Venues and Opportunities for Comparative Effectiveness Research (CER) Clinical Trials

Information and Perspectives from Member Agencies of the Diabetes Mellitus Interagency Coordinating Committee (DMICC)
DMICC Meeting of October 21, 2010

Updates on the Diabetes Research Strategic Plan and the Special Statutory Funding Program for Type 1 Diabetes Research
Judith Fradkin, M.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Chair, DMICC
A final draft of the Diabetes Research Strategic Plan was sent to DMICC members for clearance and members were thanked for their thoughtful comments. NIDDK has already utilized recommendations from the Plan to highlight emerging scientific areas in a new request for applications. In addition, a final draft of the Evaluation Report on the Special Statutory Funding Program for Type 1 Diabetes Research has been sent through NIH Executive Secretariat for clearance; DMICC members received a courtesy copy with an invitation to comment.

Post-modern Planning of a Clinical Trial: The U34 Mechanism
David Nathan, M.D., Harvard Medical School
Incidence of type 2 diabetes continues to increase, generating a challenge to health care providers to choose among the numerous available medications for reducing blood glucose levels at diagnosis and maintaining glycemic control over time. Nine new classes of anti-diabetic drugs have become available since 1995, but there have been few direct comparisons of available medications. The Glycemia Reduction Approaches for Treating Diabetes Trial: A Comparative Effectiveness (GREAT) study, a multicenter clinical trial being planned by Massachusetts General Hospital and the George Washington University Biostatistics Center, seeks to provide this critical information.

The primary aim of the GREAT Study, which is still in the planning stages, is to examine five different medications that are commonly used to treat type 2 diabetes and to compare their effectiveness in lowering and maintaining hemoglobin A1c levels over time in recent-onset type 2 diabetes when used in combination with metformin. In addition, other attributes of the medication combinations, including adverse events, acceptability, and effects on cardiovascular risk factors, quality-of-life, and other outcomes, will be compared. Finally, in a subset of the study cohort, the relative effects of early combination therapy will be compared with the traditional sequential approach. The study tentatively plans to recruit a total of 7,500 patients with less than 3 years duration of type 2 diabetes: 5,500 for the drug comparison cohort and 2,000 drug-naïve patients for the treatment strategy cohort. Patients in the drug comparison arm will be randomly assigned to, in addition to metformin, one medication in each of these tentative classes: sulfonylurea, thiazolidinedione, DPP-IV inhibitor, GLP-1 agonist, or insulin. Planned follow-up is for a minimum of 4 years and a maximum of 7 years.

Recognizing that administrative activities of a trial of this magnitude are significant, the GREAT team applied for a Multi-Center Clinical Study Implementation Planning (U34) Grant from

NIDDK. Implementation planning grants are intended to support all administrative study group activities that are required in order to begin recruitment of patients. The 2-year planning grant enabled establishment of a small, tightly organized planning committee that undertook tasks such as: completing the protocol; preparing the manual of operations; preparing requests for applications for central laboratories, reading centers, a drug distribution center, and clinical centers; recruiting and selecting clinical centers; establishing subcontracts; and determining recruitment strategies. This alternative method for planning clinical trial activities could utilize a smaller number of investigators, take less time, cost less, and take advantage of subcontracts.

Conducting Efficient Randomized Controlled Trials in Large Patient Populations
Joe Selby, M.D., M.P.H., Kaiser Permanente

Health Maintenance Organizations (HMOs) may provide a significant resource for the conduct of large-scale randomized clinical trials. The HMO Research Network (HMORN) has 16 member health systems--six of which are Kaiser Permanente systems--covering a total of 12 million active individuals. All member systems now have established electronic health records, and over half use the same electronic health records system. Members share data only by agreement and on a project-by-project basis, utilizing the virtual data warehouse—a standardized, distributed dataset. HMORN collaborates on six major, Federally funded collaborations, each supporting multiple projects. For example, HMORN participates in the Agency for Healthcare Research and Quality's (AHRQ) Developing Evidence to Improve Decisions about Effectiveness (DEcIDE), which includes the Diabetes Multi-Center Research Consortium that analyzes and coordinates AHRQ's diabetes-related CER portfolio.

There are multiple reasons for the participation of large systems, such as HMORN, in randomized clinical trials. First, there is a need for data in the systems; the systems' leaders and physicians want evidence on what works, in order to inform guidelines, treatment strategies, and policy decisions. Second, the recruitment has been done and data is already being collected; these systems have defined populations with excellent clinical data and some elements of follow-up are already captured in the health systems database. Third, the providers are willing to participate; many physicians are interested in participating in clinical trials, and researchers within the systems are natural collaborators. Finally, participation in trials by these systems can be viewed as a marketing plus.

The HMORN proposed a new consortium project as a part of the NIH Roadmap initiative, called the Coordinated Clinical Studies Network (CCSN), which was funded from 2004-2007. The "feasibility contract" explored the possibility of linking clinical networks together for enhanced research capabilities, motivated in part by NIH's desire to determine whether a network that was formed to answer questions in one field could be adapted to examine questions in related, but different fields. The CCSN created an opportunity to develop further HMORN's capabilities, multi-site projects, and infrastructure. As part of this project, the HMORN generated a Collaboration Toolkit which includes recommendations for improving provider participation in clinical trials, tools to support recruitment and primary data collection, tools for navigating research review and compliance processes, and a guide to understanding and designing cluster randomized trials within the context of HMORN. More information on the Collaboration Toolkit is available at: http://www.hmoresearchnetwork.org/resources/collab_toolkit.htm

The NIH-HMORN Collaboratory was recently proposed by the NIH Director, Dr. Collins, to strengthen ties between NIH and the larger scientific community with the populations, data, and researchers of the HMORN systems. This effort includes three distinct interests: 1) mega-epidemiology, including large-scale collection of DNA and tissue specimens of population-based genetic epidemiologic research; 2) health systems research to monitor the impact of health care reform; and 3) clinical trials/CER to leverage the populations and clinicians within HMORN systems to address practical questions through clinical trials. An initial meeting was held in March 2010 with representatives from NIH and HMORN, and a 1-year planning grant was issued in August 2010. The current plan is to issue three Funding Opportunity Announcements during 2011 on: 1) building infrastructure, 2) mega-epidemiology, and 3) comparative effectiveness/clinical trials.

Update on New CDC-NIDDK Initiative: Natural Experiments and Effectiveness Studies of Policies for Diabetes Prevention and Control
Edward Gregg, Ph.D., Centers for Disease Control and Prevention (CDC)
Traditionally, randomized clinical trials are the gold standard for informing public health decision making. For example, results from proof-of-concept trials, including the Diabetes Control and Complications Trial, when diffused to clinical care providers, can lead to changes in care management, followed by policies of health care systems and policies aimed at access and reimbursement. This trajectory has led to a decrease in complications risk in the diabetic population. Although the Diabetes Prevention Program demonstrated that type 2 diabetes can be prevented or delayed in people at high risk for the disease, it is unknown which of the various implemented public health policies will lead to a reduction of diabetes risk in the general population. Population-targeted policy innovations such as screening approaches, economic incentives and disincentives, and legislative initiatives remain untested, and thus lack experimental evidence to demonstrate their effectiveness. In addition, it is difficult to test system- and population-targeted policies in randomized clinical trials.

To begin to address these issues, the CDC and NIDDK are sponsoring a joint initiative to develop a 5-year multi-center research network to examine naturally occurring, population-targeted health policies to test their effectiveness on diabetes prevention, control, and health inequalities. The funding request to create this network solicited proposals of population-targeted policies and interventions from health systems, business and community organizations, and government agencies. Interventions needed to be aimed at prevention of diabetes and/or its complications, and needed to be ongoing or imminent. The studies will quantify the impact of population-targeted policies on preventive behaviors, quality of care, morbidity, and intended and unintended intervention consequences. Because the cost of the interventions was underwritten outside of this network, these studies will maximize and capitalize on investments made by other sources.

The studies proposed by the five funded network sites were mostly health system-based policies and included a combination of primary and secondary prevention. They included a wide range of outcomes with most assessing diabetes incidence, utilization, and control, measured at the employer, health plan, or large clinic level. Examples are: employer-based detection, outreach, incentives, and telephone coaching for primary prevention among high-risk adults from five employers; systematic post-partum screening of women with a history of gestational diabetes;

and health plan-administered diabetes prevention programs delivered in YMCAs to high-risk adults. The network serves to assist collaboration, improve and maintain design and protocol quality, generate common metrics, and facilitate future studies using common protocols and an established framework.

Using Clinical and Translational Science Awards (CTSA) Infrastructure to Conduct and Disseminate Clinical and Cost Effective Diabetes Research
Athena Philis-Tsimikas, M.D., Scripps Whittier Diabetes Institute
The vision of the CTSA consortium is to improve human health by transforming research and training environments to enhance the efficiency and quality of clinical and translational research. The consortium has five defined strategic goals to enhance: 1) the national clinical and translational research capability; 2) the training and career development of clinical and translational scientists; 3) consortium-wide collaborations; 4) the health of our communities and the Nation; and 5) T1 translational research. Through its strategic goals and across the current 55 centers, the consortium aims to help develop the next generation of clinical research to speed the translation of basic biomedical research results into improved patient care.

Key elements of CTSA sites include experience in trial design; provision of research education, training, and career development leading to an advanced degree; experience with community-based participatory research; clinical resources; and expertise in topics such as bioinformatics, biostatistics, and clinical research ethics. CTSAs are also expected to foster bi-directional and effective collaboration within an institution and between institutions and industry, foundations, and community physicians as appropriate, as well as among other CTSAs. Recently, the CTSA CER Key Function Committee was established to build the field of CER and patient-centered outcomes research by creating a learning community across CTSA institutions, spurring the development of methods, expanding training and education, promoting community and public engagement, applying CER findings, and sharing successes and lessons learned. Additional information on CTSAs is available at: https://www.ctsacentral.org/

Project Dulce was described as an example of diabetes translational research that has benefitted from collaboration with the Scripps CTSA. Initiated in 1997, Project Dulce utilizes nurse case managers and promotoras (peer educators) to conduct diabetes care and education in collaboration with the patient's primary care provider in the community health center environment. Project Dulce used a multi-disciplinary, team approach to translate results of the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study in real-world settings to multilingual, underserved populations with low rates of literacy. Improvements in clinical, behavioral, and cost outcomes were observed in evaluation of the program's effectiveness. Through the CTSA, researchers were able to expand Project Dulce to investigate translation of the Diabetes Prevention Program into a population of high-risk, Latina women who had a history of gestational diabetes. More information on Project Dulce can be found at: http://www.scripps.org/services/diabetes/project-dulce

Peer Support for Diabetes: A Template for Comparative Effectiveness Trials in the Veterans Administration

Sandeep Vijan, M.D., M.S., U.S. Department of Veterans Affairs (VA)

Providing sufficient self-management support to diabetes patients is difficult for many outpatient practices; many patients with diabetes do not receive the help they need between clinic visits as care management programs are often time-consuming and labor- and resource-intensive. A promising approach is peer support: sharing of experiences and provision of mutual support among patients with the same chronic illness and similar self-management challenges. Peer-led group and training sessions have been successful, but it is still challenging for patients to attend frequent, face-to-face sessions.

To address this challenge, the VA supported a randomized clinical trial to compare a diabetes peer support program, delivered by telephone, with usual nurse care management in improving glycemic control. Because many VA patients are regionalized, such a program could connect people locally and lead to the development of a support community. In addition to an initial session to review health data, patients in the intervention arm also participated in a group session to set diabetes-related behavioral goals, receive brief training in peer communication skills, and be paired with another age-matched participant. Paired peer partners were encouraged to talk weekly using a telephone platform that recorded call frequency and duration and provided automated reminders promoting peer contact. Intervention participants were also offered three optional, 90-minute, patient-driven group sessions at months 1, 3, and 6 to share concerns, questions, strategies, and progress on goals.

Participants received the intervention or standard care for 6 months and were followed for an additional 6 months. For the primary outcome of hemoglobin A1c levels, participants in the intervention arm demonstrated an average reduction of 0.29%, whereas participants in the control arm demonstrated an average increase of 0.29%. For another outcome, a reduction in blood pressure values, no significant differences were observed between the intervention and control arms, although baseline values were already near the expected targets. For self-reported outcomes, intervention participants had significantly greater improvement in diabetes social support scales—as expected, given the nature of the intervention—but did not demonstrate differences in diabetes-specific distress or in medication adherence.

These promising findings need to be considered in the context of several important limitations of the study, including the lack of diversity—only male veterans participated—and the short duration of the intervention. They suggest, however, that a reciprocal peer model, in which peers provide support to each other, can be an effective and efficient approach to help people with diabetes help each other and themselves. Because the intervention used peers, rather than medical staff, and used inexpensive phone technology, delivery of the intervention was low cost. Low-cost interventions are likely to be far easier to disseminate, which could potentially yield a high return on investment. From a health care staff perspective, the intervention was far less time-intensive than other tested programs that achieved similar or smaller improvements in glycemic control.

Research within the VA system has certain advantages that promote a lower cost structure for research: 1) its electronic medical records with extensive integrated data allows ease of

identifying and recruiting potential patients and for follow-up; 2) it has a large existing research infrastructure and experience; and 3) as a national system, it leads to easier collaboration across sites. A current question in VA is the generalizability and broader applicability of VA research and how to disseminate this type of work. Therefore, VA is strongly evaluating less traditional approaches to interventional research, with a particular focus on how to roll out interventions that have had success on a smaller scale.

Unique Diabetes-Related Research Opportunities in the Department of Defense (DOD)
COL Robert A. Vigersky, M.D., DOD

DOD maintains a serum repository in which 75% of active duty service members have provided three or more longitudinal specimens, collected every 2 years. These, in addition to records of immunizations, deployments, military assignment data, records from pre- and post-deployment health assessments, as well as select medical outcomes, constitute a cohort where health events can be assessed longitudinally with minimal ascertainment bias. As of 2007, the repository held over 43 million specimens from more than 10 million individuals and continued to collect approximately 2 million specimens each year. This resource can be valuable for health research, and specimens are usable, pending Institutional Review Board (IRB) approval, by the broad scientific community. For example, a cluster of type 1 diabetes was observed among active duty military; between 2005-2006 six, non-obese, white navy pilots presented with the disease at the same base. Samples in the repository and health records of the patients allowed for longitudinal observations of vaccinations, serology, and diagnosis to develop a timeline of when the patients became positive for autoantibodies and to ascertain their genetic risk for type 1 diabetes.

The DOD's Pharmacovigilance Center aims to provide timely and actionable medication safety information by monitoring medical product exposures to ensure that these medications maintain and improve the health of the forces and beneficiaries of the DOD Healthcare System. Partners of the Pharmacovigilance Center include the U.S. Food and Drug Administration, TRICARE Management Activity/DOD, Surgeon General, and Telemedicine and Advanced Technology Research Center/U.S. Army Medical Research and Material Command. The scope of the Pharmacovigilance Center includes: passive surveillance, directed surveillance, active surveillance, and risk management/risk mitigation. Seven uniformed services and beneficiaries are eligible for analysis, totaling data from over 9 million people and almost 90 million prescriptions in 2009.

The current military endocrinology workforce includes 33 adult and 16 pediatric endocrinologists located at several different sites in the U.S. and in Germany. This network has enabled several multi-center studies. For example, three studies are looking at the etiology of type 1 diabetes. The first examined the prevalence of type 1 diabetes among active duty military in 1997-2007 utilizing the Defense Medical Surveillance System; the second is establishing active surveillance for type 1 diabetes at eight medical treatment facilities; and the third is a case-control study for the genetic and environmental risk factors for type 1 diabetes. The military is an optimal population in which to conduct such case-control studies: the serum repository allows for measurements of serial autoantibody levels and viral serologies, there is a network of endocrinologists established, and the study should be able to recruit an adequate number of newly diagnosed type 1 diabetes patients in 1-2 years. In another example, investigators are conducting a multi-center study to evaluate computer-assisted decision support for primary care

in type 2 diabetes. By inputting a target hemoglobin A1c and patient information (laboratory data, medical and medication history), the system will generate a recommendation for therapy to primary care providers. The trial will include over 500 patients with 30 primary care providers in 3 geographic locations and last for 1 year, with possible extension.