DSS: Diabetes **S**urgery **S**tudy

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Abstract

Type 2 diabetes mellitus (T2DM) is a major contributor to cardiovascular disease (CVD). Individuals with T2DM are at particularly high risk for CVD morbidity and mortality. Medical management of glycemia and CVD risk factors has been shown to ameliorate complications of T2DM and CVD events. However, variable response to treatment, suboptimal compliance, and adverse effects limit the success of medical management strategies for T2DM. The Roux-en-Y gastric bypass (RYGB) has resulted in dramatic remission in T2DM in many severely obese patients. Positive response to RYGB has been estimated to be as high as 82%. In retrospective studies, superior clinical outcomes for those undergoing bariatric surgery have been observed compared to those undergoing conventional medical management. Currently, utilization of the RYGB is commonly limited to patients with body mass index (BMI) ≥ 35.0 kg/m^2. The efficacy and effectiveness of the RYGB for T2DM patients with BMI < 35.0 kg/m^2 have not been studied prospectively.

The present study, the Diabetes Surgery Study (DSS) is a randomized clinical trial involving type 2 diabetics with BMI from 30.0 to 39.9 kg/m^2. This program is designed to determine the relative effectiveness of RYGB combined with intensive medical management and lifestyle modification (IMM), versus IMM alone, in reducing CVD event rates and mortality in patients with poorly controlled diabetes. IMM includes rigorous lifestyle modification for weight loss and stepped pharmacologic treatment for diabetes and other CVD risk factors. The DSS is a randomized multicenter trial which provides an assessment of the effectiveness of RYGB treatment in reducing CVD risk factors and also provides information on the feasibility, cost, and safety of a larger trial.

The DSS is being conducted collaboratively by multiple research centers. The study has recruited and randomized 120 patients to two arms (60 to RYBG with IMM, and 60 to IMM alone) and will follow them for 60 months to assess safety, efficacy and compliance with clinical and research procedures. The primary outcome is assessed at one year, and is a composite of parameters of optimal diabetes management: glycosylated hemoglobin (HbA1c) < 7.0%, fasting LDL cholesterol < 100 mg/dl (2.59 mmol/L) and systolic blood pressure < 130 mmHg. The Intervention continues for a total of two years and then patients will have three years of observational-only follow-up, for a total of 5 years under observation. The purpose of follow-up in years 2-5 is to determine the durability of the outcomes and to monitor for adverse events and complications.

The DSS is the first randomized clinical trial comparing surgical and medical treatments of T2DM with respect to CVD endpoints in patients with a BMI less than 35.0 kg/m^2. The randomized clinical trial is clearly justified to establish whether RYGB substantially reduces risk factors for CVD events and all-cause mortality. Studying this group will specifically increase the applicability of the trial to the broader diabetic population, both nationally and internationally.

A. Specific Aims

Type 2 Diabetes Mellitus (T2DM) is a serious health problem that has increased dramatically worldwide due to the high and increasing prevalence of over-nutrition and subsequent obesity.[1] Medical management of T2DM is often of limited success.[2] Recent data on the relative effectiveness of Roux-en-Y gastric bypass (RYGB) surgery as a treatment for T2DM suggests that it may be significantly more effective in managing diabetes and its co-morbidities than medical management alone.[3,4,5] Data supporting the RYGB have been retrospective, and have been largely limited to regimens intended mainly for the treatment of morbid obesity, with other benefits being viewed as ancillary. No randomized clinical trials have been performed to evaluate the effectiveness of the procedure in reducing adverse health outcomes in patients with T2DM with a BMI less than 35.0 kg/m^2. A small prospective cohort suggests improvement in diabetic parameters, without excessive weight loss, in all patients in this weight range.[6]

The present study (the Diabetes Surgery Study, or DSS) examines the effects of RYGB on key risk factors for cardiovascular disease (CDV). . It has two diabetes treatment arms : **Intensive Medical Management ("IMM")**, which includes both medical and lifestyle components, in comparison to **IMM plus RYGB surgery ("RYGB").** The research is a collaborative effort involving multiple clinical centers. One hundred twenty qualifying diabetic volunteers are recruited, randomized with equal probability within each clinic to either IMM or IMM plus RYGB surgery, with two years of active intervention followed by three years of observational-only follow-up. The primary outcome is assessed 12 months after the intervention begins and is a composite endpoint of diabetes and cardiovascular disease (CVD) risk factor resolution: HbA1c < 7.0%, LDL cholesterol < 100 mg/dl and systolic blood pressure (SBP) < 130 mmHg. The study will also inform the research team with regard to the feasibility of conducting a larger, longer trial examining CVD events. Importantly, this study will establish the feasibility of recruitment, treatment, high quality data collection, and retention across study sites. The study will also provide an opportunity to collect data and serum samples that can be used to study the underlying biological processes mediating the effects of study treatments.

Given the alarming international growth of T2DM and promising initial findings of RYGB as a treatment, we strongly believe that a randomized international clinical trial is timely and will provide extremely valuable information about the role that RYGB surgery might play in the management of this serious medical condition.

B. Background and Significance

Type 2 Diabetes Mellitus

The last 30 years have witnessed a worldwide epidemic of T2DM and of T2DM-linked diseases, associated primarily with increasing obesity. In the US, the prevalence of obesity (defined as BMI ≥ 30.0 kg/m^2) has more than doubled during that time.[7] At present, about one-third of all US adults have a BMI ≥ 30.0 kg/m^2; by international standards (BMI ≥ 27 kg/m^2), over 50% of the US population is obese.[8,9] These epidemic increases in body weight have been pervasive, affecting men and women, individuals of all ethnic groups and individuals of all ages. The effects of obesity are also increasingly being felt in Europe, South America, the Middle East and Asia.[10] Rates of obesity increase have not been entirely uniform, but some of the largest recent gains have been in relatively less developed areas such as Brazil, Mexico and parts of Asia.[11]

Obesity is associated with a host of serious chronic health problems in addition to T2DM, including CVD, cancer, gastro-esophageal reflux disease, obstructive sleep apnea, osteoarthritis, varicose veins and kidney failure.[12] Perhaps the most important of these is T2DM. Even at the low end of the weight distribution, the link between body weight and T2DM is very strong. An individual with BMI of 24.0 kg/m^2 is considered to be normal weight by US standards, but is 2 to 4 times more likely to get T2DM than an individual with a BMI of 20.0 kg/m^2.[13] The relative risk of diabetes in individuals in the "obese" range (BMI ≥ 30.0 kg/m^2) is over 10 times the risk of someone of "normal" weight (18.5 ≤ BMI ≤ 24.9 kg/m^2).[14] Among some ethnic groups, the diabetes/obesity link is even stronger. Asian-Americans, African-Americans, Hispanic-Americans and Native Americans are particularly prone to central obesity-induced diabetes and show susceptibility to diabetes at a much lower BMI than Americans of European ancestry. This increased sensitivity to diabetes in Asians is an important reason why there has been a call to revise cut-off points for defining clinical overweight and obesity

in Asians. The World Health Organization has proposed redefining obesity in some populations to BMI as low as 25 kg/m^2.[15] Data on the rising prevalence of diabetes in India are illustrative.[1]

The most important health consequence of T2DM is CVD, which is the eventual cause of death for nearly two-thirds of patients with diabetes mellitus. Cardiovascular mortality in type 2 diabetic adults is 2- to 4-fold higher than in adults without diabetes. In women, the age-adjusted prevalence of major CVD is doubled by T2DM. For diabetic women versus non-diabetic women, the age-adjusted relative risk of a first myocardial infarction is 1.5 to 4.5; among men the comparable relative risk is 1.5 to 2.0. Similarly, the relative risk of a first stroke is 2.0 to 6.5 for female diabetics versus female non-diabetics, and 1.5 to 2.0 for male diabetics versus male non-diabetics. Diabetes is the most potent risk factor for the development of congestive heart failure among women with existing coronary heart disease. Not surprisingly, this is seen especially in women with an elevated BMI. Diabetes is the leading cause of end-stage renal disease in the US and CVD is the leading cause of death among patients with chronic kidney disease. Microalbuminuria is an early marker for the development of end-stage renal disease in persons with diabetes. Furthermore, microalbuminuria is associated with greater risk of cardiovascular mortality, stroke, coronary heart disease events and increased severity of coronary artery disease.[16,17]

Treatment of Obesity-Related T2DM

State-of-the-art non-surgical treatment for T2DM is comprised of intensive lifestyle modification along with pharmacologic management of glucose intolerance and co-morbidities, especially dyslipidemia and hypertension. Lifestyle management alone that focuses on restriction of energy intake and increased physical activity in order to reduce body weight has been shown to significantly reduce risks of CVD and other conditions related to T2DM. In the recent Diabetes Prevention Program, lifestyle modification alone reduced the incidence of T2DM by 58% over a period of 2.8 years in individuals at high risk.[18] Lipid-lowering agents have also been shown to reduce all-cause and CVD mortality in type 2 diabetics.[19] These results form the basis for the American Diabetic Association (ADA) recommendation to reduce fasting serum LDL cholesterol in all persons with diabetes. [20, 21] The beneficial effects of anti-hypertensives have similarly been demonstrated in large trials involving type 2 diabetics[22,23] and are the basis of the ADA's recommended blood pressure goals.

Although medical management of diabetes is clearly worthwhile, it is often difficult to achieve treatment goals. Shortcomings include incomplete response to medication, difficulty in achieving lifestyle and medical regimen compliance, side effects and cost. Indeed, it has been estimated in the US that 93% of individuals with T2DM do not meet the ADA goals of HbA1c < 7.0%, LDL < 100 mg/dl, and blood glucose < 130/80 mmHg.[2]

Since many diabetic patients in a community setting do not meet the ADA recommended treatment goals,[2] other avenues should be explored for the management of T2DM. Bariatric surgery, particularly RYGB, may have a role in the management of T2DM. The rationale is that T2DM is associated with overweight and obesity.[24] Retrospective data have shown that gastric bypass surgery results in complete remission of T2DM in up to 82% of type 2 diabetics, often before major weight loss has occurred. Moreover, associated co-morbid illnesses are significantly improved.[25]

Current NIH eligibility criteria for bariatric surgery are based in part on BMI.[26] Patients might be considered for surgery if BMI is greater than 35 kg/m^2 in the presence of co-morbid illnesses or greater than 40 kg/m^2 in the absence of co-morbid conditions. The presence of a co-morbid illness alone is not used as an indication for bariatric surgery. There are thus many patients with T2DM who do not fit the traditional NIH BMI criteria – specifically those with BMIs less than 35 kg/m^2.

Bariatric surgery works, at least in part, by reducing the digestive system's absorptive capacity.[27] Currently, the two most common operations are the RYGB and the laparoscopic adjustable gastric band.[28] The gastric bypass involves circumventing most of the stomach, duodenum and proximal jejunum. Intestinal continuity is reestablished via a small gastric pouch and this pouch is connected to a Roux limb of jejunum. The RYGB is a combined restrictive and malabsorptive operation. The gastric band reduces the functional size of the stomach by creating a very small virtual gastric pouch between the band and the gastro-esophageal junction. Thus, the amount of food that can be eaten at one time is severely limited and the gastric band is classified as a purely restrictive operation. The RYGB and gastric banding both typically induce weight losses in morbidly obese patients that are considerably larger than can be produced by conventional medical and lifestyle management.

The RYGB produces an average reduction in excess body weight of about 50% at 10 or more years after surgery.[29,3] The gastric band appears to produce substantial but less dramatic results, although outcomes beyond 5 years are just recently becoming available.[30] Both operations dramatically improve diabetes, hypercholesterolemia, and hypertension.[5,31] In T2DM patients, nonrandomized retrospective comparisons with conventional medical management suggest that the gastric bypass is particularly effective.[32] Complete remission rates as high as 83% have been reported for morbidly obese type 2 diabetics, with improvement in essentially all patients.[4] Pories, et al. demonstrated a mean drop in HbA1c from 12.3% to 6.6%. Interestingly, the glycemic response occurred within days of surgery, long before significant weight loss had occurred.[3] With adjustable gastric banding, resolution rates for T2DM are about 64%.[33] A randomized study of adjustable gastric banding for the treatment of early T2DM demonstrated remission in 73% of patients who underwent surgery in addition to medical treatment while remission only occurred in 13% of patients who only had medical treatment. Remission appeared to correlate in this study with weight loss.[34] The mechanism for the more substantial T2DM improvement with RYGB may have to do with changes in incretin, anabolic peptide or adipokine levels or the effect of bypassing the foregut.[35]

Importantly, mortality in obese patients falls following the RYGB. A Canadian study that compared outcomes over 6 years in 1035 obese patients receiving RYGB surgery with a matched group of obese patients who did not undergo bariatric surgery reported an 89% reduction in mortality ($p<0.001$) and an 80% reduction in co-morbid illness with RYGB.[36] In a retrospective matched cohort study comparing 7925 patients who underwent RYGB with 7925 severely obese individuals who applied for driver's licenses, the all-cause mortality was decreased by 40% in the surgery group compared to the control group. The cause-specific mortality for diabetes was decreased by 92% for patients who underwent surgery.[37]

The Swedish Obesity Subjects (SOS) study showed a 10-year mortality hazard ratio of 0.71 ($p=0.04$). [38, 39,40] Most patients in this study had undergone restrictive surgery, for which long-term results are less favorable than for patients who undergo RYGB.[41]

Recently, Cohen, et al reported on their series of 37 RYGB patients, all with T2DM and up to 48 months follow-(mean follow-up 20 months).[6] The preoperative BMI was less than 35 kg/m^2 in all patients with a mean BMI of 32 kg/m^2. T2DM resolved in all patients undergoing the RYGB. Mean operating time was 58 minutes, and mean hospital stay was 30 hours. Mean fasting plasma glucose dropped from 146 mg/dl preoperatively to 88 mg/dl postoperatively, and fasting plasma LDL cholesterol fell from a mean preoperative level of 148 mg/dl to 115 mg/dl. The authors reported no morbidity or mortality associated with the procedure. There is no evidence that less obese patients lose inordinate amounts of weight following the RYGB for gastric cancer.[42]

RYGB appears to be very safe in patients with BMI below 35 kg/m^2. The RYGB operation is an invasive procedure that has a significant risk of complications. However, the risks associated with the surgery decrease based on both hospital staff and surgeon experience,[43,44] as well as with female gender and decreasing patient size.[45] In the largest meta-analysis examining laparoscopic RYGB at high volume centers, the mortality rate is 0.16%. [46] The risk of other complications include gastric perforation (0.2%), pulmonary complications (1.4%), wound infection (2%), early bowel obstructions (3.3%), stenosis of the gastrojejunal anastomosis (5.1%), bleeding (1.4%), pulmonary embolism (0.45%), and leak (2.6%). The incidence of internal hernia is 3-4% and requires an additional laparoscopy.[47] However, these rates are related to surgeon experience and patient characteristics (e.g., male gender, higher age and larger BMI, and co-morbidities, all of which increase complication rates), so that calculating the exact risk is challenging. Other serious risks during the first few years after RYGB include peptic ulcers at the gastrojejunal anastomosis, gallstones, uncontrollable vomiting, and nutritional complications should pregnancy occur. Less critical complications during the first few years include food intolerances (sugar, lactose, alcohol, and some textures), temporary hair loss, cold sensitivity, diarrhea, and constipation. Long-term complications may include food intolerances, vitamin and mineral deficiencies (primarily iron, calcium, vitamin D, vitamin B12, folic acid), widening of the gastrojejunal anastomosis, peptic ulcers, and interaction with prescription medicines.[48] In summary, determining the potential of RYGB to improve health in type 2 diabetics, and comparing that to the risks associated with the surgery in type 2 diabetics, requires a randomized trial that formally and rigorously evaluates outcomes, benefits and risks. At the time of inception of the DSS, however, there had been no such randomized study.

Protocol Overview

The evidence reviewed above strongly points to the need for a large randomized, controlled trial to evaluate the risks and benefits of RYGB surgery in the management of type 2 diabetics with BMI from 30.0 to 39.9 kg/m^2. The primary outcome would be incidence of CVD events and overall mortality. In the context of rapidly increasing T2DM rates worldwide and the absence of consistently effective medical management procedures, such a trial would be important. We believe that an international trial would be particularly desirable because the global burden of obesity-related diabetes is so substantial. However, we believe that it is premature to initiate a full-scale clinical trial evaluating RYGB with CVD events or mortality as the primary outcome measures. Thus, we propose the current study with a composite outcome based on CVD risk factors. Funding from private industry (Covidien, Inc) has been secured.

The current study is a diabetes and CVD risk-factor trial designed to demonstrate the ability of the investigative group to recruit and randomize T2DM patients with BMI of 30.0-39.9 kg/m^2 to RYGB surgery plus IMM or to IMM alone; to administer these treatments successfully and consistently across all study sites; to follow patients for up to 5 years; and to measure risk-factor outcomes and process variables. This preliminary study is powered to detect between-group differences in CVD risk reduction (i.e., a composite measure encompassing glycemic control and reductions in LDL cholesterol and systolic blood pressure).

Secondary goals include the analysis of between-treatment differences in 12-month changes in weight, waist circumference, diastolic blood pressure, fasting glucose, fasting insulin, lipid profile, and urine microalbumin. Use of medications (as measured by dosages and cost) is tracked, and standardized questionnaires for quality of life (SF-36) and depression (CES-D) are administered. These will also be analyzed for differences between treatment groups. Complications from surgery are also tracked. Secondary goals are followed through 24 months to further assess durability of the results. Observational-only follow-up in years 3-5 will further assess the long-term durability of results.

In addition to examining the feasibility of conducting a multi-center trial of RYGB surgery with CVD endpoints in patients with obesity-related T2DM, we are also collecting blood for future measurements of a variety of process variables in these patients. The blood draws take take place in the context of a nutritional challenge. At six of the seven blood draws, participants are also asked to complete a five-question visual analog scale survey assessing satiety.[49] We hope these will allow us to better understand the biological mechanisms underlying the effects of RYGB on T2DM.[50] It has conventionally been thought that the beneficial effects of the surgery were largely due to its effects on energy intake. However, observational studies have not fully supported this view. In particular, resolution of T2DM appears to occur much more rapidly with RYGB than with gastric banding, raising the possibility that there may be additional factors involved in the beneficial effects of RYGB.

Binge eating is not uncommon in the obese population and in those seeking help with weight loss (25% or more).[51] Furthermore, weight loss is more difficult to achieve in patients with binge eating disorder. To explore relationships between binge eating, treatment group, and treatment efficacy, a brief 8-question version of the Revised Questionnaire for Eating and Weight (QEWP-R) are administered periodically.[52]

After 30 years of clinical use of RYGB for the treatment of morbid obesity and its rapidly increasing use worldwide, a randomized study to evaluate its benefits and risks in patients with T2DM is long overdue. Our study contributes needed information about a procedure that has received limited prior scientific scrutiny. Moreover, we will gain information about an increasingly large population segment that has usually been excluded from bariatric surgery.

C. Preliminary Studies/Research Team Experience

Successful completion of the current study requires technical expertise in the areas of bariatric surgery and behavioral and pharmacological interventions for the management of T2DM, and clinical trials design and data collection and analysis. In addition, it requires close coordination of research activities and quality control across multiple centers. It also requires effective safety monitoring. The investigative team proposed for the research is very well qualified in all of these areas.

Dr. Sayeed Ikramuddin, Principal Investigator, is a surgeon with extensive experience in the development of and performing the laparoscopic RYGB surgical procedure. He has trained many surgeons in this technique, both in the U.S. and internationally, and is well respected internationally by the bariatric surgery community. His specific research specialty is the effects of gastric bypass surgery on the biology of T2DM. He has 40 peer-reviewed publications and has participated in the multi-center Swedish Adjustable Gastric Band trial as the PI for the University of Minnesota site. The inspirational leader of this effort from its inception, he partnered with the international experts in public health, endocrinology, weight management and biostatistics and has marshaled the international group of investigators in India, arguing forcefully for the importance of the best science and for international scope.

Co-Principal Investigators Drs. John Connett, Robert Jeffery, John Bantle, Charles Billington, Judith Korner, Lee-Ming Chuang, Wei-Jei Lee, Michael Sarr and Adrian Vella bring extensive experience in biostatistics, multi-center clinical trials, obesity research and research in metabolic diseases to the research group.

John Connett, PhD, is the head of the Division of Biostatistics at the University of Minnesota. He is responsible for directing the statistical and data coordinating center for the studies. Dr. Connett has served as the principal investigator for the coordinating center for several large-scale clinical trials, including 1) the Lung Health Study, the largest clinical trial ever undertaken in pulmonary disease and 2) the COPD Clinical Research Network, an ongoing umbrella group of 10 clinical centers with the objective of conducting clinical trials to prevent complications of chronic obstructive pulmonary disease. Dr. Connett serves on the data and safety monitoring board for studies of asthma, retinopathy of prematurity, sickle cell disease, ocular hypertension, urinary incontinence and others and is a member of the NHLBI Clinical Trials Review Group. Dr. Connett is also an Associate Editor of the Journal of Clinical Trials.

Robert Jeffery, PhD, is a professor in the School of Public Health at the University of Minnesota. He is responsible for developing the diet and exercise components of the IMM protocol and administering the coordination of these activities across all centers. He has been conducting research on lifestyle modification procedures for obesity treatment for more than 25 years. He has conducted more than a dozen randomized trials on these procedures and is widely recognized as an expert in the field. Dr. Jeffery also has considerable experience in multi-center lifestyle modification trials. He developed and supervised dietary interventions for a 4-center trial investigating the effects of weight loss, sodium intake reduction and potassium intake increase on blood pressure. He developed the dietary intervention for a multi-center trial evaluating the effectiveness of dietary fat restriction in delaying recurrence of post-menopausal breast cancer. He is currently the principal investigator of one of the participating centers in Look AHEAD, a multi-center trial evaluating the effectiveness of lifestyle interventions that promote weight loss on CVD events in individuals with T2DM. This trial includes 18 US centers and over 5000 patients with T2DM. Dr. Jeffery has been the chair of the Clinical Operations Committee for this trial. He is also Director of the University of Minnesota Obesity Prevention Center, Principal Investigator of a National Cancer Institute center grant on Transdisciplinary Research on Energetics and Cancer (TREC) and Epidemiology Core director for the Minnesota Obesity Center, an NIDDK obesity center grant.

John Bantle, MD, is an endocrinologist and professor in the Department of Medicine at the University of Minnesota. He is also an Associate Director of the General Clinical Research Center. Dr. Bantle is an investigator in three active multi-center, NIH-sponsored, clinical trials. These are: Epidemiology of Diabetes Intervention and Complications (EDIC) for which he is PI, Look AHEAD for which he is coPI, and Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) for which he is PI. Dr. Bantle has considerable experience in research focusing on weight loss interventions for type 2 diabetes mellitus as well as pharmacologic management of diabetes and its complications. He has 60 peer reviewed publications in the area. Dr. Bantle's primary role in this trial is to develop and coordinate the pharmacologic portion of the IMM procedure for the trial.

Charles Billington, MD, is an endocrinologist and professor with 18 years of experience in obesity treatment and medical weight management at the University of Minnesota and the Veterans Administration. Dr. Billington is Associate Director of the Minnesota Obesity Center, an NIDDK obesity center grant. He has served as President of the North American Association for the Study of Obesity and on the NIH National Task Force on

the Prevention and Treatment of Obesity. Dr. Billington has extensive research experience in basic science and clinical studies of obesity. Dr. Billington participated in development and implementation of the medical management and lifestyle modification protocol and directs studies of biomarkers and other predictors of risk factor changes.

Judith Korner, **M.D., Ph.D.** is Assistant Professor in the Department of Medicine and Division of Endocrinology and Metabolism at Columbia University and Attending Physician at Columbia University Medical Center in New York. Dr. Korner received her medical degree at the College of Physicians and Surgeons of Columbia University where she also obtained her Ph.D. in Biochemistry and Molecular Biophysics. She completed her internship and residency in Internal Medicine, served as Chief Medical Resident, and completed her fellowship in Diabetes, Endocrinology and Metabolism at Columbia University Medical Center. She is board certified in Diabetes, Endocrinology and Metabolism. Dr. Korner's research is focused on the pathophysiology and treatment of obesity and type 2 diabetes. She has NIH funding to investigate peptide hormones that control hunger and food intake, particularly in association with bariatric surgery. She is the Principal Investigator of a NIH-funded trial to study the effects of leptin administration after gastric bypass surgery on body weight and neuroendocrine function. She has published original research as well as chapters and review articles on weight regulation and obesity therapy and serves on the Editorial Board of the journal Obesity. She is the Director of the Weight Control Center at Columbia University Medical Center that specializes in the medical treatment of obesity or excessive weight gain. As co-Principal Investigator of the DSS study at the Columbia University site, Dr. Korner evaluates subjects for pharmacotherapy intervention and contribute to the design and implementation of mechanistic studies of weight loss and glucose homeostasis.

Lee-Ming Chuang, MD, is an endocrinologist and professor in the Department of Medicine, National Taiwan University School of Medicine. He is also director of the Diabetes Education Center of the National Taiwan University Hospital (NTUH). Dr. Chuang is an active investigator in Sanford Asia-Pacific Program on Hypertension and Insulin Resistance (SAPPHIRE), a multi-center, NIH-sponsored study. Dr. Chuang has considerable experience in research focusing on diabetes/obesity pathogenesis and management, including experience in international clinical trials of many new drugs. He has over one hundreds peer reviewed publications in the area of diabetes and obesity studies. Dr. Chuang's primary role in this trial is to develop and implement the pharmacologic portion of the IMM procedure for the trial at National Taiwan University Hospital.

Wei-Jei Lee, MD, PhD, is a professor of surgery at National Taiwan University and the executive superintendent of Min-Sheng General Hospital. He has pioneered laproscopic gastrointestinal surgery in Taiwan and Asia. He is the past Present of Taiwan Endoscopic Surgery Society and the current Present of Asia-Pacific Metabolic and Bariatric Surgical Society. His specific research interests are gastric cancer, endoscopic surgery, bariatric surgery and metabolic effect of gastrointestinal surgery. He has 160 peer-review publications and is in charge of many clinical and basic research projects. He has set up the Asia pacific Endoscopy Bariatric Surgical Center in Min Sheng General Hospital which is the leading center in Asia, both in clinical service and research.

Michael Sarr, MD received his MD degree from the Johns Hopkins School of Medicine. He did a 2-year NIH research fellowship at the Mayo Clinic and a further postdoctoral fellowship at Johns Hopkins Hospital before joining the staff in the Department of Surgery at the Mayo Clinic in 1985. He is currently the James C. Masson Professor of Surgery, Vice Chair of Research in the Department of Surgery, and Chair of the Division of Experimental Surgery. His research interests include in vivo and in vitro control of smooth muscle contractile activity with a primary interest in extrinsic neural control. His clinical interests include pancreatic surgery, bariatric surgery, and abdominal wall hernias.

Adrian Vella, MD is a Professor of Medicine in the Division of Diabetes, Endocrinology and Metabolism at the Mayo Clinic Rochester, MN. He has expertise in clinical diabetes management and carbohydrate, physiology and is a recognized expert on incretin physiology and the use of tracers to measure physiological processes. Dr. Vella has received multiple NIH awards related to the treatment of type II diabetes. He performs or directly supervise recruitment as well as any studies in the General Clinical Research Center.

Other investigators at the University of Minnesota are Daniel Leslie, Kumar Belani, Joyce Schone, Avis Thomas, Qi Wang, and Stanley Williams.

Daniel Leslie, MD, is an assistant professor in the Department of Surgery, Division of Gastrointestinal Surgery at the University of Minnesota. He is completing his fellowship training in minimally invasive surgery and are assistant professor in July 2007. His clinical interests include minimally invasive endocrine and gastrointestinal surgery in addition to current and future applications of natural orifice transgastric endoscopic surgery. He studied structure/function relationships between endotoxin and endotoxin binding protein derived from *limulus polyphemus* during postdoctoral study. At this time, Dr. Leslie is designing protocols to analyze the entero-endocrine response to different bariatric operations and developing web-based software to more efficiently track patient outcomes from our database. He has assisted in standardizing the surgical protocol at each of the centers and participates in controlling the quality of post-operative patient care and data collection for the RFCT.

Kumar Belani, MD, is a Professor of Anesthesiology, Medicine, Pediatrics and Public Health at the University of Minnesota. He has spearheaded the India Development Programs at the University. Dr. Belani is a Board Member and also serves on the Advisory Committee for the One World Hospital and Healing Centre, Bangalore, India. He is a clinician and an established researcher and has conducted projects in the US, India, Japan, Austria and France. Dr. Belani's responsibilities include serving on the Mortality and Morbidity Review Board for the risk-factor clinical trial and for the observational cohort study.

Joyce Schone, RD, LD is a clinical dietitian at the University of Minnesota Medical Center, Fairview. She has worked as a clinical dietitian for 20 years, with extensive experience in bariatric surgery and weight management since coming to the University of Minnesota 12 years ago. Ms. Schone is certified in adult weight management through the American Dietetic Association (ADA). In addition to her degree in dietetics, she holds a degree in Corporate and Community Fitness. She has assisted in the development of the lifestyle intervention protocol, coordinates the medical intervention, and counsels patients during lifestyle intervention visits.

Avis J Thomas, MS, Fellow of the Society of Actuaries, is a research fellow and biostatistician at the University of Minnesota. She has published in cardiovascular disease, socioeconomic status and race/ethnicity as predictors of long-term health outcomes, effects of parental diabetes, side effects of RYGB surgery, prostate cancer, clinical trial design, and bone marrow transplants. She has been heavily involved in development of the manual of operations, and manages day to day operations at the statistical center, and performs statistical analyses.

Qi Wang, MS. Ms Wang earned her Master's degree in Biostatistics at the University of Minnesota, and is employed in the Biostatistical Design and Analysis Center of the University's Clinical and Translational Research Institute. Her role in this study is to carry out data analyses and graphics of DSS follow-up data for publications and presentations.

Stanley E. Williams, PhD, is research coordinator for the Division of Gastrointestinal Surgery. He has thirty years experience in the design, conduct and management of clinical trials, including conduct of the data coordinating center for the POSCH trial under Henry Buchwald, MD, PhD. Dr. Williams provides systems support for several clinical aspects of the study.

Other investigators at the University of Columbia in New York include Heather Bainbridge, RD, and Drs. William Inabnet, Marc Bessler and Leaque Ahmed.

William B Inabnet, MD, was Chief of Endocrine Surgery at the University of Columbia in New York and moved to Mount Sinai Hospital in New York City as the Chief of the Division of Metabolic, Endocrine and

Minimally Invasive Surgery. Dr Inabnet has completed a fellowship in endocrine surgery at Cochin Hospital in Paris, France where he trained under Professor Yves Chapuis, a world leader in the field of endocrine surgery.

An international authority in the field of minimally invasive endocrine surgery, Dr Inabnet is also a leader in the field of minimally invasive bariatric surgery with an interest in type 2 diabetes. Dr Inabnet is site PI and a co-investigator for the 5-year Longitudinal Assessment of Bariatric Surgery and holds numerous leadership positions in the American Association of Endocrine Surgeons, American Association of Metabolic and Bariatric Surgery and the American College of Surgeons.

Dr Inabnet has authored more than 100 peer-reviewed articles and book chapters, as well as 3 textbooks including the soon-to-be released book entitled Endocrine Surgery: Principles and Practice. He lectures throughout the world and was recently inducted into the Society for University Surgeons as well as the French National Academy of Surgery, a rare honor for non-French surgeons.

Marc Bessler, M.D. is Chief of the Division of Minimal Access/Bariatric Surgery at New York-Presbyterian Hospital/Columbia University Medical Center in New York. He is also Director of the Center for Metabolic and Weight Loss Surgery, Director of the Minimal Access Surgery Center, Professor of Clinical Surgery and Attending Surgeon at Columbia University Medical Center. His clinical specialties include surgical management of morbid obesity, gastroesophageal reflux disease, esophagus and hernia surgery and laparoscopic surgery of the stomach. Dr. Bessler's research interests include hormonal, oncologic and immune responses in laparoscopy as well as minimally invasive techniques in general and bariatric surgery including natural orifice surgery. He has authored over 70 peer-reviewed articles and book chapters. As Co-Investigator of the DSS at Columbia University, Dr. Bessler evaluates and manages surgical patients in the study.

Leaque Ahmed, MD was trained in endocrine and pancreatic surgery at Columbia University Medical Center and serves as Director of Bariatric Surgery at Harlem Hospital Center, where he has performed over eight hundred minimally invasive weight loss procedures. In addition to obesity surgery, he specializes in minimally invasive thyroid and parathyroid surgery and pancreatic surgery. He is also the Director of Bariatric Program at the Bronx VA.

Other investigators in Taiwan include Dr. Keong Chong.

Keong Chong, MD, is an attending physician in the Department of Internal Medicine, Division of Endocrinology and Metabolism at the Min-Sheng General Hospital in Taiwan. He is fellowship-trained in endocrinology and diabetes mellitus; he received his credential from National Taiwan University Hospital in June 2008. His clinical interests include functional genomic and proteomic approaches to metabolic syndrome, neurohormonal changes of obesity, and both basic science and clinical studies of bariatric surgery for diabetes.

Other investigators at Mayo Clinic in Minnesota include Dr. Michael D Jensen and Dr. Jim Swain.

Michael D. Jensen, MD holds the Tomas J. Watson, Jr. Professor in Honor of Dr. Robert L. Frye at the Mayo College of Medicine, Rochester, MN. He is the Chair of research for the Division of Endocrinology and Nutrition, the Director of the Obesity Treatment Clinic at Mayo Clinic and of the Department of Medicine Obesity, Weight Management and Nutrition Research Program. His clinical interests are primarily focused on obesity and diabetes. Dr. Jensen's research involves the study of obesity, body fat distribution, and fatty acid/energy metabolism, focusing specifically on the effects obesity and body-fat distribution on health and on the determinants of body fat distribution. His studies have identified the relative contributions of different fat depots to lipid fuel metabolism, including the role of intra-abdominal fat. He received a MERIT award from NIH to continue his studies in this area and has been funded for 22 consecutive years by NIH to conduct his research. His laboratory also stimulated the renewed interest in non-exercise activity as an important physiologic regulator of weight, beginning with a publication in the journal Science. He has served on NIH,

Mayo and foundation scientific review panels and has contributed to professional associations both by committee work and in elected office. Dr. Jensen has published more than 170 original research articles, together with over 50 invited papers and book chapters. He is currently co-chair of the NHLBI Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

James M. Swain, MD was the Director of Bariatric Surgery at Mayo Clinic in Rochester, MN and is now a bariatric surgeon with Scottsdale Healthcare in Scottsdale, AZ. He has over 12 years of experience with bariatric surgery was involved early in the development and implementation of laparoscopic gastric bypass. Dr. Swain has proctored over 30 surgeons in minimally invasive bariatric surgery. Specific bariatric surgery interests include the treatment of non-alcoholic fatty liver disease and type II diabetes. Dr. Swain has been involved with multiple bariatric device-related trials. He also chairs the Mayo Clinic Bariatric Workgroup which is composed of over 50 surgeons, endocrinologists, nutritionists, psychologists, and allied health workers.

Overall, the investigative team is highly qualified in all the technical disciplines needed for this trial. The overall level of experience in managing large and complex research studies demonstrates that this team is able to manage the current project well and bring it to a successful and timely conclusion.

D. Research Design & Methods

Overview and Organization

This study is designed to compare the outcomes of the gastric bypass and intensive medical management for the treatment of T2DM. This is not primarily a study of the treatment of morbid obesity, although all patients enrolled in the trial will have class I or II obesity (BMI 30.0-39.9 kg/m^2). The primary alternative hypothesis is that, one year after intervention, surgery in conjunction with IMM will achieve greater reduction in diabetes and cardiovascular disease risk factors than IMM alone in patients with a BMI 30.0-39.9 kg/m^2 and T2DM. Overall diabetes and cardiovascular disease risk level is determined using a dichotomous composite measure; to be classified as lower risk, the patient must meet three criteria: HbA1c < 7.0%, LDL Cholesterol < 100 mg/dl and SBP < 130 mm Hg.

Dr. Sayeed Ikramuddin from the Department of Surgery at the University of Minnesota is the overall Principal Investigator of the project. Coordinating functions and data management will also be centered at the University of Minnesota. Dr. John Connett supervises data collection, management and analyses. Drs. Jeffery and Bantle develop and supervise the IMM component. Dr. Ikramuddin coordinates the surgical intervention.

All participating institutions are clinical sites for the trial. The study has a Steering Committee to provide overall scientific guidance, a Clinic Operations Committee, an Intervention Committee, and a Data Safety Monitoring Board (DSMB). Investigators from each of the centers participate on these committees, except for the DSMB. All study procedures are be approved by the Steering Committee. The Steering Committee meets twice per year at a minimum and reports annually to the study sponsors and to the DSMB.

Study Design

Design and Hypotheses

T2DM patients meeting study entry criteria are randomized with equal probability to one of two study groups: (1) IMM (2) RYGB with IMM, and followed for five years. The primary goal for the risk factor trial is to determine which of these two interventions is more effective in achieving, 12 months after entry into the trial, a satisfactory composite diabetes and CVD risk factor profile: (1) HbA1c < 7.0%, (2) LDL < 100 mg/dl and (3) SBP < 130 mmHg. Secondary goals include comparing the two treatment groups for changes in other measured outcomes including body weight and BMI, waist circumference, diastolic blood pressure, fasting glucose, lipid profile, and urine microalbumin. Use of medicines, total diabetes- and CVD-related treatment costs, mortality, CVD events, and complications of surgery are also be tracked, and comparisons between treatment groups are made as appropriate. A sample size of 120 patients (60 each in the IMM and RYGB

groups) is necessary to achieve adequate power to distinguish clinically significant changes in the primary and secondary outcome measures. An additional objective is to provide evidence that a larger, longer-term clinical-outcomes trial is feasible. To this end, the investigators must demonstrate that they can recruit, treat and complete 12 months of follow-up and risk factor assessment for the required number of patients at the participating clinical centers. The intervention continues for a total of 24 months after randomization. There are additional observational-only follow-up in years 3-5. Results in years 2-5 are used to assess the durability of treatment effects and treatment differences.

Methods

Recruitment

Potential participants are identified from the patients in the clinical practices of participating endocrinologists

and other health providers, and by public advertising. Patients with a physician's diagnosis of T2DM who are interested in finding out more about the study are screened initially by telephone and invited to an informational seminar. Potential patient participants are informed that the sponsors of the trial will cover all expected surgical and medical costs of the trial, including co-pays, that are not covered by insurance.

Screening by phone

Prospective recruits are briefly screened by phone (including a brief review of key eligibility requirements) and scheduled for a seminar visit. They are mailed a copy of the informed consent, and the "trial agreement." The trial agreement is a one-page document describing the two-year commitment they are making, and asking for their signature.

Seminar Visit

At this meeting, the purpose of the study, the procedures to be used in both treatment groups, and the potential risks and benefits associated with participating in the study are explained. Another copy of the informed consent and trial agreement are given to candidates for the study to take home and discuss with their families. Prospective participants are also be asked to complete a 2-week run-in, in which they keep a daily log of physical activity, food intake, and twice-daily blood glucose tests. The data from the log itself will not be kept.

Eligibility Visit 1

At a subsequent eligibility visit, a full history and physical examination is performed to further assess inclusion/exclusion criteria for participation in the trial. The exam includes blood and urine tests. The signed informed consent document and trial agreement are returned, and patients have an opportunity to talk to a doctor and ask questions. Study staff verify that prospective patients understand the potential risks and benefits of participating in the trial.

Eligibility Visit 2

Prospective participants who remain interested in the study and meet initial eligibility criteria (including blood and urine tests) are scheduled for a cardiac stress test and 12-lead EKG to confirm eligibility. The CES-D (depression) and SF36 (quality of life) questionnaires are given, and fasting blood tests and the mechanism challenge is carried out. (At the clinic's discretion, the CES-D may be given at either Eligibility Visit 1 or Eligibility Visit 2.)

Review by Eligibility Committee

After all eligibility criteria are known, the eligibility committee meets to make a final decision about the patient's eligibility. No objective inclusion/exclusion criteria is dismissed. The committee considers the patient's overall medical profile, any specific abnormalities that have been uncovered, and any subjective impressions they have formed about the patient's suitability for the trial, social support system, etc.

Informed Consent

Participants go through a thorough consent procedure designed to make sure that they fully understand the study and the random assignment to either RYGB or IMM and are willing to be in either arm of the trial. Prospective participants are told that the research trial is designed to test whether bariatric (RYGB) surgery in combination with a high intensity, state of the art medical management program for treating T2DM to lose

weight improves the health of obese persons with T2DM compared to intensive medical management alone. It is clearly explained that such participation includes lifestyle modification counseling and the use of prescription drugs. Participation in the trial includes the benefit of active medical treatment for T2DM and closer monitoring of health and well being than is conducted in normal medical care. There is the possibility of extra benefit due to the surgery. Risks include the potential for increased complications in the surgery group. Once informed of the purpose, risks, and possible benefits of participation, the prospective participants are asked to describe back to the study coordinators the procedures to be used in each study group and the risks and benefits involved in each before signing the consent form to make sure that they understand the study. Participants I indicate through a checkbox whether or not they consent to have blood from the mechanism challenge stored for future studies.

Randomization

Participants are randomized following computerized review and checking that all eligibility criteria are met. Data on baseline depression testing must be received by the DCC, edited and entered into the data management system; BMI and HbA1c values are checked (and must be supplied manually if they have not yet been received by the DCC); lab data that has been received by the DCC are checked; and the clinic coordinator are asked to verify that all inclusion criteria have been met.

The DCC has constructed separate randomization schedules for each clinical center. There is a target of thirty randomized patients from each center. Each randomization schedule is based on a random permuted block design, with block sizes of 2, 4 and 6, to ensure approximate balance within each schedule at any point in time. The schedules are computer generated using a pseudo-random number generator in SAS. The clinic coordinator has limited remote log-in access to the DCC's computer system. For each patient, the clinic coordinator logs on, verifies eligibility criteria, and if appropriate is given a randomization assignment ('RYGB' or 'IMM'). This assignment is be shown online, and repeated in an email to the clinic coordinator and the DCC. The clinic coordinator is required to echo back the treatment assignment to the DCC by transmission of the Randomization Assignment Confirmation form. In the event that a center cannot recruit and randomize thirty patients, the Steering Committee determines the policy for additional patients at sites with additional capacity.

Eligibility requirements

Inclusion criteria

1. Age 30 to 67 years at eligibility visit.
2. Diagnosed with T2DM at least 6 months prior to enrollment, under the active care of a doctor for at least the six months prior to enrollment, HbA1c ≥ 8.0 % and HbA1c ≤ 14.0%.
3. Body Mass Index (BMI) ≥ 30.0 kg/m^2 and ≤ 39.9 kg/m^2 at eligibility visit.
4. Willingness to accept random assignment to either treatment group.
5. Expect to live or work within approximately one hour's traveling time from the study clinic for the duration of the two-year trial.
6. Willingness to comply with the follow-up protocol and successful completion of the run-in (described below).
7. Written informed consent.

Exclusion criteria

1. Cardiovascular event (myocardial infarction, acute coronary syndrome, coronary artery angioplasty or bypass, stroke) in the past six months.
2. Current evidence of congestive heart failure, angina pectoris, or symptomatic peripheral vascular disease.
3. Cardiac stress test indicating that surgery or IMM would not be safe.
4. Pulmonary embolus or thrombophlebitis in the past six months.
5. Cancer of any kind (except basal cell skin cancer or cancer in situ) unless documented to be disease-free for five years.
6. Significant anemia (hemoglobin 1.0 g/dL or more below normal range) or history of coagulopathy.
7. Serum creatinine ≥ 1.5 mg/dl.
8. Serum total bilirubin greater than the upper limit of normal in the absence of Gilbert's syndrome, or alkaline phosphatase or ALT greater than twice the upper limit of normal.

9. History of stomach surgery, bile duct surgery, pancreatic surgery, splenectomy, or colon resection.
10. Gastric or duodenal ulcer in the past six months.
11. History of intra-abdominal sepsis (except for uncomplicated appendicitis or diverticulitis more than six months prior to enrollment).
12. Previous organ transplantation.
13. Self-reported HIV-positive status, active tuberculosis, active malaria, chronic hepatitis B or C, cirrhosis, or inflammatory bowel disease.
14. Currently pregnant or nursing, or planning to become pregnant in the next two years.
15. History of alcohol or drug dependency (excluding caffeine and nicotine) in the past five years.
16. Active psychosocial or psychiatric problem that is likely to interferer with adherence to the protocol.
17. Depression: A score of 17 or higher on the CES-D will disqualify a participant unless, at the clinic's discretion, the candidate is referred to a licensed psychologist or psychiatrist for a formal psychological evaluation. In that case, the formal psychological evaluation and recommendation are important factors in the determination of eligibility by the eligibility committee. If this evaluation clearly indicates potential risks associated with depression, the participant may not be randomized. If the evaluation is equivocal or unclear, the eligibility committee must take this into account in rendering their decision
18. Current participation in a conflicting research protocol.
19. Presence of any chronic or debilitating disease that would make adherence to the protocol difficult.
20. 12-lead EKG indicating that surgery would not be safe.
21. Serum c-peptide $\leq$ 1.0 ng/ml 90 minutes post-challenge.
22. Exclusions may also be made at the discretion of the attending physician or the eligibility committee.

Run-in

As part of the eligibility review, prospective participants are asked to keep a log for two weeks, recording food, physical activity, and glucose levels. This is done to test their willingness to comply with the study's requirements. Prospective participants do not comply with run-in instructions are not considered for randomization.

Interventions

Intensive Medical Management (IMM)

The IMM intervention is intended to optimize individual patient's diabetic control and CVD risk factors.. The IMM intervention is comprised of lifestyle counseling for diet and physical activity and pharmacologic management of diabetes and its co-morbidities.

Goals of Treatment

The goals of treatment are based on the American Diabetes Association 2008 Standards of Care. [20] There arel be 5 major types of goals for each patient as follows.

1. Glycemia:
    a. HbA1c < 7.0% in an assay with upper limit of normal 6.0%; with other assays, the HbA1c goal is < 1.0% above the upper limit of normal.
    b. Preprandial capillary plasma glucose 70 – 130 mg/dl (3.0 – 7.2 mmol/l).
    c. Peak postprandial glucose < 180 mg/dl (10.0 mmol/l).
2. Lipemia:
    a. Fasting plasma LDL cholesterol < 100 mg/dl (< 2.6 mmol/l).
    b. Fasting plasma HDL cholesterol > 50 mg/dl (1.3 mmol/l) for women.
    c. Fasting plasma HDL cholesterol > 40 mg/dl (1.1 mmol/l) for men.
    d. Fasting plasma triglycerides < 150 mg/dl (1.7 mmol/l).
3. Blood pressure < 130/80 mmHg
4. "Baby Aspirin" (75-100 mg per day)
5. Smoking cessation

Patients are seen for pharmacologic management of these conditions a minimum of once per month for the first 6 months. During months 7-12, all patients are seen at least quarterly; if any of the first three treatment goals are unmet, they are seen monthly. During months 13-24, patients are seen quarterly. Vital signs (pulse, temperature, respiration, blood pressure, weight and BMI) are obtained at each study visit. Height and weight are measured periodically, as described in the Functional Endpoints table. A variety of fasting and post-prandial blood drawsare taken periodically, as described in the Functional Endpoints table. Patients are asked to use a finger stick to measure their blood glucose at home daily, if needed. Blood glucose records are reviewed at each medical visit. All medication changes are carefully documented.

Weight loss and increased physical activity are used to achieve the first three goals. Additional treatment methods that are employed are described below.

Lifestyle counseling for weight management and physical activity

The lifestyle intervention program is modeled closely after that used in the Diabetes Primary Prevention Trial and the LookAHEAD diabetes treatment studies, both of which have been shown to produce average weight losses of 7 to 9% of initial body weight and to sustain weight losses of half that magnitude for up to four years.[53,18] The methods have also been shown to be of similar effectiveness in men and women from a variety of ethnic backgrounds. Lifestyle intervention goals are the same in both treatment arms: reduce BMI to <25 kg/m^2 and increase in physical activity expenditure to > 1 hour per day of moderate activity. Lifestyle treatment is comprised of group sessions (using closed groups consisting entirely of patients from the same treatment group) as well as individual face-to-face counseling sessions with patients and trained intervention staff. For non-surgery patients, the lifestyle intervention begins approximately one week following randomization, allowing some variation in timing so that small groups can start the intervention at the same time. Sessions are weekly for the first six months, every two weeks during months 7-9, monthly during months 10-15, and then quarterly thereafter. Surgery patients have a similar schedule for lifestyle counseling, except that it is shifted back approximately 3 months, until they can eat solid foods; during the first three months, they are seen individually by bariatric surgery nutritionists. Patients are weighed at each treatment session. There are energy intake and exercise goals that should result in weight losses of 1 to 2 lbs per week.

Meal Plans: At each session, patients are given a structured meal plan indicating the food they should eat for 5 breakfasts and 5 dinners during the next week. The meal plan indicates specific portion sizes and provide information on the calories and grams of fat in these foods. A shopping list is also provided each week. Previous studies have demonstrated that providing structured meal plans to patients improves weight loss; the TRIM studies have then incorporated these plans into their standard behavioral program.[54] Once patients achieve ideal body weight, the calorie goal is adjusted to produce maintenance of body weight.

Diet: For non-surgery patients, the structured meal plans and the patients' overall dietary intervention are based on an individualized calorie goal (1200, 1500 or 2000 calories/day), determined from the patients' baseline body weight to produce an estimated weight loss of one to two lbs/wk. Once patients achieve ideal body weight, the calorie goal for patients in both arms is adjusted to produce maintenance of body weight.

Patients are also asked to restrict fat intake to approximately 20% of calories. A daily fat goal in grams is prescribed for each patient (for example, patients eating 1500 calories/day are given a fat goal of 33 gm/day). These goals have been used successfully in prior TRIM studies.

Patients are asked to record their calorie and fat intake daily for 6 months and then one week per month for the remainder of the 24-month program. They are given food diaries and calorie/fat guides and are instructed to record all food they consume and the calories and fat grams in these foods.

The skills required to make appropriate dietary changes are modeled, practiced and reinforced throughout the program.

Training in the Use of Behavioral Strategies: The major features of the behavior modification program are as follows:

Self-monitoring: Self-monitoring involves the systematic observation and recording of eating and exercise behaviors by the patient and is an important aspect of self-control. Patients self-monitor energy and fat intake,

energy expended in exercise and body weight. These records are reviewed by the therapist at each treatment meeting.

Stimulus control: Stimulus control refers to a set of behavioral procedures designed to help patients change the environmental cues associated with eating behavior. Patients are be instructed to reduce the visibility of food in their home; to impose limits on where, when and with whom they eat; to avoid distractions while eating; and to eat slower.

Problem solving: Patients are taught to use problem solving strategies to deal with situations that pose difficulties for changing their eating and exercise habits. Patients are taught to define the problem, brainstorm solutions, select a solution and evaluate its success.

Social assertion: Being able to assert oneself in social situations is an important part of gaining control over eating behavior. Patients are taught to behave assertively in social situations involving eating and exercise. Patients role play the handling of difficult interpersonal situations (e.g., being offered high calorie foods and eating out).

Goal setting: Patients are taught the importance of short-term goal setting for enhancing motivation and will set daily and weekly goals for energy intake and expenditure, behavior change and weight.

Feedback: Patients are taught to use calorie intake and exercise totals as an ongoing source of feedback on the results of efforts at behavior change. The therapists monitor their progress of patients and encourage small steps toward behavior change.

Cognitive strategies: Negative thinking (e.g., perfectionism, pessimism, self-doubt) often interferes with behavior change. Patients are helped to recognize their own negative thoughts and to counter them with thought-stopping and/or positive self-statements.

Relapse prevention: Based on Marlatt's and Gordon's relapse prevention model, patients are taught to recognize precursors and consequences of dietary “lapses.” Potential high risk situations are identified and patients plan strategies for dealing with these situations.

Spouse and family involvement: The treatment program includes training in techniques for involving spouses and other members of the family in weight loss efforts.

Maintenance: In later months of the program, patients begin to focus on issues related to maintenance. They are helped to see the differences between weight loss and maintenance and are encouraged to become their own “therapist,” learning to identify problems related to eating and exercise and possible solutions to these problems.

Exercise Intervention

The exercise and nutrition interventions begin at the same time.

Patients receive an exercise intervention similar to that used in the best available behavioral treatment programs. Patients are strongly encouraged to develop an exercise program based primarily on walking. They are taught to calculate the energy cost of walking and to record their energy expenditure in their self-monitoring diary. Initially, patients are instructed to expend 250 kcal/wk -or equivalent metric units (50 kcal on each of 5 days). For a 150 kg person, walking a half km would use 50 kcal and thus the patient would need to walk a half km 5 days in the week to fulfill this goal. The goal is gradually increased over time, with each increase made at four-week intervals, until patient reach the goal of > 1 hour of moderate activity per day.

The skills required for developing and maintaining an exercise program are modeled, practiced and reinforced throughout the program through the use of exercise information quizzes and skills training (e.g., warming up, cooling down, taking pulses). Patients also are trained to utilize the behavioral strategies discussed above to help them implement and maintain an active lifestyle. Specifically, they are asked to self-monitor their exercise every day throughout the program and are taught to use problem-solving strategies to deal with barriers to exercise.

Pharmacological Interventions

Patients not achieving any of the first three treatment goals (glycemia, lipemia, blood pressure) will have additional support added as detailed below. Treatments to achieve goal four (aspirin use) and five (smoking cessation) are also detailed below. Goal achievement status are assessed at every study visit and medication support are increased at each study visit until goal is achieved, limiting side effects occur or patient refuses further therapy. Further, once patients have lost weight and achieved other lifestyle goals, medications are considered for reduction or removal based on medication stop criteria for both arms of the study as described below.

Treatments are applied using the following decision tree. Study physicians may modify the rules, as needed, if there is a good reason based on an individual patient's circumstances.

A. Weight management
   1. If the patient's weight is not under control, then the physician may add Orlistat, which has well evidenced effectiveness in contributing to weight control and is generally well tolerated.[55] Alternately, they physician may add any medication for weight management approved by the US FDA (for US clinics) or approved the US FDA and TFDA (for clinics in Taiwan).

B. Glycemia
   1. In addition to the fasting glucose measured in periodic chemisty panels, blood glucose is monitored in the hospital (for surgery patients) using a finger stick, and is monitored at home using finger sticks and a home monitor. Patients will keep logs and report their results to the endocrinologist. The frequency of home finger sticks is determined on a case by case basis.
   2. Add metformin and titrate to 2000 mg daily if necessary and tolerated. Metformin is accepted throughout the world as first line treatment for T2DM based on effectiveness, tolerability and lack of associated weight gain.[56]
   3. Add glucagon-like peptide 1 (GLP-1) analog (Exenatide or Liraglutide when FDA approved) and titrate to full dose if necessary and tolerated if these medications are available. The GLP-1 agonists are newer treatments that have not yet had their place in consensus treatment determined, but are attractive because of strong effect on glycemic control, with weight loss in many patients. The GLP-1 analogs must presently be administered by subcutaneous injection and are sometimes not tolerated. For those patients intolerant to GLP-1 agonists, or situations where Exenatide is not legally approved, an alternative medication is the recently available DPP4 inhibitor Sitagliptin (increases GLP-1 action by inhibiting breakdown).[57]
   4. Add sulfonylurea, Thiazolidinedione (TZD), or any medication for glycemai approved by the US FDA (for US clinics) or approved by the US FDA and TFDA (for clinics in Taiwan) and titrate as necessary. These are standard treatments for T2DM everywhere
   5. Add insulin and titrate as necessary. This is the last treatment option after all other treatments have failed. This is also a standard treatment for T2DM everywhere.[56]

C. Fasting plasma LDL cholesterol
   1. Add HMG-CoA reductase inhibitor (statin) and titrate as necessary and tolerated. Statins are accepted as the first line of treatment for LDL excess in view of effectiveness, tolerability and evidence of long term reduction of heart disease.[58]
   2. Add Ezetimibe 10 mg daily. Ezetimibe is well tolerated and contributes additional LDL lowering effect.[59]

D. Fasting plasma HDL cholesterol
   1. Recommend increased exercise. This intervention builds on the foundation of lifestyle intervention for activity described above. The treatment option to be offered to the patient is more intense exercise for the purpose of increasing HDL. A specific exercise plan to achieve higher levels of activity is developed as an individualized plan with each patient needing this therapy.
   2. Add fenofibrate or gemfibrozil. Fibrates are known to be effective at increasing HDL levels and are well tolerate, but must be used with caution in the presence of treatment with statins for LDL. The treatment plan will prioritize LDL and statin therapy ahead of HDL and fibrate treatment.

E. Fasting plasma triglycerides
   1. Optimize glycemic control. Secondary treatment for triglycerides is delayed pending establishment of glycemic control goals unless the triglyceride levels are greater than 300 mg/dl and therefore requiring primary triglyceride treatment.
   2. If glycemia has been controlled or triglycerides are greater than 300 mg/dL, add Fenofibrate or Gemfibrozil. Fibrates are safe and effective therapy for hypertriglyceridemia, but again, in the event of risk or adverse events from the combination of statin and fibrate, the treatment priority is lowering LDL with statins (unless the triglycerides themselves pose a major risk as indicated by levels above 300 mg/dl).
   3. Add fish oils high in omega 3 fatty acids. Fish oils can contribute to management of high triglyceride values and are well tolerated. When used in this study program, fish oil therapy is accompanied by instruction on the additional calories and on food substitutions that may moderate a weight-increasing effect of this treatment.

F. Blood pressure
   1. Add an angiotensin converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker (ARB). Angiotensin pathway modifying medications are accepted as the first line of therapy for hypertension among diabetic patients owing to strong evidence of renal protective effects.[60]
   2. Add hydrochlorothiazide or similar diuretic. Diuretics, particularly thiazides, have been among the most widely used hypertension management tools and recent data reinforces the vascular protective effect of these medications.[61]
   3. Add a beta blocker. Beta blockers are recognized for their benefit in treatment of hypertension and in the context of established vascular disease can play an additional role in ischemia protection.[61]
   4. Add additional agents as necessary. Several other anti-hypertensives are available and are employed on an add-on basis as needed to achieve goal.[61]

G. Aspirin

   1. Add 75-100 mg aspirin daily unless contraindicated. Patients in the surgery arm or with a history of a gastrointestinal disorder or inflammatory or bleeding disorders should receive coated enteric aspirin, unless contraindicated. Patients in the surgery arm begin taking aspirin one week after surgery.

H. Smoking cessation
   1. Recommend smoking cessation at each study visit for patients who smoke. Patients are referred for formal smoking cessation programs at the option of the practitioner and patient.
   2. Offer pharmacologic support with nicotine gum, nicotine patches, bupropion or varenicline. The practitioner may prescribe medical support for smoking cessation based on clinical judgment. There is no limit to the number of smoking cessation attempts supported by medication.

I. Microalbuminuria

   1. Add an ACE inhibitor or ARB. In the event that a patient develops microalbuminuria in clinic follow-up and that patient is not hypertensive or not treated with an antagonist of angiotensin pathways, an ACE inhibitor or ARB is prescribed for renal protection and risk reduction.

J. Gallbladder Protection

   1. In addition to the pharmacological intervention for diabetes and CVD, patients in the surgery arm are prescribed ursodiol, 300 mg capsules, 2 times daily, beginning one week after surgery and ending six months after surgery, for the prevention of gallstones.

Medications are reduced or stopped in response to changing clinical status, either post surgery or post lifestyle intervention. The medication stop rules are as follows:

A. Reduce or discontinue hypoglycemic medications if any of the following are true:
   1. there is an episode of serious hypoglycemia with loss of consciousness or confusion sufficient to prevent self-treatment
   2. mild symptomatic hypoglycemia occurs more than twice weekly on a frequent basis

3. home glucose monitoring values are less than 70 mg/dl frequently
4. hemoglobin A1C is less than 6.0%
5. at the discretion of the treatment team, hypoglycemic medicines may be decreased when the lifestyle intervention is introduced.

B. Reduce or eliminate antihypertensive medications if either of the following are true:
1. systolic blood pressure is less than 110 mm Hg or diastolic blood pressure is less than 70 mm Hg at two consecutive clinic visits
2. there are symptoms attributable to hypotension

C. Reduce or eliminate antihyperlipidemia medications if both of the following are true:
1. fasting LDL cholesterol is less than 80 mg/dl on two consecutive visits
2. fasting triglycerides are less than 150 mg/dl on two consecutive visits

The study will pay for all prescription medicines not covered by insurance, and will also cover co-pays for insured medicines. Insurance is billed whenever possible.

Risk monitoring

More intensive risk monitoring is initiated in the peri-operative period, in response to significant weight loss, or at any other time needed in the judgment of the site study physician. During such periods, medications may be suspended and clinical monitoring may be more intensive in accord with relevant clinical practice.

Ferritin, vitamins B_1, B_{12} and D, PTH, blood chemistry, hematology, and liver function panels are monitored throughout the two-year intervention (see Table 1 for timing), and corrective action is taken as needed. Participants are notified if abnormal lab values occur. Vitamin B_{12}, PTH, serum calcium and a complete blood count will also be assayed as 60 months.

Intervention Training

LIFESTYLE: Lifestyle intervention staff at each center will have training equivalent to a master's level dietitian or nurse practitioner. The primary interventionist at each center is required to participate in a training session conducted by Dr. Jeffery at which the intervention protocol for interventionists is reviewed in detail. The same intervention materials are used at each site. In addition, regular conference calls are held during the study (with the interventionists from each center) to ensure that all issues are handled in a similar fashion at each centers.

PHARMACOLOGIC: Pharmacologic intervention is conducted by endocrinologists at each center. Protocol training is conducted by Dr. Bantle prior to the initiation of the study and reinforced by periodic conference calls.

Quality Control

A quality control committee comprised of members from each of the study sites was formed prior to study initiation, and review of recruitment, clinic procedures, data management are performed at a quality control meeting. Written protocols for assessment visits are reviewed to clarify the order of assessments, measurement procedures and standard responses that should be given to inquiries related to questionnaire completion. Staff collecting physical measures (anthropometry and blood) are individuals trained and monitored by the quality control committee.

Comprehensive face to face training sessions are conducted for staff at each clinic prior to the clinic's initiation in the trial. These training sessions include a review of the background, purposes, and design of the study; recruiting methods; baseline measurements and determination of eligibility; informed consent procedures; randomization; the treatments and treatment schedules; forms completion and data transmission; documentation and reporting of adverse events and mortality; the follow-up schedule and technical procedures required at each visit; components of the intensive medical management protocol; drawing, processing, storing, and shipping blood specimens; and other aspects of the study.

Instruments and devices used in data collection (i.e., scales) are serviced on a regular schedule, as recommended by the manufacturer.

All investigators and coordinators are provided with the protocol, manual of operations, and a complete set of case report forms. Each clinic, surgery, and lifestyle intervention session will have standardized instructions in the protocol and manual of operations and at least one case report form. The standardized instructions must be followed, and case report forms must be completed and transmitted to the Data Coordinating Center, where the staff reviews them for omissions, consistency and plausibility.

Surgical Intervention

Patients in the surgical intervention (RYGB) arm undergo RYGB surgery in addition to lifestyle counseling for diet and physical activity and pharmacologic management of diabetes and its co-morbidities as appropriate in the post-operative setting.

RYGB Surgery

Surgical Centers of Excellence

All surgical patients undergoing bariatric surgery undergo standard workup and postoperative care as established by their site. The US clinics are American Society of Metabolic and Bariatric Surgery (ASMBS) and Surgical Review Corporation-designated Bariatric Surgery Center of Excellence. No centers of excellence have yet been established in Taiwan. Procedures are performed by designated surgeons only. The study's overall PI will insure that appropriate surgical techniques are used.

Pre-operative Preparation

Post-randomization, all surgery patients undergo a one- to two-week diet with meal replacement, using Optifast™ or Slimfast™, or a similar product. Pre-operative deep venous thrombosis prophylaxis is administered two hours prior to surgery, as deemed necessary by the surgeon, and is continued for the duration of the hospital stay.

Standardization of Operative Technique

Operative suites must use a standardized regimen of equipment needed to perform the RYGB surgery for each patient. These include appropriate drapes, gowns, sponges, skin stapler, local anesthetic with needles for infiltration, a skin blade, laparoscopic trocars, sequential compression devices (SCDs), appropriate suture, endo-GIA stapler devices with appropriate reloads, an ultrasonic dissector, suction-aspirator device, laparoscopic scissors, Veress needle, surgicel, a closed suction drain, fibrin glue sealant, insufflation tubing and sterile dressings for the incisions.

Patients are placed supine on the operating table and general anesthesia is induced. Intravenous antibiotics are administered and an oro-gastric tube is placed. A transurethral bladder catheter is placed sterilely and attached to a gravity collection bag. All bony protuberances are appropriately padded, SCD's may be applied, and tape and straps are used to establish secure patient positioning on the table and footboard throughout the procedure. The abdomen will then be prepped and draped sterilely.

The operation is performed laparoscopically using a standardized technique of antecolic, antegastric Roux-en-Y gastric bypass with a 100 cm biliopancreatic limb and a 150 cm Roux limb. The operation begins with the establishment of pneumoperitoneum. A total of 5 or 6 laparoscopic ports are placed, and a liver retractor device of the surgeon's preference is used to provide adequate visualization of the upper stomach. The oro-gastric tube is removed after confirming decompression of the stomach.

The surgeon then starts the operation by creating a 20 mL gastric pouch. This is accomplished by first incising the peritoneal reflection of the angle of His to expose the left crus of the diaphragm and separate the gastric cardia and fundus from the left crus. The hepatogastric ligament on the lesser curvature of the stomach is then divided with the harmonic scalpel, and the retrogastric window is visualized. Multiple firings of a laparoscopic triple linear cutting stapler device are used to construct the pouch.

The ligament of Treitz is then identified and the bowel is marched 100 cm distally and divided, creating distal biliopancreatic limb and proximal Roux limb. The Roux limb is then marched 150 cm distally, and at this location a jejunojejunostomy is constructed between Roux limb and distal biliopancreatic limb. There are numerous safe and effective ways to create this anastomosis, and these decisions are left to each surgeon. An anti-obstruction stitch is placed and the mesenteric defect is closed using suture.

The proximal Roux limb is then brought adjacent to the gastric pouch in the antecolic, antegastric position and the gastrojejunostomy is constructed. There are numerous safe and effective ways to create this anastomosis, and these decisions are left to each surgeon. The anastomosis is tested with saline immersion to test for gastrointestinal leak, which is repaired if found.

The Petersen defect is closed using non-absorbable suture.

A closed suction drain may be left adjacent to the gastrojejunal anastomosis and sutured to the skin. All ports are then removed and the skin is stapled or sutured and sterile dressings are applied.

At the surgeon's discretion and interest in performing a safe operation for the patient, the operation may be converted to an open technique in the rare event of difficult adhesions, visualization or technical mishap. These patients will still be enrolled in the trial.

In-patient Hospital Care

Patients are admitted to a post-surgical general ward for routine post-operative care. Each patient will have a routine post-operative upper gastrointestinal contrast study (UGI). Post-operative diet is clear liquid which is started after a negative UGI and (if appropriate) after a flatus or bowel movement. In the event of a gastrointestinal anastomotic leak, patients will undergo immediate laparoscopic exploration and additional drainage. The hospital stay is two days minimum. The timing for removing closed suction drains is at the discretion of the operating surgeon.

Post-operative Outpatient Care

At home, patients are on clear liquids for one week and then advanced to pureed foods at the time of the first clinic visit, which will occur at 7 days after surgery. Vitamin B12, a multivitamin with iron and other minerals, and a calcium supplement with Vitiamin D are started within one month of surgery; if appropriate, patients are given a prescription for ursodiol. Patients are advanced to a soft diet at approximately one month, and will eventually return to a regular consistency diet as tolerated.

Surgical Data Collection

All data are reviewed by a separately established data monitoring board to be established by the University of Minnesota School of Public Health.

Outcome measures

1. Primary composite outcome, 12 months post-randomization:
    a. HbA1c < 7.0%
    b. Systolic blood pressure < 130 mm Hg
    c. LDL cholesterol < 100 mg/dl
2. Secondary outcomes: baseline to 12 months, with additional follow-up to 60 months:
    a. Changes in weight and BMI
    b. Change in waist circumference
    c. Change in fasting glucose
    d. Change in fasting insulin
    e. Change in serum total cholesterol, HDL cholesterol, and triglycerides
    f. Changes in urine microalbumin/creatinine ratio and resolution of co-morbid renal function illness.
    g. Use of medications (as measured by dosages and cost)
    h. Total cost of diabetes- and CVD-related medication
    i. Measures from three surveys: Quality of life (SF-36), depression (CES-D), and a brief version Questionnaire for Eating and Weight Patterns-Revised (QEWP-R) to assess binge eating disorder. The surveys are collected at baseline, 6 months, 12 months, and 24 months.
    j. Mortality
    k. Cardiovascular events (myocardial infarction, stroke, other serious CVD)
    l. Complications from surgery and other adverse events
    m. Durability of the primary composite outcome and its components at 24, 36 and 60 months.

Endpoints

The primary outcomes of interest are the measurements of HbA1c, LDL cholesterol and systolic blood pressure at 12 months after the start of IMM or the date of RYGB. Secondary outcomes are body weight, waist circumference, fasting glucose, fasting insulin, total cholesterol, HDL cholesterol, triglycerides, urinary microalbumin, use of medications, total cost of care, and measures of quality of life and depression. Data regarding cardiovascular events and mortality will also be collected and documented when possible. The occurrence of nonfatal events is detected by (1) reports during structured clinic and telephone interviews with patients and (2) spontaneous reports from patients or their family contacts. CVD events and mortality are documented with copies of hospital admission and discharge summaries, emergency room records, death certificates and autopsy reports when available. The primary outcome measurements will require visits to the clinic where the patient was randomized at 12 months after intervention, and the results are recorded on a Laboratory Results form and a standard quality-of-life instrument (the SF-36) or depression questionnaire (CES-D). Outcome measures are re-assessed at 24 months for assessment of the durability of any treatment effect.

Observational-only follow-up will continue in years 3-5. Mid-year phone calls or emails will uncover deaths and serious adverse events. In years 3-5, each site will provide compensation to patients for transportation costs, parking, time off work, etc, as approved by their IRB. Annual medical visits will assess the following endpoints:

1. HbA1c
2. Blood pressure
3. Fasting LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides
4. Fasting glucose
5. Urine creatinine and urine albumin
6. Weight and BMI
7. Waist circumference
8. Use of medications
9. Serious adverse events and severe adverse events that involve hypoglycemia or might be related to RYGB

Additionally, the following tests are conducted at the 5-year visit only:

1. Serum parathyroid hormone (PTH)
2. Serum calcium
3. Complete blood count (CBC)
4. Serum Vitamin B12

Peri-operative data points will include co-morbid illness and medications, length of stay, operative time, estimated blood loss and peri-operative complications. Information on surgical outcomes is collected on a standardized form.

Clinical laboratory tests are obtained according to the schedule in the table below. Laboratory results are collected and entered onto data forms according to manual of operations.

These forms are e-mailed or scanned and transmitted to the Data Coordinating Center on the day of the clinic visit, the day of surgery or on the day laboratory results become available.

Functional Endpoints: non-lab procedures through 24 months

	Through Randomization					Intervention and Post-Intervention (Time Measured for Earliest Intervention)																
Non-lab procedures	Seminar Visit	Eligibility Visit 1	Eligibility Visit 2	Committee Meeting	Randomization	Intervention	1 week	1 month	2 months	3 months	4 months	5 months	6 months	7 months	8 months	9 months	10 months	11 months	12 months	15 months	18 months	21 months	24 months
Run-in log distributed	X																						
Demographic Information		X																					
Inclusion/Exclusion Criteria		X			X																		
Medical/Obesity History		X																					
Prior Weight-Loss Meds & Treatment		X																					
Medical Management (post-rand.) And Current Medications		X	X		X	N	S	X	X	X	X	X	X	X?	X?	X	X?	X?	X	X	X	X	X
Tobacco use		X				N	S	X	X	X	X	X	X	X?	X?	X	X?	X?	X	X	X	X	X
Vital Signs: Pulse/Blood Pressure/Weight		X			X	N	S	X	X	X	X	X	X	X?	X?	X	X?	X?	X	X	X	X	X
Temperature and Respiration Rate							S																
Height		X																	X				
Waist Circumference					X			X		X			X			X			X	X	X	X	X
Physical Exam (Endocrinologist)		X			S			X		X			X			X			X	X	X	X	X
Exam by Surgeon			X		S	S	S	S		S			S			S			S		S		S
EKG and Cardiac Stress Test			X																				
Informed Consent		X			X																		
Review Overall Eligibility				X																			
Treatment Assigned					X																		
Questionnaires: Quality of Life (SF-36), depression (CES-D), Satiety (SAT) and Binge Eating Disorder (BED)			X										X						X				X
Slimfast/Optifast/etc (1 week)					S																		
RYGB (surgical group)						S																	
Lifestyle modification (see text)*							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event reporting							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Functional Endpoints: lab procedures through 24 months

	Through Randomization			Intervention and Post-Intervention (Time Measured for Earliest Intervention)												
Lab Test	Eligibility Visit 1	Eligibility Visit 2	Randomization	Intervention	1 month	2 months	3 months	4 months	5 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Hemoglobin A1c	X				X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipid Profile		X			X	X	X	X	X	X	X	X	X	X	X	X
Safety: Ferritin; Vitamins B_{12}, D; PTH			X				X					X				X
Safety: Vitamin B_1			X				S					S				S
Chemistry and liver function (elig)	X			S?			X			X		X				X
Chemistry and liver function (non-elig)			X	S?			X			X		X				X
Creatine kinase			X				X			X		X				X
Fasting glucose							X									
Hematology (CBC,complete blood count)	X						X			X		X				X
INR (clotting time)			S?													
Urinalysis			S													
Mechanism challenge: C-peptide, glucose, insulin, frozen sample**		X								X		X				X
Urine pregnancy test	X			S												
Spot urine microalbumin/creatinine			X									X				X

S = for surgery patients only (if on the day of surgery, then done in the morning)

N = non-surgery arm only.

S? = for surgery patients, at the physician's discretion.

X? for patients in both arms, if not at goal.

definitions: (IMM) = (Medical Management) + (Lifestyle Modification)

Time is measured from date of intervention, not date of randomization.

Chemistry and liver function (eligibility): Creatinine, ALT, alkaline phosphatase, and bilirubin. These tests are needed for determining eligibility.

Chemistry and liver function (non-eligibility): NA, K, P, Mg, Ca, AST, and albumin.

*Lifestyle modification may be weekly, bi-weekly, monthly or quarterly; the schedule differs by arm. See text.

**Mechanism challenge (C-peptide, glucose, insulin, and frozen samples): Patient begins in a fasting state. Dynamic testing is carried out following a 15-minute standardized mixed meal (Ensure, 237 ml, 250 kcal, 6 g fat, 40 g carbohydrate and 9 g protein), with blood specimens collected at times -15, -1, 15, 30, 60, 90 and 120 minutes after ingestion. Similar mixed meal simulations have been previously used to evaluate cc-peptide response and the dynamic response of gut hormone such as GLP-1 and ghrelin. The C-peptide, glucose, and fasting insulin specimens are processed immediately for assay. If the participant consented, the mechanism specimens are processed and then frozen for later assay according to a mechanism studies plan that is to be submitted for separate evaluation and support (support for these assays is not part of this submission). C-peptide and glucose are measured twice (fasting and 90 minutes); insulin is measured once (fasting).

Functional endpoints: years 3-5

	30 months	36 months	42 months	48 months	54 months	60 months
Telephone or email contact	X		X		X	
Weight, Height, Waist Circumference, Blood Pressure		X		X		X
Tobacco Use		X		X		X
Annual Lab tests: HbA1c, fasting serum lipids, fasting glucose, urine creatinine, and urine albumin		X		X		X
Five-year lab tests: PTH, calcium, CBC, Vitamin B12						X
Current medication use		X		X		X
Adverse event reporting	X	X	X	X	X	X
Collect two aliquots of fasting serum and two aliquots of fasting plasma, to be frozen and stored for future scientific use (U.S. sites only)		X		X		X*
Mechanism challenge: C-peptide, glucose, insulin, frozen sample**						X

* This can also be fulfilled by performing a full mechanism challenge and storing samples

**This is the same 2-hour mechanism challenge as in years 1-2.

Adverse Events Reporting Policy (through 24 months)

Adverse events and conditions may be detected on follow-up visit forms, or they may be spontaneously reported by trial participants or someone who knows them.

- In case of a death, the DCC and Covidien should be notified within 24 hours of clinic awareness. Thorough documentation (including a completed DSS-AE form and the cause of death) should be provided within seven days.
- Serious or severe (grade 3 or higher) adverse events, or any adverse event involving a medical device from Covidien, must be made known to the DCC within 24 hours of the clinic becoming aware that the AE has occurred; an email is sufficient for the initial notification. The DCC will then immediately notify the DSMB and Covidien. Thorough documentation must be reported on form DSS-AE within 5 working days of clinic awareness. (See "exceptions" paragraph below.)
- Moderately severe (grade 2) adverse events that are not serious and do not involve a medical device must be reported on form DSS-AE within 5 working days. (See "exceptions" paragraph below.)

If complete information is not available in the allotted time, the clinic will provide as much information as is available; provide a best guess if necessary. For serious or severe adverse events, the clinic will obtain medical records to verify and document the adverse event.

Adverse events that are not serious, do not involve a medical device from Covidien and are mild (severity grade 1) do not need to be reported; they are noted in the participant's chart, and care is given as appropriate. Changes in medicine are reported on form DSS-Med at the next scheduled visit.

Exceptions: the normal expected effects of RYGB surgery do not need to be reported. These include: needing an IV up to three days post-operatively, and levels of nausea, vomiting, dysphagia, anorexia and weight loss that would be considered normal for RYGB patients.

In addition to prompt reporting of AEs that are severe or serious, the DCC will periodically provide the DSMB with a complete statistical summary of all AEs that have been reported by the clinics. These periodic summaries are provided at every DSMB meeting.

Adverse Events Reporting Policy (years 3-5)

The study is observational only during years 3-5. During years 3-5, only serious adverse events, severe hypoglycemic events, and severe adverse events that may be related to RYGB are reported. The site will notify the DCC when the site has reasonably complete information about the adverse event. There is no DSMB oversight after the last patient has completed his or her 24-month intervention visit. However, adverse events during years 3-5 are reported to the DSMB if they occur before the final DSMB meeting to review all outcomes from years 1-2. .

Participant Time Requirements

An expectation of participation in the study is in person attendance at the study clinic for all required visits. Visits are required weekly for the first six months of the study and then semi-monthly, monthly, or quarterly thereafter. These visits can be expected to take roughly 30 minutes for the lifestyle modification only and 1-1½ hours if the visit also requires medical review. Visits requiring a set of "mechanism challenge" blood tests will take 2- 2½ hours. These visits are additional time away from their everyday activities. Patients in the surgical arm will stay in the hospital 2 nights following the RYGB. They are able to go back to work after 2-4 weeks and have a 10 pound maximum lifting restriction for 6 weeks after surgery.

Subject Retention

A systematic protocol is followed to minimize subject attrition. Participants who miss a clinic visit are called by the site nurse coordinator. Lifestyle counseling may be done by phone. Top priority is placed on attendance for data collection visits. Participants are scheduled by phone, sent written reminders and called the day before each data collection visit. Missed visits are rescheduled and followed up at least three times.

Data Analysis

As in previous sections, this is described separately for the risk-factor clinical trial and the observational cohort study.

Data Analysis Plans.

For the risk-factor clinical trial, the primary aim is to compare the effects of the two treatment regimens (RYGB and IMM versus IMM alone) on a composite outcome at 12 months. The dichotomous composite outcome is considered a success if all three of the following conditions are met: HbA1c < 7%, LDL < 100 mg/dl, SBP < 130 mm Hg. Otherwise, the composite outcome is a failure. The individual components of the composite outcome will also be examined, as well as additional measures including body weight, body mass index, waist circumference, total cholesterol, fasting glucose urine microalbumin and others as measured at 12 months post-randomization. For the primary composite outcome, the objective is to compare the proportions of success between the two groups at 12 months, and logistic regression stratified by site is used. Durability of outcome is re-assessed at 24 months. For the quantitative variables, the appropriate test of the null hypothesis that the two groups are not different is an analysis of variance (possibly after transforming the dependent variables using a log or square root transformation) with two factors: (1) treatment group, and (2) clinical center. The latter is a stratifying variable. Analyses will also be conducted using regressions adjusted for clinical center. Analyses of the primary composite risk-factor endpoint are on an intention-to-treat basis. Every effort is made to retain patients in the study through at least 12 months. For patients who do not attend the 12-month or subsequent annual visits, values are imputed using multiple imputation. Other methods of imputation (e.g., 'hot deck' imputation or last-observation-carried-forward [LOCF]) are considered as well. Secondary analyses will also be carried out in which the effects of baseline covariates are taken into account. These would include, e.g., age, gender, duration of diabetes, smoking history, history of previous or concurrent illnesses, and other relevant variables. Such analyses are based on logistic regression for dichotomous outcomes, and on analysis of variance for quantitative outcomes. Additional analyses may be based on repeated-measures analyses by treatment group of the primary outcome measures at four time-points: one, three, six and twelve months after randomization. These analyses can be conducted using PROC MIXED or PROC GENMOD (for generalized estimating equation analyses) in SAS.[62]

Secondary analyses of major CVD events and mortality are undertaken using proportional hazards regression models.[63] Such analyses permit control for other baseline factors such as age, gender, other comorbidities, medications, adherence to the treatment regimen, etc.

Time is measured from the date of intervention, not the date of randomization, though every effort is made to keep the interval between these to 2 weeks or less. In some cases, the lifestyle intervention may be delayed (either to allow surgery patients a recovery period, or so that a handful of non-surgery patients can form a closed small group where everyone begins at same time). However, the lifestyle intervention will not be delayed by more than 60 days in the non-surgery arm. The lifestyle intervention is delayed approximately 3 months in the surgery arm, until patients are tolerating a reasonable range of foods. The date of intervention used in statistical analyses is the date of earliest intervention, which will usually be either surgery or the medical intervention.

Statistics and Power Calculations

Sample Size Considerations

The primary goal is to determine which of two treatment regimens – RYGB plus IMM, or IMM alone – is most effective in attaining a satisfactory composite risk-factor profile (HbA1c < 7%, LDL < 100 mg/dl, SBP < 130 mm Hg). Additionally, we will compare the effects of the two treatments on body weight, BMI, waist circumference, diastolic blood pressure, fasting glucose, total cholesterol, HDL cholesterol, urine microalbumin, and other

measurements. Based on prior data we estimate that, in the RYGB group, by the 12-month visit, (1) 90% of patients will have HbA1c < 7%; (2) 90% will have SBP < 130 mm Hg, and (3) 80% will have LDL cholesterol < 100 mg/dl. Conservatively assuming independence of these measures, the overall probability of a satisfactory outcome on the composite endpoint is estimated to be 65%. This estimate of 65% success in the surgery group is based on previous studies.[1, 4, 5, 25, 31, 32] In contrast, the expected success rate in the IMM group for the same endpoint is estimated to be no higher than 30%. The estimate of 30% success rate for the IMM arm is also based on previous studies; [18, 21-23] It should be stressed again here that the goal here is success on a composite of risk factors: HbA1c < 7%, and LDL <100 mg/dl and systolic blood pressure of 130 mm Hg. A sample size of 106 patients (53 in each group) will yield 95% power to detect a difference between the groups of this magnitude. Assuming a 12% rate of losses to follow-up at 12 months, we will need to randomize 120 participants to achieve 95% power.

Sample size estimates are similar for detecting significant treatment effects in secondary quantitative outcomes (e.g., fasting glucose levels, total cholesterol, etc.). To detect, with 95% power, a difference between the groups of magnitude equal to 0.5 standard deviations in a quantitative outcome, a total sample size of 110 evaluable patients is needed.

It is also important, for the purposes of planning for a larger clinical-endpoints trial in the future, that the investigators prove that they can recruit, randomize, treat, and follow up a substantial number of patients over a 2-year recruitment period. We feel that demonstrating that we can enter 120 patients and achieve follow-up rates of at least 88-90% at 12 months would provide a strong basis for conducting the larger trial.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will include at least the following: one endocrinologists, one surgeon with expertise in bariatric surgery, and one statistician with expertise in clinical trials. Responsibilities of the DSMB will include: (1) approving the study protocols and informed consent materials and procedures prior to startup; (2) approving the plan for documenting and reporting adverse events; (3) approving plans for data analysis; (4) monitoring recruitment, eligibility, and adherence to protocol prior to randomization; (5) monitoring follow-up rates and adherence to the follow-up protocol; (6) monitoring adverse events; (7) providing recommendations regarding early termination of the studies for any reason; (8) providing recommendations regarding modifications of the protocol as necessary to protect patients or to preserve the scientific objectives of the study; (9) advising the investigators regarding whether an urgent announcement of study results or an expedited publication may be required; and (10) reviewing the primary manuscripts on study results to ensure that the findings are valid and presented accurately and completely.

The DSMB will meet once prior to study start-up to review and approve the protocol. Meetings will occur at 6-month intervals subsequently until the operational period of the study is completed. One or more meetings are held after that to review the primary outcome results and primary papers emanating from the studies.

Data on adverse events in years 3-5 may be gathered during the study's operational period (i.e. before the last patient finishes his or her 24-month visit). In this case, the DSMB will still be operational and is informed of the adverse event.

Steering Committee Governance

The voting members of the Steering Committee consist of the following: one surgeon from each site; one endocrinologist from each site; Robert Jeffery, lifestyle interventionist; and John Connett, senior statistician. The principal investigator will vote only when there is a tie. For purposes of governance, the Taiwanese and New York operations will each be treated as a single site. The voting members of the steering committee must approve by simple majority any changes to the protocol or uses of frozen samples. They are also the final

arbiter of all information, except where otherwise provided for the Data Safety Monitoring Board.The voting members of the Steering Committee will decide if samples are to be used, by majority vote. It is expected that most frozen samples are used by local researchers. However, some samples may be shipped between clinics to increase the number of samples for a specific investigation, where this is appropriate.

E. Human Subjects Research

Risks to the Subjects

Human Subjects Involvement and Characteristics

Subjects in the proposed Risk-Factor Clinical Trial (RFCT) study will include 120 women and men, 30 to 67 years of age, diagnosed with Diabetes Mellitus Type 2 (T2DM), and with a BMI ≥ 30.0 kg/m^2 and ≤ 39.9 kg/m^2. The age criterion was chosen to include those with T2DM that would be in the risk group for the primary cardiac disease endpoints. Subjects must be willing to accept random treatment assignment and demonstrate compliance with food, activity and glucose logs during the run-in period. Subjects who have serious physical or psychological disorders, whose cardiac or physical condition will not allow participation in exercise, and women who are pregnant or anticipate becoming pregnant are excluded.

The proposed research is a collaborative effort between multiple institutions, each of which are clinical sites for the trial. The study will have a steering committee to provide overall scientific guidance, a clinic operations committee, an intervention committee, a Data Safety Monitoring Board, and a morbidity and mortality review board. Investigators from each of the centers will participate on these committees. All study procedures are approved by the Steering Committee. The Steering committee will meet twice per year at a minimum and will report annually to the study sponsors and to the DSMB.

Sources of Materials

Participants will provide physiological and questionnaire data specifically for research purposes. Laboratory and clinical data are obtained. Blood specimens are obtained for clinical studies as well as for later research assays. Data are collected at clinic visits and in hospital during surgery.

Patients are assigned a coded patient number and no personal data such as name, social security number or other identifiers or privileged data is shared outside of the clinic, where the patient is seen for treatment. The data coordinating center will only have the coded patient numbers. Only the local treating (investigator and coordinator) staff are able to match coded data to the patient. That protected patient data is kept in a locked cabinet in a secure room in each clinical site.

Potential Risks

The risks of IMM are those of standard medical treatment, and are increased in a small way by the more intense medical management, particularly of glycemia in diabetes. There is a small increased risk of hypoglycemia relative to standard practice, although many of these patients would receive similar treatment to the IMM in standard practice.

Mortality after gastric bypass

Overall mortality after laparoscopic Roux-en-Y gastric bypass is very low when performed by experienced surgeons. The largest meta-analysis on bariatric surgery mortality was presented by Dr. Henry Buchwald to the Central Surgical Association on March 10, 2007 in Chicago, IL. Thirty day mortality after laparoscopic Roux-en-Y gastric bypass was 0.16%.[46]

MacDonald, et al. published one of the largest series of diabetics who have undergone gastric bypass with long-term follow-up and compared these patients to control patients who were diagnosed with T2DM at the time of evaluation for gastric bypass but did not undergo gastric bypass. The patients were relatively well-matched for age, BMI, weight, % with hypertension, and male/female gender, although there were more non-white patients in the control group. After a mean length of follow-up of 9.0 years in the post-gastric bypass group, 14 of 154 patients had died (9%). After only 6.2 years follow-up in the non-operated control group, 22 of 78 patients had died (28%). The incidence of death per patient-year of follow-up was 1% in the surgical group and 4.5% in the non-surgical control group.[32]

The largest series of obese diabetic patients (who were also hypertensive and hyperlipidemic) with BMI 30.0-34.9 kg/m^2 who have undergone laparoscopic gastric bypass was by Cohen, et al. and published in 2006.

Thirty-seven patients underwent LRYGB and there were no mortalities; follow-up range was 6-48 months. All patients had complete remission of diabetes and lipid disorder while one patient out of the 37 continued to required anti-hypertensive medication treatment.[6]

Greater obesity increases surgical risk.[64,65,45] There have been no large series of patients with BMI 30.0-34.9 kg/m^2 who have undergone Roux-en-Y gastric bypass. Extrapolating from a data set which provides strong evidence of much higher mortality rates in the super-obese (BMI ≥ 50 kg/m^2) suggests that 30-day mortality in patients who are less obese is lower.

Most analyses examining surgeon experience and the laparoscopic learning curve for Roux-en-Y gastric bypass have defined 100 cases as the number required in order to minimize complication rate and mortality.[44] [66] [67] Drs. Ikramuddin, Kellogg, and Leslie each have extensive experience with laparoscopic bariatric surgery. Each has completed 12 months of focused minimally invasive bariatric surgery fellowships, and they have a combined experience of over 3000 laparoscopic gastric bypasses.

There are publications documenting a mortality rate of 1-2% per year during the years following gastric bypass or any type of bariatric surgery. However that has not been the experience of “Centers of Excellence” (designated by the American Society for Metabolic and Bariatric Surgery and the Surgical Review Corporation) or our center at the University of Minnesota. There are a number of series with long follow-up after obesity surgery, and these have not documented this mortality rate.

Pories, et al. performed RYGB on 608 patients a 14 year time period and maintained follow-up of 97% of these patients. Late mortality (after 30 day peri-operative period) has occurred in 25 of 608 patients (4.1%). The causes of late death included 12 emotional causes (3 suicides, 3 cases of alcoholic cirrhosis from return to drinking, 1 case of bulimia, 1 case of pernicious anemia related to refusal to comply with vitamin B12 treatment, 1 case of alcoholic hepatitis), 4 deaths from automobile crash, and 12 from non-emotional causes (four primary cardiac, 2 cancer, 1 atherosclerosis, 1 pneumonia, 1 AIDS, 1 peritonitis, 1 pulmonary embolus, and 1 from sepsis from a later operation). An additional 17 patients overall (2.8%) were lost to long-term follow-up.[3]

Christou, et al. performed open RYGB on 272 consecutive patients and evaluated 228 patients with mean follow-up of 11.4 years. Seven patients died post surgery at: 4.8 years of suicide, 5.7 years of suicide, 6.6 years of liver failure, 8 years of unknown cause, 8.8 years of pulmonary embolus, 8.8 years of cardiac failure, and at 13 years of cerebrovascular accident, for a 3.2% long term post operative mortality rate.[68]

Total surgically related mortality in this study will occasion the following actions:
1. One death attributable to surgery: suspend randomization for emergency DSMB review;
2. Two deaths attributable to surgery: stop the study.

Experience with the RYGB operation has shown that patients do not drop below ideal weight.[69] While most commonly used for the treatment of morbid obesity, it was originally devised to treat peptic ulcer disease in normal weight individuals.

The following major complications may occur as the result of a RYGB surgery: [47,70,71, 72]
1. Death occurs in 1 patient out of 600 (0.16%) within the first 30 days.
2. Leak of one of the intestinal connections
3. Pulmonary thrombosis
4. Bleeding
5. Stenosis of the gastrojejunal anastomosis
6. Bowel obstruction
7. Incisional hernia
8. Wound infection
9. Gallstones

10. Peptic ulcers at the gastrojejunal anastomosis
11. Gastric perforation or staple line dehiscence
12. Pneumonia
13. Depression, suicide, divorce, and unintended pregnancy.

The following other complications may also occur:

1. Vitamin and mineral deficiencies, particularly iron, calcium, Vitamin B12, Vitamin D, and folic acid. Other deficiencies are possible. All patients must have annual blood testing for the rest of their lives, to watch for deficiencies, and must take vitamin and mineral supplements for the rest of their life. Most deficiencies can be corrected with oral supplementation.
2. Difficulty tolerating some food textures
3. Intolerance of sugar (“dumping syndrome”), lactose, and alcohol.
4. Temporary hair loss, cold sensitivity, and other symptoms related to inadequate protein intake and/or rapid weight loss
5. Vomiting
6. Diarrhea
7. Constipation
8. Widening of the gastrojejunal anastomosis
9. The surgery may interact with prescription medicines. Some medicines may not be absorbed; others may be absorbed too quickly.
10. The lifestyle treatment is low risk. The diet recommended is a balanced one and we recommend a minimum intake of 1200 calories to allow for adequate nutrition. The exercise recommended is a mixture of low- and moderate-intensity activities that are increased gradually over time. The highest exercise goal (2500 kcal/wk above baseline) can be achieved by walking for about 1 hour each day.
11. There is a small risk of bleeding and infection associated with venipuncture.
12. The alternative treatment for these diabetics would be to seek standard care in their community.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Subjects are recruited through mass media advertisements and mailings to targeted groups such as worksites that have diverse populations or clinics, and from the clinic practices of the investigators and local referring endocrinologists and other physicians. The study is described to interested individuals at group orientation sessions at which time all questions that subjects have are addressed. After considering the study for at least 1 week, subjects are invited to an assessment session and asked to sign an approved consent form.

Consent forms are provided in each country’s most common language. Consent is obtained through direct interaction with discussion by a health care provider or associate who has been specifically trained for the task. Consents are retained on file for the duration of the study. Patients are afforded time away from the health care institution for deliberation and are provided the opportunity to have any further questions answered.

Protection Against Risks

To protect against risk all operations are performed by surgeons expert in the fields of bariatric and minimally invasive surgery. Safety screening and medical monitoring are performed by a safety committee and reviewed at twice-yearly intervals by the Data and Safety Monitoring Board.

Every attempt is made to decrease the incidence of peri-operative complications. Surgical procedures are done under strict protocol, which has been developed in face-to-face meetings with all participants in medical and surgical on numerous occasions. Expert site reviewers are on hand for the first five cases at each institution. All data regarding adverse outcomes are immediately reported to the Morbidity and Mortality committee, which reports to the sponsors as well as the steering committee. Other outcomes and quality issues are reviewed at the bi-annual meeting of the quality control committee via videoconference. Each site has extensive training in minimally invasive and bariatric surgery and functions as part of a multidisciplinary bariatric program.

All sites and investigators have agreed to the above protocols for the Intensive Medical Management and Surgical Management.

Subjects who are found to be consuming inadequate diets or engaging in potentially unsafe exercise without adequate prior conditioning are counseled accordingly. The minimum dietary intake goals for those in the non-surgery arm are set at 1200 calories per day to provide participants with sufficient calories for a nutritionally adequate diet. In addition, to reduce the risk of injury, all participants are taught to warm-up before and cool-down after exercise, and they are shown how to do appropriate stretching exercises. If an injury/illness does occur (due to the exercise or from other causes), the participant's exercise goals are reduced and/or alternative exercise suggested (if appropriate).

All adverse events are reported immediately to the Data Coordinating Center, the Steering Committee and the Data and Safety Monitoring Board. Severe adverse events (serious illness or death) are considered immediately by the Steering Committee and the Data and Safety Monitoring Board.

Potential Benefits of the Proposed Research to the Subjects and Others

The benefit likely to accrue to study participants is excellent treatment of diabetes through application of IMM. Excellent diabetic control is associated with better long term clinical outcomes in Diabetes Mellitus Type 1 and is likely to benefit in T2DM. The study question – does RYGB surgery improve on the clinical outcome seen with IMM alone – is well balanced with respect to risk and benefit. Improved diabetic control, and potentially associated weight loss may well balance the risk of surgery in this clinical situation.

Importance of the Knowledge to be Gained

Type 2 Diabetes Mellitus (T2DM) is a serious health problem that has increased dramatically worldwide due to the high and increasing prevalence of obesity. The last 30 years have witnessed a worldwide epidemic of T2DM and of T2DM-linked diseases, associated primarily with increases in obesity. At present, about one-third of all adults in the US are clinically obese by US standards (BMI ≥ 30 kg/m^2)[8] and by international standards (BMI ≥ 27 kg/m^2) obesity prevalence exceeds 50% in the US.[9] The impacts of obesity are also increasingly being felt outside the US, in Europe, South America, the Middle East, and Asia.[10] Rates of obesity increase have not been entirely uniform, but some of the highest recent gains have been in relatively less developed areas such as Brazil, Mexico, and parts of Asia.[11] Medical management of T2DM is of limited success.[2]

Data and Safety Monitoring Plan

A Data and Safety Monitoring Board (DSMB) will include at least the following: one endocrinologist, one surgeon with expertise in bariatric surgery, one behavioral scientists, and one statistician with expertise in clinical trials. Responsibilities of the DSMB will include: (1) approving the study protocols and informed consent materials and procedures prior to startup; (2) approving the plan for documenting and reporting adverse events; (3) approving plans for data analysis; (4) monitoring recruitment, eligibility, and adherence to protocol prior to randomization; (5) monitoring follow-up rates and adherence to the follow-up protocol; (6) monitoring adverse events; (7) providing recommendations regarding early termination of the studies for any reason; (8) providing recommendations regarding modifications of the protocol as necessary to protect patients or to preserve the scientific objectives of the study; (9) advising the investigators regarding whether an urgent announcement of study results or an expedited publication may be required; and (10) reviewing the primary manuscripts on study results to ensure that the findings are valid and presented accurately and completely.

The DSMB will meet once prior to study start-up to review and approve the protocol. Meetings occur at 6-month intervals subsequently until the operational period of the study is completed. One or more meetings are held after that to review the primary outcome results and primary papers emanating from the studies.

Women and Minority Inclusion in Clinical Research

The study is approximately 50% male and 50% female and will have sufficient sample size to allow analyses by gender, although with reduced power. We expect that 25% of the U.S. study population are minority. In our most recent U.S. weight-loss study 23% of participants were minority overall. The most heavily represented minority groups were African-Americans and Native Americans. To encourage minority participation, some advertisements and recruitment seminars are specifically focused on minority groups and organizations. By using this technique, we expect to recruit minority populations in comparable proportion to that found in the

cities of Minneapolis and St. Paul (about 20%), and considerably higher than those found in the metropolitan area as a whole (about 6%).

Inclusion of Children

The lowest age for inclusion in this study is 30 years.

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