

# **Federally Sponsored Comparative Effectiveness Research in Diabetes**

## **Information and Perspectives from Member Agencies of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) DMICC Meeting of April 30, 2010**

Many of the member agencies of the DMICC conduct or support comparative effectiveness research (CER) studies that can help identify optimal approaches for prevention and treatment of diabetes and/or its complications. Member agencies whose missions include regulation or reimbursement also have an interest in CER studies. The DMICC met on April 30, 2010, to hear about examples of federally supported CER in diabetes and to identify gaps and opportunities. One common thread in these discussions was the need for CER to be applicable to “real world” situations for patients, policy makers, and other stakeholders.

As noted by several speakers, the American Recovery and Reinvestment Act (ARRA) of 2009 provided over \$1 billion in funding for CER, and charged the Institute of Medicine (IOM) to form a consensus committee and solicit stakeholder input to recommend national priorities for spending CER funds designated for the Secretary of the Department of Health and Human Services (DHHS). The resulting IOM report, [“Initial National Priorities for Comparative Effectiveness Research”](#) (2009), includes a comprehensive discussion of CER research and federal activities in CER.

### **CER Overview: The 2010 NIH Vision for CER—Michael S. Lauer, M.D., FACC, FAHA, National Heart Lung and Blood Institute (NHLBI)**

Dr. Lauer highlighted two definitions of CER, one from the Congressional Budget Office (CBO; 2007) the other from the IOM report (2009):

**CBO:** “...a rigorous evaluation of the impact of different options that are available for treating a medical condition...”

...may compare similar treatments, such as competing drugs--or analyze different approaches  
...may focus on medical risks/benefits, or weigh costs.”

**IOM:** “CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.”

Using as an example the once-common medical practice of bloodletting, Dr. Lauer provided a historical context for CER and also traditional challenges to this research, illustrating how, even with evidence, it can be hard to shake beliefs and change practice. He described modern examples of the same phenomenon, in which there have been widely accepted procedures or treatments whose assumed benefit did not withstand rigorous scientific testing. For example, a recent NHLBI-supported clinical trial demonstrated that, contrary to then-common thought and

practice, angioplasty is less, not more, beneficial than medical treatment for an occluded coronary artery caused by heart attack. He noted that continuing challenges to conducting CER and/or implementing its results include: (1) logic, belief, personality, hope (and hype); (2) excessive reliance on observational data; (3) real conflicts of interest; and (4) inertia.

The National Institutes of Health (NIH) has been supporting CER studies for decades. This work has been further stimulated by ARRA, which included allocations of \$400 million for NIH, \$300 million for the Agency for Healthcare Research and Quality (AHRQ), and \$400 million for the Office of the DHHS Secretary to support CER. It also called for formation of a federal coordinating council for CER and the 2009 IOM report on CER top priorities. Although CER continues to spark controversy due to the challenges outlined above, Dr. Lauer noted that it is a national and NIH priority. For the future, NIH envisions: clinical trials that are cheaper, faster, and more pragmatic; a role for NIH in the new Patient-Centered Outcomes Research Institute called for in the Patient Protection and Affordable Care Act (2010); and that CER will continue to be conducted for the benefit of patients, the most important stakeholders in CER.

### **Diabetes CER—Judith Fradkin, M.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**

Dr. Fradkin highlighted four major issues that are the focus of diabetes CER studies: (1) levels of control (A1C, blood pressure, blood lipids), for staving off diabetes health complications; (2) diabetes prevention; (3) early intervention; and (4) comparison of medications. Many aspects of the first two have already been addressed through a number of clinical trials spearheaded and/or supported by NIDDK, such as the Diabetes Control and Complications Trial and its follow-up Epidemiology of Diabetes Interventions and Complications study; the United Kingdom Prospective Diabetes Study; Action to Control Cardiovascular Risk in Diabetes (ACCORD) (led by NHLBI); and the Diabetes Prevention Program. While some gaps and questions remain regarding specific prevention and treatment options and goals, particularly among specific populations (e.g., glycemic control in patients who are older and/or have multiple comorbidities), overall, these and other diabetes CER studies have provided a robust evidence base for diabetes control and prevention strategies.

However, the benefits of aggressive intervention early in the course of type 2 diabetes (versus in long-established disease, such as was studied in ACCORD) remain an open question. Yet, due to the threat of complications, this is a critical question, especially among youth with type 2 diabetes who could potentially develop complications at a younger age and thus live with them longer. This population is being studied in the NIDDK-led Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, which is comparing the effectiveness of three different treatment regimens in children 10-17 years of age by measuring a relatively short-term outcome, time to failure of glycemic control. Dr. Fradkin noted that determining the long-term benefits of treating the newly diagnosed, and whether early intervention alters the course of disease, will require a substantial and sustained investment. Similarly, performing rigorous comparisons of oral medications for type 2 diabetes to determine which regimens (e.g., monotherapies, combination therapies) provide the greatest benefit when, and to whom, will require a major research investment; currently, there are no data supporting which drug(s) is the best one to add after the first line recommended drug, metformin. The most appropriate outcomes to measure for such studies also remain a question—e.g., A1C, body weight/body composition, cardiovascular disease (CVD) risk factors, beta cell preservation, and safety.

Moreover, it is extraordinarily challenging with current clinical trial designs to have enough statistical power to assess the comparative effectiveness of interventions in ameliorating diabetes complications. Assessing the benefits of early, aggressive intervention and conducting comparisons of medication regimens to determine those of greatest benefit (and to whom) are the current major challenges for diabetes CER.

#### **CER at NHLBI—Michael S. Lauer, M.D., FACC, FAHA, NHLBI**

Dr. Lauer provided a case for conducting CER in CVD: Per capita Medicare spending varies greatly throughout the country; however, higher medical expenditures do not appear to lead to better outcomes. At the same time, more expensive treatments may be being adopted in the absence of rigorous assessments of their impact; nearly half of the recommended CVD clinical practice guidelines developed by the American College of Cardiology (ACC) and the American Heart Association rely on expert opinion alone, while only 11 percent have a robust scientific evidence base from multiple randomized controlled trials (RCTs). NHLBI has been supporting various types of CER studies in CVD, including drug vs. drug; surgery vs. medical treatment; lifestyle approaches vs. medical treatment; and surgery vs. surgery. For example, the STICH trial found that adding left ventricular reconstructive surgery to coronary artery bypass surgery did not improve outcomes for patients with heart failure. Dr. Lauer added that a substantial amount of CER is observational work based on analyses of treatments and outcomes in electronic health records (EHR) from large numbers of people; the HMO Research Network is the largest example of this. The NHLBI equivalent of the HMO Research Network is the [Cardiovascular Research Network](#), which involves 15 integrated health care systems providing care to 11 million people, most of whom are captured in EHRs. A number of CVD-related studies are being supported through this network. The studies provide opportunities for collaboration between federal and non-federal institutions; e.g., a study on defibrillator use is a collaboration between the HMO Research Network, AHRQ, NHLBI, and the ACC. Following a brief summary of ongoing NHLBI CER studies, including research supported by ARRA funds, Dr. Lauer noted that the 2009 IOM report listed a number of priorities for CER research in CVD. Moving forward, NHLBI sees continued support of CER as an important opportunity to bolster the evidence base for practice. Also, while the large-scale observational studies in CER are very informative, it will be important to continue to conduct and improve clinical trials, and to add diagnostic tests to the items studied in clinical trials.

#### **AHRQ CER Progress Report—Barbara A. Bartman, M.D., M.P.H., and Christine Chang, M.D., M.P.H., AHRQ**

Dr. Bartman described the structure and process of AHRQ's [Effective Health Care \(EHC\) program](#), which was established in 2005 to improve the quality, effectiveness, and efficiency of health care delivered through Medicare, Medicaid, and S-CHIP programs by focusing on the research base and clinical effectiveness. Diabetes is one of a number of priority conditions addressed through this program, which has now been augmented by ARRA funds. The EHC program conducts its business in three parts: evidence synthesis, in which experts systematically review and compare evidence on treatment effectiveness, and identify relevant knowledge gaps (Evidence-based Practice Centers (EPCs)); evidence generation, in which experts harness information from existing data to address knowledge gaps (Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network); and evidence communication/translation, in which writers convert the information generated by the EPCs into plain language for consumers,

clinicians, and policymakers (Eisenberg Center). Stakeholder input is an important aspect of the work of both the EPCs and the DEcIDE Network.

Dr. Chang provided a more detailed description of the EPC systematic review process—how comparative effectiveness topics are generated and selected; the methods used to collect, compare, and assess evidence relevant to specific questions and outcomes for each topic; how the strength of the evidence is rated; and generation and dissemination of final reports for patients, clinicians, and other end-users and partners (e.g., NIH, the U.S. Preventive Services Task Force, and others). Input is collected from a variety of stakeholders (patients, clinicians, policymakers, funders, organizations, and researchers) throughout the review process to help make the final products both relevant and useful for users—e.g., for informing policy decisions, research agendas, guidelines, and health care decisions. Further, she described how the EPCs identify, flesh out, and prioritize research gaps for a particular topic. Dr. Chang also provided several examples of comparative effectiveness reviews conducted by the EPCs that are related to diabetes, including a completed review on “Comparative Effectiveness, Safety, and Indications of Pre-mixed Insulin Analogues for Adults with Type 2 Diabetes,” and one in the process of being updated, “Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes.” (More information about the EPCs and their role in the EHP is available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-evidence-based-practice-centers-epcs/> )

Dr. Bartman provided a more detailed description of the processes used by the DEcIDE Network to generate evidence and accelerate practical studies. The Network is comprised of academic, clinical, and practice-based centers with access to electronic health information databases and the capacity to conduct accelerated research. In 2008, the Network developed consortia to focus on specific topics, including cancer, CVD, and diabetes. The goals of the Diabetes Multi-Center Research Consortium (DMCRC) are to support studies that address research gaps identified in systematic reviews, support harmonization of studies in diabetes, and to utilize and link data from multiple sources (e.g., administrative claims, electronic medical records, registries); it is hoped that the DMCRC may also be able to support studies with new data collection in the future. The Coordinating Center for the DMCRC is the HMO Research Network, and the affiliate center is at Johns Hopkins University. The DMCRC has multiple studies in progress, and several consortium committees are working on a variety of other activities, such as data/methods validation issues and soliciting stakeholder input. Dr. Bartman closed with a description of future efforts and goals for the DEcIDE Network.

(More information about the DEcIDE Network is available at: <http://effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-the-decide-network/> )

### **Diabetes CER and the FDA (Part I): Regulatory Requirements for Diabetes Drug Approval—Hylton V. Joffe, M.D., M.M.Sc., U.S. Food and Drug Administration (FDA)**

Dr. Joffe discussed the FDA’s requirements for diabetes drug approval, an issue that overlaps with CER. FDA has published two guidance documents on diabetes for use by sponsors seeking to develop and get diabetes drugs approved: “Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (draft)” and “Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.” The

agency intends to develop a single, unified guidance for diabetes once the draft document has been finalized. FDA uses A1C as the efficacy endpoint; no improvement in micro- or macrovascular endpoints is required. In traditional phase 3 studies, investigational drugs may be tested in placebo-controlled or active (i.e., treatment)-controlled trials, but the latter are typically studies simply to establish that an investigational drug is not inferior to a drug(s) already in use. Prior to the recent diabetes guidances, study populations used for FDA approval of diabetes drugs were less diverse in terms of disease progression and complications, limiting how well they represented a drug's efficacy in a "real world" diabetes population. The diabetes CVD guidance now highlights the elevated CVD risk for people with diabetes and asks sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase CVD risk. The guidance outlines ways to quantify risk, and requests minimum sample sizes for study over particular time periods, and the number of total major CVD events that need to be seen for valid assessments of drug safety regarding CVD both pre- and post-marketing. He described some examples of how sponsors are addressing CVD safety, such as through dedicated CVD trials separate from the diabetes efficacy trial, or conducting a "superiority trial" to show CVD benefit of the investigational drug. Dr. Joffe ended by highlighting some examples of active-controlled trials for diabetes drugs, such as ADOPT, which is comparing rosiglitazone vs. metformin vs. sulfonylurea.

### **Diabetes CER and the FDA (Part II): Post-marketing Surveillance and Evaluation of Drug Safety at the FDA—Hui Talia Zhang, M.D., Ph.D., FDA**

Dr. Zhang described the goals and activities of post-marketing safety assessments by the FDA, noting that the RCTs that demonstrate a drug's efficacy for FDA approval are conducted under "ideal" conditions and have limitations when it comes to ascertaining all the safety issues that may be encountered with a drug in "real world" settings (including long-term effects). Components within the FDA's Office of Surveillance and Epidemiology focus on comparative safety issues in post-marketing assessments. The Divisions of Pharmacovigilance I and II focus on information collected through the Adverse Event Report System (AERS) to detect events that signal safety issue(s) and possible trends or risk factors. Because the AERS is supposed to receive any adverse event reports about drugs on the U.S. market, the population "studied" is much larger and more diverse than in a typical RCT, the time period for data collection is longer, and broader data are also available (e.g., about "off-label" use); however, there are also limitations to the AERS data that constrain the assessments that can be made—e.g., the data cannot be used to calculate incidence rate for events. Using a variety of data sources, the Division of Epidemiology conducts and supports epidemiology reviews, extramural research, and, newly, intramural research, to further evaluate safety issues for drugs; this research includes collaborations with federal partners.

Dr. Zhang also noted that the FDA Amendment Act of 2007 has given FDA new regulatory authorities that directly affect safety issues—e.g., FDA can require post-marketing safety studies by sponsors, and require sponsors to make safety-related labeling changes. The Act also required FDA to develop a system for active post-marketing surveillance; FDA's goal is to develop a nationwide electronic safety monitoring system through the Sentinel Initiative. In closing, Dr. Zhang noted that sources of post-marketing drug safety detection include the AERS, a sponsor's post-marketing safety data, medical literature, clinical trials of the drug for other uses, and revisiting the pre-marketing data to perform meta-analyses. In conducting comparative

safety assessments, being cognizant of methodological limitations of analytic epidemiology studies is important, as is validation of safety issue signals through analysis of multiple data sources.

### **Diabetes CER and CMS—James Rollins, M.D., M.S.H.A., Ph.D., Centers for Medicare & Medicaid Services (CMS)**

Dr. Rollins addressed CER from the perspective of payers and policy makers. CER is being performed not only by federal agencies, but by commercial insurers, to identify treatments with better outcomes and assist decision-making (e.g., guidelines for treatment, payment policies). There are a number of diabetes treatments for which CER would be very useful in coverage decisions by private organizations. CER could also provide information on the impact of different options available for treating the Medicare population. CMS covers millions of Medicare beneficiaries with diabetes, with costs that are predicted to jump from \$45 billion to \$171 billion in the next 25 years. Current law is silent on the use of CER by CMS for decision-making. Under current policy and law, CMS generally covers any treatment that is “reasonable and necessary,” regardless of its effectiveness or its cost relative to alternative treatments; CER is not used in these decisions.

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*For general information about the history, goals, membership, and activities of the DMICC, please see the [DMICC web page](#) or the publication, [“DMICC: Coordinating the Federal Investment in Diabetes Programs To Improve the Health of Americans.”](#)*

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#### Speakers

Dr. Bartman, AHRQ  
Dr. Chang, AHRQ  
Dr. Fradkin, NIDDK  
Dr. Joffe, FDA  
Dr. Lauer, FDA  
Dr. Rollins, CMS  
Dr. Zhang, FDA

Dr. Heindel, NIEHS (by phone)  
Dr. Jerkins, CSR  
Dr. Jett, NINR  
Dr. Khalsa, NIDA  
Dr. Koller (for Dr. Roman), CMS  
Dr. Krasnewich, NIGMS  
Dr. Kugler, DOD  
Dr. McLaughlin, NIBIB  
Dr. Ommaya (for Dr. Pogach), VHA  
Dr. Rosenblum, NCRR  
Dr. Shen, NEI  
Dr. Wu, HRSA

#### DMICC Members Attending

Dr. Fradkin, NIDDK, Chair  
Dr. Garfield, NIDDK, Executive Secretary  
Dr. Acton, IHS  
Dr. Atkinson, NIDCR  
Dr. Avilès-Santa, NHLBI  
Dr. Bartman, AHRQ  
Dr. Dankwa-Mullan, NCMHD  
Dr. Duffy, NCCAM  
Dr. Dutta, NIA  
Dr. Gao, NIAAA  
Dr. Grave, NICHD  
Dr. Gregg (for Dr. Albright), CDC  
Ms. Hayes, HHS OASH,

#### DMICC Members Not Attending

Dr. Chavez, NIMH  
Dr. Graham, HHS OMH  
Dr. Li, NHGRI  
Dr. Parks, FDA  
Dr. Penn, NINDS  
Dr. Peyman, NIAID  
Dr. Post, DOA  
Dr. Siegel, NLM  
Dr. Wong, NIDCD

