Long-term Outcomes of Bariatric Surgery
Diabetes Mellitus Interagency Coordinating Committee (DMICC) Meeting

May 23, 2013
Draft Meeting Summary

Current Major Bariatric Surgery Long-term Outcome Gaps—David Arterburn, M.D., M.P.H., Group Health Research Institute
Potential Paths Forward for Obtaining Needed Long-term Bariatric Surgery Outcomes—Anita Courcoulas, M.D., M.P.H., University of Pittsburgh Medical Center

Drs. Arterburn and Courcoulas, the Co-Chairs of the Long-term Outcomes of Bariatric Surgery meeting, jointly presented a synthesis of the conference results to the DMICC. Dr. Courcoulas commented that the 1.5-day meeting, attended by international experts, represented an exciting collection of multidisciplinary studies intended to address the current outcomes of bariatric surgery and consider future directions for the field to obtain needed long-term bariatric surgery outcome data. The charge for the workshop was to answer the following questions:

- What is the firmly established evidence on the long-term health and economic outcomes of bariatric surgery?
- What are the major gaps in the evidence on the long-term health and economic outcomes of bariatric surgery? Will any of these gaps be addressed via ongoing, currently funded research studies? Would closing these gaps provide compelling evidence for providers, patients, and payers?
- What is the optimal design needed to address any of these major gaps in evidence? What would be the appropriate outcome measures? Is that optimal design feasible and if not, what is an acceptable alternative?

The meeting agenda was designed to review current studies; consider long-term aspects of bariatric surgery; reflect on the perspectives of the payers, medical research organizations, and other stakeholders;; and discuss the gaps and how to leverage current studies. Clinical research reviewed included the Longitudinal Assessment of Bariatric Surgery (LABS), Teen LABS, Swedish Obese Subjects (SOS), Utah Obesity Study, and ongoing NIH-sponsored and non-NIH-sponsored randomized clinical trials (RCTs). Outcomes considered included survival; weight loss durability; cardiovascular disease (CVD) outcomes (*e.g.*, hypertension, lipids); lung disorders (*e.g.*, sleep apnea, asthma); diabetes (*e.g.*, mechanisms, micro- and macrovascular events); and the impact of bariatric surgery on cancer. Also considered were outcomes of patients receiving bariatric surgery for treatment of relatively moderate obesity (body mass index (BMI) of 30 to 35), which is important because insurance does not generally cover bariatric surgery for people with a BMI of less than 35. Perspectives from payer organizations and care delivery systems (*e.g.*, Kaiser Permanente, U.S. Department of Veterans Affairs [VA]) were presented. Organizations such as the Patient-Centered Outcomes Research Institute (PCORI) and the Agency for Healthcare Research and Quality (AHRQ) provided additional perspectives.

Drs. Arterburn and Courcoulas reported that some of the most compelling findings presented at the meeting came from the SOS, the largest prospective study on bariatric surgery to date, although not a randomized controlled trial. More than 2,000 patients were tracked for 20 years following one of three separate surgical procedures: gastric bypass, vertical-banded gastroplasty, or gastric banding. A new

technique, sleeve gastrectomy, was not included in this seminal study of long-term outcomes. Durable weight loss was found following all of the techniques, with gastric bypass resulting in the highest percentage of body weight loss. All of the techniques were superior to the usual care of medical management. The SOS study presented a number of important findings. First, it demonstrated that patients who underwent bariatric procedures had an 80 percent risk reduction of diabetes incidence, suggesting that diabetes can be reduced significantly through durable weight loss. Beyond diabetes remission, the patients who underwent bariatric surgery experienced a 37 percent risk reduction in major CVD events over time. Bariatric surgery also reduced the incidence of cancer by 33 percent during a 16-year follow-up. Interestingly, the reduction occurred primarily in female patients. The overall survival curve of bariatric surgery patients showed a 29 percent reduction in mortality over 16 years compared to medical management. Additional manuscripts have determined that bariatric surgery is more favorable than medical management for long-term effects related to body weight, diabetes incidence and remission, albuminuria, CVD incidence and CVD risk factors, cancer, drug costs, and mortality. Importantly, glucose and insulin, rather than BMI, are predictors of long-term effects. A follow-up study to the SOS is ongoing; updated data from contemporary procedures are needed to inform current medical practices.

The Utah Obesity Study, funded by the NIH, is a more recent evaluation of 1,156 severely obese control and gastric bypass patients. The study employed a unique prospective approach to recruit patients seeking bariatric surgery and equally obese individuals not seeking bariatric surgery. The study confirmed prior findings: a 62 percent rate of diabetes remission was achieved after 6 years. Other favorable results were found for hypertension and diabetes incidence.

The Longitudinal Assessment of Bariatric Surgery (LABS) is an observational prospective cohort involving multiple clinical sites and centers across the United States. The distinguishing feature of LABS is the approach to data collection: measurements are performed on a standardized assessment. The first of three LABS phases, which is a short-term safety study, has been completed; this 30-day trial showed a mortality of 0.3 percent. A composite adverse outcome endpoint was created and determined to be 4.3 percent. The composite adverse end point was lowest among patients who did not have a history of deep-vein thrombosis or venous thromboembolism or of obstructive sleep apnea and who were in the middle range of the spectrum of body mass index for the cohort. The second phase of LABS includes a long-term safety and efficacy study of bariatric operations. LABS 2 outcome domains include weight loss and body composition, diabetes, CVD, behavioral/psychosocial factors, gender issues, nutrient deficiencies, and economic impact. The laboratories will collect many biospecimens in a large repository, which will be available for ancillary studies as well. The emphasis of LABS is on retention and obtaining complete and standardized data from subjects. The third phase of LABS is examining the physiological mechanisms by which these procedures can result in diabetes remission, and psychosocial outcomes. Additional ancillary studies are investigating topics ranging from reproductive outcomes to cognitive functioning.

The largest randomized trial of bariatric surgery in the moderately obese to date is the Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study performed by the Cleveland Clinic. One hundred and fifty patients were randomized to gastric bypass, sleeve gastrectomy, or intensive medical therapy. Approximately 34 percent of patients had a BMI lower than 35. Gastric surgery resulted in lower levels of glycated hemoglobin (an indicator of diabetes) as well as lower medication use and improvements in lipids and hypertension compared to the control medical therapy group. Patients in this study will be followed for 5 years.

Another study compared the diabetes remission rates for people who received conventional medical therapy, to those who received either of two bariatric surgery procedures, laparoscopic gastric bypass or biliopancreatic diversion (BPD). The 2-year trial followed 60 patients with a history of diabetes. Patients who underwent the bariatric surgical procedures experienced a higher rate of diabetes remission than the

control medical therapy group: At 2 years, none of the medical therapy patients had experienced diabetes remission, while 75 percent of gastric bypass and 95 percent of BPD patients did achieve diabetes remission. Surgical patients were able to discontinue use of medications to treat their diabetes within 15 days of surgery, and the procedures resulted in better glucose control. This study also showed that baseline BMI was not a significant predictor of remission.

Additional RCTs addressing the type 2 diabetes patient population were discussed, including NIH-funded feasibility pilot studies to address outcomes of bariatric procedures in people with BMI less than 35. The Surgery or Lifestyle with Intensive Medical Management in the Treatment of Type 2 Diabetes (SLIMM-T2D) compares banding and bypass procedures to medical treatment. Patients were consulted for their surgical preference prior to the treatment and then were randomized to receive either surgery or medical treatment. The enrollment of the band subjects was delayed due to regulatory issues with its use in lower BMI subjects. The Triabetes Study is a pilot feasibility study in comparing two types ofbariatric surgery to an intensive lifestyle intervention similar to the one used in the Action for Health in Diabetes (Look AHEAD) trial. Triabetes-2 enrolled 20 subjects in each of three trial arms. The 4-year follow-up will conclude next year. The Surgery or Lifestyle Intervention for Diabetes (SOLID) trial wasintended to be a randomized trial, but was converted to an observational trial as recruitment into the surgical arm was difficult due to a lack of insurance coverage for lower BMI individuals. . The Calorie Reduction or Surgery: Seeking Remission for Obesity and Diabetes Study (CROSSROADS) used a population-based, shared decision-making approach to identify participants and found that very large numbers of potential participants were needed to recruit one at equipoise for surgical versus medical treatments. The 32 member cohort includes some participants with BMIs less than 35. The Improving Diabetes Through Lifestyle and Surgery (IDeaLS) study is seeking to enroll a cohort with one-half of its participants below a BMI of 35. The Stampede II trial is investigating the mechanisms underlying the bariatric surgery outcomes. One trial addressing the obstructive sleep apnea patient population is the Apnea, Bariatric, Continuous Positive Airway Pressure (ABC) trial, which will compare bariatric procedures with respect to sleep apnea outcomes.

Features common to many of the ongoing trials include an intensive lifestyle intervention control group, a subset of participants with BMI under 35, and specific feasibility and diabetes treatment endpoints. These similarities can potentially be leveraged to increase statistical power by pooling data. Each of the studies faces challenges, however: the feasibility of randomization and retention after randomization among subjects is difficult, and there is debate about whether there is true equipoise among various treatment arms. Even the SLIMM-T2D trial, which asked patients which procedure they would prefer, experienced an 11 percent post-randomization dropout rate. Further, it is difficult to fund surgical procedures for potential enrollees with a BMI less than 35, for whom insurance coverage is often unavailable, or contingent on prior failure of a 6-month intensive lifestyle intervention.

The consensus from the conference was that many research gaps have been filled. For example, it is clear that bariatric surgery procedures are superior to medical lifestyle interventions for short- and long-term weight loss, and for initial type 2 diabetes remission. Quality of life was found to be related to weight-change durability, and was therefore better in participants who underwent bariatric procedures than in control participants. Nutritional problems were found to be predictable and preventable through nutritional management. And there is growing consensus that mortality also decreases following bariatric procedures.

Major research gaps remaining include: the need for standardized reporting of surgical complications; the long-term durability of diabetes remission; the impact of bariatric procedures on microvascular complications and cardiovascular complications of diabetes need to be investigated; more research is needed to compare outcomes in the growing number of available surgical procedures; more evidence is needed to solidify conclusions on patient mortality; a better understanding of long-term cost effectiveness,

and improved predictors of which potential patients are most likely to benefit are critical for informing health-care policy; improved evaluation of mental health outcomes; an improved understanding of the apparent increase in risk for alcohol use, suicide, binge eating, and depression in bariatric versus nonsurgical patients are of considerable importance; reproductive health outcomes need to be better understood, including pregnancy-related complications; and sufficient numbers of study participants with a BMI less than 35 are needed to better understand long-term outcomes and benefits from bariatric surgery in this key group.

The meeting participants discussed how to obtain evidence efficiently to move the field forward toward addressing the research gaps. It is clear that additional follow-up funding will help to address the long-term durability of diabetes remission and weight loss from bariatric surgery, along with an opportunity to standardize long-term outcome collection across multiple studies. RCTs provide one mechanism to address the key gaps, as they offer the strongest study design and reduce concerns about confounding between interventions. Non-NIH-sponsored RCTs also provide the opportunity to pool additional subjects. Limitations of RCTs include the heterogeneity in study design and data collection, potential unwillingness of participants to accept randomization between medical and surgical treatments, and a need for better statistical methods and increased power. As many as 10-fold more subjects and 10 years of follow-up might be needed to consider outcomes, including CVD, microvascular events, death, and cancer; this level of effort might not be possible in the current fiscal climate. Potential collaboration across healthcare and payer organizations such as the VA and Wellcome Trust might help to fund an RCT addressing important bariatric surgery outcomes for patients with T2D. To address the concern of controls, one idea is to leverage control populations from other NIH-funded lifestyle studies, such as Look AHEAD, in a case-control design, and evaluate a combined endpoint. The strengths of this approach include the efficient follow-up of existing cohorts and rigorous statistical analysis, while limitations include heterogeneity across studies and the complication that no lifestyle patients without diabetes or prediabetes were enrolled in the original studies. Some expansion of the surgical cohort might be needed as techniques such as sleeve gastrectomy increase in popularity.

Valuable information may also be obtained from existing clinical databases. The national VA cohort and health maintenance organization (HMO) research network totals 43,000 bariatric cases and 3.5 million controls. These data can be used to guide future randomized trials as well as to answer questions regarding mortality, cost, and comorbidities. Strengths to this approach include a large sample size, efficient electronic data collection, high retention rates, and a diversity of surgical centers and populations; limitations such as a lack of quality-of-life data and incomplete clinical data must be overcome.

Drs. Arterburn and Courcoulas commented that there is no easy route forward, as each approach has different strengths and limitations. The most cost- and time-efficient method is to analyze existing databases and cohorts. Expanding existing large observational cohorts (e.g., LABS, Utah Obesity Study) would be the next most cost- and time-efficient approach. The most expensive but scientifically rigorous approach is to design and execute an appropriately powered RCT. In conclusion, Drs. Arterburn and Courcoulas agreed that the meeting provided an opportunity for significant discussion about the outcomes of bariatric surgery, which is important to allow patients, providers, and policy makers to make informed choices about which procedure to select, how to optimize long-term follow-up, and whom to cover.

Closing Comments—Judith Fradkin, M.D., Chair, DMICC, NIDDK, NIH

Dr. Fradkin expressed appreciation to the speakers, DMICC members, and meeting attendees for their participation. She encouraged the participants to consider what can be done within limited budgets to address the key issues regarding bariatric surgery. Dr. Fradkin said that hopefully, research investigators will consider submitting R01 applications to study the identified gaps. The next DMICC meeting will be the *Ad Hoc* DMICC Planning Meeting on Type 1 Diabetes Research on June 6 to 7, 2013, which will

evaluate the management of the special type 1 diabetes funds. External scientists will contribute their input on proposals collected from across the NIH and Centers for Disease Control and Prevention (CDC) that present opportunities for research on type 1 diabetes. Dr. Fradkin encouraged DMICC members to attend the Planning Meeting. Two DMICC meetings are planned for fiscal year (FY) 2014. One meeting will address diabetes in youth, and the other meeting will be led by the National Institute on Aging (NIA), which recently sponsored a meeting to consider research questions related to CVD and diabetes in the elderly. Dr. Fradkin thanked the DMICC members for their efforts and adjourned the meeting.

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."

Speakers
Dr. Arterburn, Group Health Research Institute
Dr. Courcoulis, University of Pittsburgh Medical Center
Dr. Wong, NIDCD

DMICC Members Attending
Dr. Fradkin, NIDDK, Chair
Dr. Roberts, NIDDK, Executive Secretary
Dr. Alekel, NCCAM
Dr. Bartman, AHRQ
Dr. Gillikan (for Dr. Frant), NLM
Dr. Graves, CSR
Dr. Koller (for Dr. Roman), CMS
LCDR Plummer (for Dr. Kugler), DOD
Dr. Saydah (for Dr. Albright), CDC

DMICC Members Not Attending
Dr. Atkinson, NIDCR
Dr. Alvilés-Santa, NHLBI
Dr. Bosetti, NINDS
Dr. Bourcier, NIAID
Dr. Chavez, NIMH
Dr. Conroy, NIBIB
Dr. Dankwa-Mullan, NIMHD
Dr. Dutta, NIA
Dr. Gao, NIAAA
Dr. Grave, NICHD
Dr. Heindel, NIEHS
Dr. Khalsa, NIDA
Dr. Krasnewich, NIGMS
Dr. Li, NHGRI
Dr. Olson, HHS
Dr. Parks, FDA
Dr. Pogach, VHA
Dr. Post, DOA
Dr. Rosenblum, NCATS
Dr. Shen, NEI