of these drugs in understudied populations (eg, the elderly, women, racial minorities, and patients with chronic kidney disease) for key outcomes such as mortality and hospitalizations for HF.

University of California at Los Angeles Stroke and CV Disease Outcomes Research Center

Center Theme: Addressing Racial/Ethnic and Socioeconomic Disparities in Care for and Outcomes of Stroke and CV Disease

Substantial racial, ethnic, and socioeconomic disparities in care quality and outcomes are well-documented for stroke, heart disease, and their associated risk factors.47 The University of California at Los Angeles (UCLA) Outcomes Research Center’s vision is to address racial, ethnic, and socioeconomic disparities in the care and outcomes of patients with stroke and CVD. UCLA will elucidate causes of these disparities, generating and testing sustainable interventions at both the individual and community levels, with the ultimate goal of redressing these issues in underserved populations.

Disparities in care are aggravated by severe resource constraints in the safety-net system. These disparities are likely to worsen, given that minority and low-income persons are often reliant on these services, and national solutions to address the lack of universal healthcare coverage appear remote or incremental.48 Inadequate health insurance coverage is clearly one cause of disparities in stroke and CVD treatment, but there are others, including patient and provider attitudes, beliefs, and knowledge; communication roadblocks; and barriers in linking patients to needed community resources.49 To address these factors, new care delivery models that target these weaknesses must be crafted and tested for their impact, not only on health care and outcomes but on cost and sustainability in safety-net settings.

UCLA’s projects are synergistic in that they apply a larger-scale long-term agenda and complementary approaches to stroke risk factor control in underserved populations. Researchers have also created partnerships with community organizations that share interests in improving health for underserved communities. These partnerships are being formalized through the creation of a Center Community Council that will apply lessons learned from this research to (1) expand and develop new stroke prevention interventions in underserved communities in Los Angeles (LA) County; and (2) export effective interventions to other communities that are comprised of large, vulnerable, at-risk populations.

Project 1: “RCT of an Intervention to Enable Stroke Survivors in the Los Angeles County Hospitals to ‘Stay With the Guidelines’”

This study’s goal is to create a successful and sustainable model that will optimize secondary stroke prevention and can be disseminated broadly to local public health systems. A new model will be developed for improving risk factor control in stroke survivors in the LA County safety-net public health system, which serves an ethnically diverse, indigent population in a very large urban area. Led by William Cunningham, MD, MPH, this project will test the impact of an intervention that uniquely adapts the principles of in-hospital initiation of stroke prevention reminders and educational tools on blood pressure control and other risk factors.50 This intervention will incorporate components of the Chronic Care Model, which has been successfully applied to improve quality and outcomes for other chronic diseases.51 The intervention will create group clinics that have patient self-management training, disseminate care protocols developed by a Task Force of representatives from all the county facilities and community agencies, and coordinate delivery of stroke prevention care through a dedicated nurse practitioner.

Secondary outcomes of medication adherence and patient knowledge about stroke prevention and symptoms will enable researchers to explain the intervention’s effects. Approximately 400 stroke patients will be enrolled in the study, then randomized into either interventional care or usual care, and followed for 12 months. To address sustainability, a cost analysis will be conducted from the perspective of the county healthcare system, measuring direct costs and estimating projected costs, based on models derived from published literature. Findings will be shared with local healthcare system administrators and disseminated to other U.S. metropolitan hospital system administrators.

Project 2: “Are Neighborhood Characteristics Associated with Stroke Incidence and Outcomes?”

UCLA’s second research study will generate new knowledge about the impact of neighborhood socioeconomic disadvantage on stroke occurrence, care, and outcomes. Led by Arleen Brown, MD, PhD, researchers will analyze data from the Cardiovascular Health Study (CHS)—a large, population-based, longitudinal study of CHD and stroke in adults over 65 years of age. The CHS dataset includes detailed assessments of stroke outcomes, specifically linked to individual-level risk factors, extensive clinical data collection, geo-coded participant addresses, and Medicare claims,52 thus providing a
unique opportunity to study the impact of neighborhood socioeconomic disadvantage on stroke. Researchers will use multilevel modeling techniques to test whether residence in a disadvantaged area is associated with higher stroke incidence and worse poststroke outcomes (eg, recurrent stroke, CV events, mortality, and use of services).53 Researchers will also analyze whether any observed associations between outcomes and specific neighborhood characteristics are mediated by social support and depression.

### AHA PRT Outcomes Research Centers Network Fellowship Training

In addition to carrying out these center-specific research projects, the Network also supports the training of new investigators in CVD and stroke outcomes research. Fellowship eligibility is limited to candidates with a doctoral degree who are either US citizens, permanent residents, pending permanent residents, or hold an appropriate visa. The recruitment of Network fellows began with a nationwide call for prospective participants in the fall of 2008. The initial cohort of fellows will begin their training on July 1, 2009. A second group of fellows will apply in late 2009/early 2010, and begin in July of 2010.

Each center strives to identify exceptionally motivated individuals who seek advanced research training. Centers also endeavor to recruit fellows with diverse backgrounds, such as MDs or PhDs in nursing, pharmacy, or quantitative sciences (eg, biostatistics, epidemiology, and health services research). Specific attention will be given to identifying and recruiting individuals from minority populations that have been traditionally underrepresented in scientific careers.

Center fellows will commit a minimum of 75% effort to research training. An individualized plan will be created for each fellow, tailored to each individual’s career goals. Although training components may vary across centers, each component will contain a similar core of (1) rigorous didactic training in key methodological areas (eg, biostatistics and outcomes research); (2) hands-on research experiences including project design, operations, and analysis; (3) close trainee mentorship; and (4) opportunities for cross-center networking, training, research, and presentations.

### Interactions Among the Network’s Centers

To promote collaboration among the 4 Network centers, each center has shared their individual research proposals with the other centers, and leadership representatives from each center have met several times to discuss how to integrate their projects, the Network also supports the training of new investigators in CVD and stroke outcomes research. This program will establish a unique multi-center model of collaborative CV outcomes research. Center Directors meet monthly by teleconference to establish cross-center policies, plan an annual meeting, identify opportunities for collaborative education, review progress toward common goals, and analyze growth in fellows’ career development and training.

Additionally, the centers (1) have developed a web-based infrastructure to support communication and information exchange among faculty and fellows; (2) hold an annual meeting for center investigators and fellows that includes “consultation time” for investigators to discuss research methods, projects, and potential collaborations; (3) invite leaders from each center to visit other centers, to stimulate research ideas and expand cross-disciplinary expertise; and (4) create methodological and operational “interest groups” to share analytic approaches to research and solicit feedback on project challenges.

### Network Oversight and Evaluation

Network progress will be monitored by an oversight advisory group of experienced clinical, population, and outcomes research scientists (Appendix 2). Specific responsibilities of the oversight advisory group are to (1) annually monitor the scientific progress of the centers and their projects; (2) annually evaluate the program, including an evaluation of trainee progress; (3) monitor and encourage interactions within and among centers; and (4) ensure that the outcomes of the Network are evaluated appropriately. Specific measures of Network progress will include the centers’ success in carrying out their research projects, recruitment and development of trainees, and extent of interactions among the centers.

### Conclusion

The Network will promote innovations in both analytic methodologies and interventions that will positively impact CV and stroke care and outcomes. Patient care delivery methods will be studied across various health care settings, ranging from inner-city hospitals to ambulatory clinics with diverse patient populations. Cutting edge information systems and novel technologies will assist in the translation of multivariable risk prediction models to actual patient care interfaces, and evidence-based, individualized, medical decision-making will be tested as a means for improving healthcare quality. The Network will not only support established leaders in the field of outcomes research but encourage the training of the next generation of leaders in CV and stroke outcomes research. This program will establish a unique multi-center model of collaborative CV outcomes research.

### Appendix 1: Pharmaceutical Company Members of the AHA PRT Outcomes Research Centers Network

1. AstraZeneca, LP
2. Eli Lilly and Company
3. Bristol-Myers Squibb Company
4. GlaxoSmithKline
5. Merck/Schering-Plough Pharmaceuticals
6. Merck & Co, Inc
7. Novartis Pharmaceuticals
8. Pfizer, Inc
9. Sanofi-Aventis US, LLC
10. Takeda Pharmaceuticals North America, Inc

### Appendix 2: The Oversight Advisory Group

Chairperson
David Wennberg, MD, MPH, President and Chief Operating Officer, Health Dialog Analytic Solutions; Chief Science and Products Officer, Health Dialog
Members

Bonnie Gance-Cleveland, PhD, PNP, RNC, Associate Professor Director, Center for Improving Health Outcomes in Children, Teens and Families, Arizona State University
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Jack Tu, MD, PhD, Senior Scientist, Institute for Clinical Evaluation Sciences and Professor of Medicine, Public Health Sciences, Health Policy, Management, and Evaluation, University of Toronto
Viola Vaccarino, MD, PhD, Professor of Medicine and Epidemiology, Emory University

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