Three Year Outcomes of Bariatric Surgery vs. Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Trial

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

***Please note that this study was completed in 2 Phases; 1 year results were the subject of an RC1 grant (Phase 1) and were previously published, 3 year results are part of an RO1 extension to the study (Phase 2) and are the subject of this manuscript. Please see (in red font) the specific aims of the extension (RO1, Phase 2) of the study on page 42 of this pdf document.
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30 Final Protocol......................................................................34
31 Summary of Changes..........................................................74
32 Original Statistical Analysis Plan.........................................76
33 Final Statistical Analysis Plan...............................................77
34 Summary of Changes..........................................................78
Provide a short title for this study (200 characters or less):

The Triabetes Study

T1.0 Select the type of application:
New Research Study

T2.0 Is the proposed research study limited to the inclusion of deceased individuals?
* no

T2.1 Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?
* no

T3.0 What is the anticipated risk to the research participants?
Greater Than Minimal Risk

CS1.0 CS1.0 What is the reason for this submission?
New Research Protocol Submission

CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?
no

If the study expired or if this is paper conversion, you are required to upload the last approved protocol and consent document, a completed the Research Study Renewal Report Form found on the IRB website and submit a Data and Safety Monitoring Report.

Upload the last approved protocol, consent document, Renewal Report Form and Data and Safety Monitoring Report:

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IRB # for expired study:

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?
no

CS2.0 Title of Research Study:
A Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes

Requested approval letter wording:

Research Protocol Abstract:

There has been a dramatic increase in the number of bariatric procedures performed in the last decade and bariatric surgery has been reported to result in significant changes in glucose metabolism in T2DM that often results in complete resolution of diabetes in many patients. Yet there remain many unanswered questions that require well-controlled studies to more completely inform health care decision making and clinical practice in this area. For example, it is not clear, whether diabetes is influenced by the type of surgery or by the amount of weight lost or if bariatric surgery is more effective than non-surgical weight loss induced by diet and physical activity in T2DM patients with more moderate BMIs (Class I and Class II obesity). Finally comparing the improvements in cardiovascular risk factors such as insulin resistance, cardio-respiratory fitness, hypertension and inflammation between surgical to non-surgical weight loss has not been well investigated.

Subjects between the ages of 25 and 55 years of age with T2DM confirmed by either a documented fasting blood glucose > 126 mg/dl or treatment with an anti-diabetic medication and mild to moderate obesity with a BMI between 30 and 40 kg/m2, upon successful completion of screening procedures, will be randomized to one of three treatment arms; gastric bypass, gastric banding, or a structured weight loss program. All participants will undergo detailed medical, psychological, and nutritional evaluation in addition to assessments of body composition, physical activity, and psychosocial correlates of change in body weight and behavior. A subset of patients will undergo intravenous glucose tolerance testing. Post-intervention, patients will follow intervention-specific protocols for a period of 12-months. The primary aim of this study is to determine the feasibility of performing a randomized trial comparing two major types of bariatric surgery, gastric bypass and gastric banding, versus a structured weight loss program induced by diet and increased physical activity in patients with Class I and II obesity and T2DM. A secondary aim is to obtain preliminary information regarding the effectiveness of various bariatric surgery procedures versus an intensive behavioral intervention to induce weight loss with diet and increased physical activity. Finally, we will explore the feasibility, methods for, and implementation of a range of early outcome measures including; resolution of diabetes, beta cell function, change in metabolic parameters, body composition, physical activity, and several psychosocial measures. The importance of this pilot study will be to provide crucial information necessary to plan a larger, more comprehensive and more long-term multi-center trial to further address critical unanswered questions in this emerging area.

Name of the Principal Investigator:

Anita Courcoulas

Affiliation of Principal Investigator:

UPitt faculty member

Address of Principal Investigator:

3380 Boulevard of the Allies, Suite 390
Pittsburgh, PA 15213

Recorded Primary Affiliation of the Principal Investigator:

U of Pgh | School of Medicine | Surgery
CS3.4 Identify the School, Department, Division or Center which is responsible for oversight of this research study:

U of Pgh | School of Medicine | Surgery

CS3.5 Telephone Number of Principal Investigator:

(412) 641-3678

CS3.6 Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:

courcoulasap@msx.upmc.edu

CS3.7 Fax Number:

(412) 641-3640

CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?

* no

CS3.9 Is this your first submission, as PI, to the Pitt IRB?

* no

CS4.0 List of Co-Investigators:

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CS5.0 Name of Primary Research Coordinator:

Jessie Eagleton

CS5.1 Address of Primary Research Coordinator:

3380 Boulevard of the Allies, Suite 390
Pittsburgh, PA 15213

CS5.2 Telephone Number of Primary Research Coordinator:

(412) 641-3743

CS6.0 Name of Secondary Research Coordinator:

CS6.1 Address of Secondary Research Coordinator:

CS6.2 Telephone Number of Secondary Research Coordinator:

CS6.3 Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):

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There are no items to display
CS7.0  Will this research study use any Pediatric PittNet or Clinical and Translational Research Center (CTRC) resources?
   yes

CS7.1  Please select the sites you intend to use:
   CTRC - Montefiore Hospital Clinical and Translational Research Center

CS8.0  Select the entity responsible for scientific review.
   External Scientific Review Completed – The scientific merit of this research protocol has been confirmed by an external scientific review committee as a condition of funding.

CS9.0  Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?
   *yes

CS9.1  Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?
   *no

CS10.0  Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?
   * no
   If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.o3is.pitt.edu).

CS11.0  Use the 'Add' button to upload one or more of the following:
   - the sponsor protocol (including investigator initiated studies) and/or other brochures
   - the multi-center protocol and consent form template, if applicable

   Name Modified Date
   Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).
   * no

   Is this a multi-centered study?
   * no
CS12.0 Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?
* 

CS13.0 Does this research study involve the deliberate transfer of recombinant DNA (rDNA) or DNA or RNA derived from rDNA into human subjects?
* no

Upload Appendix M of NIH Guidelines:

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CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?
* yes

If Yes, upload completed Research Fiscal Review Form:

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CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use Other to include sites not listed:
Sites:
University of Pittsburgh
UPMC

University of Pittsburgh
Campus:
Main Campus - Pittsburgh

List university owned off-campus research sites if applicable:

UPMC
Sites:
UPMC Presbyterian
UPMC Magee Women’s Hospital
UPMC Montefiore

If you selected School, International or Other, list the sites:

* For non Pitt or UPMC entities, upload documents granting permission to conduct research at that site:

CS15.1 Have you, Anita Courcoulas, verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?
* yes

CS15.2 Describe the availability of resources and the adequacy of the
facilities to conduct this study:

*  

[reviewer notes¬]

CS16.0 Special Research Subject Populations:

<table>
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<th>Categories</th>
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[reviewer notes¬]

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* no

1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)

The proposed project will address the lack of randomized controlled studies and comparative effectiveness research in bariatric surgery by utilizing a three arm randomized trial to compare surgical and non-surgical treatments for Type 2 diabetes in obese subjects. Understanding more clearly the impact of bariatric surgery compared to a non-surgical, intensive lifestyle intervention for the treatment of diabetes in the setting of obesity will have a major impact on both the science and public health for the communities of obese and diabetic patients in this country and worldwide.

1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).

Aim 1. To determine the feasibility of performing a randomized trial comparing two major types of bariatric surgery, Laparoscopic Roux en Y Gastric Bypass (RNY) and Laparoscopic Adjustable Gastric Banding (GB) versus a lifestyle weight loss intervention (LWLI) induced by diet and increased physical activity in moderately obese patients (Class I and II obesity) with T2DM. We hypothesize that: 1) A randomized design with both surgical and non-surgical arms will be both feasible and acceptable to participants and to providers 2) There will be no difference in retention rates between the LWLI and surgical arms (RNY, GB) of the study and it will provide estimates of overall retention for future studies.

Aim 2. To obtain preliminary information regarding the effectiveness of two dominant bariatric surgery procedures versus an intensive lifestyle intervention to induce weight loss with diet and increased physical activity. We hypothesize that: 1) RNY will be superior to GB and LWLI in weight lost in 12 months.

Aim 3. To explore the feasibility, methods for, and implementation of a range of early outcome measures including; resolution of diabetes, glucose control, medication usage, insulin resistance, beta cell function, body composition, objective measures of physical activity, and several psychosocial measures. We hypothesize that: 1) Participants will be willing to undergo a range of early outcome testing measures to assess metabolic change, body composition alterations, objective physical activity, and psychosocial factors. 2) Measures of T2DM improvement including an intravenous glucose tolerance test (IVGTT) will be feasible in a subset of participants in each study arm and RNY will be superior to both GB and LWLI for the clinical and metabolic improvement of T2DM. 3) The LWLI group will show improvements in physical activity compared to RNY and GB.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

BARIATRIC SURGERY AND THE TREATMENT OF TYPE 2 DIABETES:

One of the key questions in the scientific, medical and lay communities is whether or not bariatric surgery represents a long-term effective treatment for T2DM. Type 2 diabetes mellitus (T2DM) is a worldwide epidemic, and it is currently the 6th cause of death in the US and a major cause of kidney failure, blindness, amputations, heart attack and others vascular and gastro-intestinal dysfunctions. It is estimated that there will be 380 million affected individuals worldwide by 2025. The pathogenesis of T2DM is regarded as a combination of
impaired insulin secretion and insulin resistance (IR). Traditionally, treatments include intensive lifestyle modification with or without glucose lowering agents. Neither treatment alone, or in combination, results in complete amelioration of diabetes and its potential long-term complications.

Operations for morbid obesity range from purely restrictive procedures such as vertical banded gastroplasty (VBG) and adjustable gastric banding (GB) to gastrointestinal bypass procedures such as Roux-en-Y gastric bypass (RNY) and the biliopancreatic diversion (BPD). The two dominant procedures currently in use in the United States are the Roux-en-Y gastric bypass and the adjustable gastric band and they are the subject of this investigation. Dramatic improvements in glycemic control have been observed in subjects with T2DM specifically after RNY and BPD.4-7 The remarkable resolution of diabetes after these two procedures typically occurs rapidly and prior to significant weight loss, suggesting that these operations may have a direct and profound impact on glucose homeostasis. Clinical resolution, usually defined as independence from all anti-diabetic medications, was reported to occur in 47%-70% of patients after restrictive procedures (currently only the GB is in use), 80-98% after RNY and 92.5 to 100% after BPDs.8 Long-term (up to 16 years) control of glycemia after RYGB have been documented in the severely obese. Furthermore, mortality risk from diabetes over a 10-year follow-up was reduced after RNY compared to patients with T2DM matched for age, weight, and BMI who did not undergo operation (1.0% versus 4.5% for every year of follow-up).9

Although data are sparse, there is also compelling evidence that bariatric surgery can result in dramatic improvements or complete resolution of diabetes even in the non-morbidly obese.10-12 Because of this growing literature demonstrating improvements in T2DM following bariatric surgery and the fact that weight loss involving calorie restriction and physical activity is difficult for most obese patients, there is much interest by both patients and providers in offering 'metabolic' surgery to patients with Class I and II obesity (mild and moderate obesity) for control of T2DM. The Diabetes Surgery Symposium held in Rome, Italy in 2007 indicated as a major point of consensus that "gastrointestinal surgery may be appropriate for the treatment of T2DM in patients who are good surgical candidates with BMI of 30 to 35 who are inadequately controlled by lifestyle and medical therapy". However, despite these recommendations, the role of a non-operative comparison cohort for diabetes treatment has not been sufficiently addressed by current available research. A recent study by Dixon et al. demonstrated that the reduction in diabetes risk following gastric banding (GB) compared to a randomized control, non-surgical treatment group of patients with BMIs 30-40 kg/m2 was due to the amount of weight loss.13 The medical weight loss program in this study resulted in <2 kg weight loss at one year. An earlier study by Dixon et al. saw greater improvement in metabolic syndrome in those patients with a BMI of 30 to 40 kg/m2 randomized to an intensive medical management program but the improvements were still less than those in the GB group.14 In contrast, the multi-center Look AHEAD Study has shown an 8.6% weight loss and reduction in A1C from 7.3% to 6.6% at 12 months in response to an intensive lifestyle intervention. This argues that a randomized trial that includes an effective and intensive one-on-one behavioral weight loss program is urgently needed to better objectively inform practitioners as well as patients with T2DM how various surgical options compare to an effective behavioral weight loss program.

Randomization of participants into three treatment arms, as proposed in this study, will begin to answer some of these questions and is justified due to the gap in knowledge of most effective therapy for patients with T2DM in addition to the safety and risk/benefit ratio being roughly equal across all three treatment arms. A recent publication in the New England Journal of Medicine by the LABS Consortium has demonstrated a low overall risk of death and other adverse outcomes after bariatric surgery. In this study, the 30-day rate of death among the 4,776 patients who underwent RNY or GB was 0.3%. Additionally, a significant association between BMI and increased risk of mortality and adverse event rates was observed.21 Similarly, AHRQ data published in 2007 revealed a 0.19% rate of inpatient death among 121,055 bariatric surgery patients.22 Non-surgical diabetes treatment is not without risk. Seven studies published between 2002 and 2007 revealed annual mortality rates from 2.0-8.7% in patients with T2DM due to diabetic complications.23-28

In summary, there still remain many unanswered questions about the relative utility of surgical and medical treatment for the BMI strata of 30-35 and 35-40 kg/m2 that will require well-controlled studies to more completely inform health care decision making and clinical practice in diabetes treatment. For example, it is not clear, whether diabetes is influenced by the type of surgery or by the amount of weight lost or if bariatric surgery is more effective than non-surgical weight loss induced by diet and physical activity in T2DM patients with more moderate BMIs (Class I and Class II obesity). Finally comparing the improvements in cardiovascular risk factors such as insulin resistance, cardio-respiratory fitness, hypertension and inflammation between surgical and non-surgical weight loss has not been well.
1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

GAPS IN BARIATRIC SURGICAL RESEARCH:

Despite tremendous growth in the use of bariatric surgical procedures, research on these interventions continues, until recently, to be reported primarily through the case series of experienced practitioners and has focused only on selected outcomes. As a result, there is a gap between the proliferation of these procedures and the evidence base needed to understand key components of their use. This gap includes an assessment of the effectiveness of bariatric surgery in the population at large, the total impact of bariatric surgery on patients and the health care system, identification of which patients are best suited for specific surgical procedures, and the physiological mechanisms that promote sustained weight loss after surgery. Understanding the circumstances that have limited research in bariatric surgery should help direct future investigators to the challenges that need to be addressed when studying the important and increasingly performed group of weight loss procedures. Some of these perceived and identified barriers to furthering research in bariatric surgery are particularly relevant to this study. The first and one of the most important, is a lack of randomized trials in bariatric surgery and especially the lack of randomized comparisons between operative and best available non-operative treatments for weight loss. In addition, there is a lack of generalizability of bariatric surgical interventions, there is only short-term and incomplete longitudinal follow-up of bariatric surgical subjects in most studies, there is considerable difficulty in the evaluation of safety for elective bariatric procedures where serious adverse outcomes are rare, and there are problems in addressing the broad range and multiple domains of outcomes following bariatric surgery that require a very comprehensive approach to prospective research. Finally, a significant challenge for the future of bariatric surgical research is funding of high quality comparative effectiveness studies in this field. This study will address the first and last of these aforementioned barriers; lack of randomized studies and the funding of comparative effectiveness research in bariatric surgery.

The NIH-NIDDK funded LABS Consortium (U01 DK066585) is an ongoing multi-institutional, prospective and comprehensive evaluation of the safety, efficacy, and some mechanisms in bariatric surgery and will certainly begin to address some of these identified knowledge gaps such as generalizability, evaluation of safety, longitudinal outcome evaluations, and the prospective assessment of the range of outcome domains. It will not, however, provide a control group for comparison or be able to evaluate, in a randomized way, the differences between operative and non-operative treatments for weight control. The LABS phase 3 study of diabetes; “Mechanisms for Improving Type 2 Diabetes Following Bariatric Surgery” is sub study currently underway within LABS to study diabetic patients undergoing gastric bypass and to investigate mechanisms of diabetes improvement following gastric bypass versus a control, non-operated group.

THE IMPACT ON PUBLIC HEALTH:

Most current bariatric surgery patients are severely obese (BMI > 40) or moderately obese (BMI 35 – 40) with high-risk, obesity-related medical co-morbid conditions such as T2DM or severe sleep apnea. The prevalence of clinically severe obesity (BMI > 40) is 4.8%, and obesity (BMI > 30) is 32.2% among U.S. adults. The number of weight loss surgery patients is growing not only due to increases in the prevalence of moderate and severe obesity and its complications, but also to advances in surgical technique and the mounting evidence demonstrating the benefits of bariatric surgery. Gastric bypass remains the most common procedure in the U.S. with the number of gastric banding (GB) procedures growing approximately 20-25% per year. The number of bariatric surgical procedures in the U.S. increased from 13,000 in 1998, to over 100,000 in 200315 and the American Society for Metabolic and Bariatric Surgery (ASMBS) estimates that 250,000 bariatric surgery procedures were performed in 2008. The number of bariatric surgery patients will continue to increase as patients with severe obesity and moderate obesity with co-morbid conditions such as T2DM demand access to effective treatment. For example, in 2002 bariatric surgical procedures were performed on only 0.6 percent of the 11.5 million clinically eligible U.S. adults in 2002.17 Although bariatric surgery is expanding dramatically to meet the global epidemic of severe obesity, currently only 1% of eligible patients are undergoing procedures worldwide.18 Furthermore, the criteria for surgery are expanding to include a wider range of patients; including both older and younger patients, as well as patients with lower BMIs (30-35 kg/m2) and T2DM. Well-designed and well-controlled clinical studies are necessary to further define the potential role of surgical options for the treatment of diabetes in this population.

https://www.osiris.pitt.edu/...F42844113482999E9EE]]&PrintBySection=true&PrintHeaderView=true&PrintHeaderInfo=true&PrintLogo=true[1/6/2015 1:17:18 PM]
Diabetes is the most costly disease in the United States, consuming one out of every 7 health care dollars and accounting for 137 billion dollars of cost annually including both medical care costs and lost wages and productivity. Diabetes is a leading cause of death and increases the risk for heart disease six fold and multiplies the risk of stroke by four. Diabetes-related conditions are severe and disabling and include; amputations, loss of eyesight, and end stage renal disease. The projected U.S. diabetic population, alone, in 2012 is 22.7 million. Understanding more clearly the impact of bariatric surgery compared to a non-surgical intensive lifestyle intervention for the treatment of T2DM will have a major impact on both the science and the public health for the communities of both obese and diabetic patients in this country and worldwide.

2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

* yes

2.1.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specific disease or condition?

* no

2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* no

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

Comparative Effectiveness Research, Feasibility, Descriptive and Evaluative, Randomized, Active Treatment Controlled
2.3.1 Does this research study involve a placebo-controlled arm?
* no
[reviewer notes¬]

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?
* no
[reviewer notes¬]

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?
* yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

Individuals who inquire about this study will be asked to complete a brief telephone interview to assess initial eligibility, with eligible participants invited to attend a group orientation. The investigators will provide a detailed description of the study at this orientation, and subjects will be encouraged to have all of their questions regarding their participation in this study answered. Individuals who remain interested at the orientation session, will complete a screening assessment that will be reviewed by the investigators. If a patient is deemed ineligible based on review of the screening assessment, the document will be destroyed. Potential participants with BMI between 30 and 35 kg/m2 will be required to provide a note from their endocrinologist approving their participation in the study and documenting the difficult to control nature of their T2DM. If deemed eligible, individuals will be scheduled to meet with the surgeon (Dr. Courcoulas) where detailed written informed consent will be obtained and for a complete medical evaluation. Women of child bearing potential will be required to give a urine sample at this time for a pregnancy test. Subjects will then be scheduled to meet with the clinical psychologist and nutritionist to evaluate their appropriateness for this study and to determine if there are any factors that may negatively impact compliance with the surgical, medical, and/or lifestyle aspects of this study. Similar screening procedures to those described here are already in place for both surgical and non-surgical subjects at this site and they will both be adapted conform to the common flow shown in the attached flow chart. Upon successful completion of all screening procedures, individuals who remain eligible will be randomized to one of three treatment arms; one of two bariatric surgery procedures RNY or GB (Surgical Weight Loss Intervention-SWLI) or the lifestyle weight loss intervention (LWLI).

All SWLI patients will undergo further preoperative surgical testing including; blood work, upper GI to assess foregut anatomy, electrocardiogram, and chest radiograph.

[reviewer notes¬]

2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:
- all research activities
- personnel (by role) performing the procedures
- location of procedures
duration of procedures
timeline of study procedures

Pre-intervention, participants who meet the inclusion criteria will be enrolled into the study and undergo detailed medical evaluation at Magee-Womens Hospital of UPMC with Dr. Courcoulas. Included in this assessment are collection of demographic information, medication assessment, comorbidity status, height, weight, percent body fat, waist circumference, and blood pressure. Subjects who continue to meet study inclusion criteria will then be scheduled to meet with the clinical psychologist, Linda Ewing, RN, PhD and a Magee-Womens Hospital dietician for standard psychological and nutritional evaluation for bariatric surgical/diabetic candidates. These evaluations will evaluate appropriateness for the study and will determine if there are any factors that may negatively impact compliance with the surgical, medical and/or lifestyle aspects of this study.

Randomization will be by random assignment so that each participant has an equal chance of being assigned to each of the three treatments. Randomly permuted block sizes stratified by BMI will be used to ensure that representative groups are entered into all three study treatment groups. The randomization schema will be provided by the data managers of the ONRC/PAWMRC and randomization envelopes will be used to ensure allocation concealment.

Following randomization, the 40 patients assigned to the Surgical Weight Loss Intervention (SWLI) will undergo further preoperative testing including blood work, upper GI to assess foregut anatomy, electrocardiogram, and chest radiograph. All preoperative testing will take place at Magee-Womens Hospital facilities within 3 months of surgical intervention.

All 60 participants will attend a baseline research visit in the Endocrinology and Metabolism Research Center (EMRC) under the direction of Dr. Goodpaster. This visit will include assessments of body fatness, physical activity, psychosocial correlates of change in body weight and behavior, and a baseline blood draw. Body composition (fat mass, lean body mass, bone mineral content, bone mineral density, and percent body fat) will be assessed using a GE Lunar iDXA dual-energy x-ray absorptiometer (Lunar, Inc., Madison, WI). Subjects will be clothed in a lightweight hospital gown and will be instructed to remove all jewelry, hairpins, etc. that would potentially affect the accuracy of this measurement. The scanner will be calibrated each day according to the guidelines specified by the manufacturer. To assess physical activity, participants will wear the SenseWear Pro Armband (BodyMedia, Inc.) for 9 to 11 consecutive days prior to undergoing intervention. Psychosocial correlates of change in body weight and behavior will be assessed at this timepoint through administration of six questionnaires: (1 & 2) Self-Efficacy for Weight Loss and Physical Activity: Self-efficacy for weight loss will be assessed using the questionnaire developed by Clark et al. (1991) Self-efficacy for exercise will be assessed using the questionnaire by Marcus et al. (1992); (3) Outcome Expectations: The questionnaire developed by Steinhardt and Dishman (1989) will be used to assess outcome expectations for physical activity with modifications specific to eating behavior and weight loss; (4) Perceived Barriers: The questionnaire developed by Steinhardt and Dishman (1989) will be used to assess perceived barriers for physical activity with modifications specific to eating behavior and weight loss; (5) Beck Depression Inventory (BDI): The Beck Depression Inventory (BDI) is a series of 21 questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric diagnoses; (6) SF-36: The SF-36 is a multi-purpose, short-form health survey with 36 questions which yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. In addition to the above questionnaires, patients will be asked to fill out the following forms in order to capture the information detailed below (Table 1) and in the more detailed chart attached in the 'Supporting Documentation' section: Treatment Preference Questionnaire which will be used to gauge willingness to be randomized and drop-out rates; Eating and Weight History Questionnaire to assess past attempts at weight loss and weight status of the patient and the patient's family; Measure of Weight Loss Goals; Diabetes History Questionnaire; Diabetic Medication Log; Additional Treatments Questionnaire; and Physical Activity Armband Diary. Total time for completion of these questionnaires will be 30-45 minutes. Blood assays including fasting glucose, HgbA1C, insulin, lipid profiles, C-peptide, and markers of inflammation will be drawn and measured in Dr. Goodpaster's laboratory.

Table 1. Study Measures and Assessments

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Pre-intervention, a subset of 18 participants (6 from each of 3 treatment arms- gastric bypass, gastric banding, and lifestyle) will undergo frequently sampled intravenous glucose tolerance testing (FS-IVGTT) at the University of Pittsburgh Montefiore CTRC under the direction of Dr. Goodpaster. This measure will examine the effect of each of the 3 study interventions on the acute insulin response (AIRglucose) and insulin sensitivity (Si) before and after treatment. Subjects taking exogenous insulin will not be eligible for this subset outcome measure. Patients with diabetes on oral medications who enter this study will be asked to stop their medications for 5 days before metabolic testing. During this time, the participants will monitor their blood glucoses twice a day, before their morning and evening meals. If the patient obtains a fasting blood glucose value of 300 mg/dl or more they will be required to contact study staff, will be withdrawn from the IVGTT portion of the study and will be instructed on how to resume diabetic medications. Six patients from each treatment group will be admitted for an overnight stay at the CTRC between 5-7 PM and fed a standard meal of 7kcal/kg. Following the meal, patients will remain fasting (except water) until completion of all study procedures the following day. After a 12 hour fast, intravenous catheters will be placed in both antecubital veins. After fasting samples are obtained, 50% dextrose and insulin will be given in dosages calculated on the basis of body surface area due to the high body mass of obese subjects. Blood samples will be obtained at minutes -15, -10, -5, +2, +3, +4, +5, +6, +8, +10, +12, +14, +16, +19, +22, +23, +24, +25, +27, +30, +40, +50, +60, +70, +80, +90, +100, +120, +120, +140, +160, +180 for determination of insulin sensitivity and insulin secretion.

All 40 of the participants randomized to the SWLI will undergo surgery performed by Dr. Courcoulas at Magee-Womens Hospital under general anesthesia and will receive DVT prophylaxis with subcutaneous heparin and sequential compression devices on the lower limbs. On the morning of surgery, women of child bearing age will be required to undergo urine hCG testing to determine pregnancy status. Half of the participants randomized to the SWLI will undergo laparoscopic Roux-en-Y Gastric Bypass (RNY) and half will undergo laparoscopic Gastric Banding (GB). The RNY will be performed with a standard retrocolic, retrogastric technique, using a linear stapled and hand sewn gastrojejunal anastomosis. The GB will be performed using the Allergan 10 Lap Band with suture securing of the gastric cardia to prevent slippage, the placement of the infusion port on the anterior rectus muscle. Post-operative length of hospital stay will be 48 hours for the RNY participants and 24 hours for the GB participants. All SWLI participants will undergo upper GI radiography prior to discharge to rule out any anastomotic leaks or obstructions.

The 20 participants randomized to the Lifestyle Weight Loss Intervention (LWLI) will receive a standard behavioral weight control program that will be delivered in an in-person format under the direction of Dr. Jakicic at the PAWMRC located in Birmingham Towers. This intervention is based on the intervention developed for the Diabetes Prevention Program (DPP) and the Look AHEAD Study (a multi-center study of adults with T2DM). Dr. Jakicic and colleagues have adapted these intervention materials into an ongoing 12-month intervention.
for weight loss to treat class II and III obesity. During the initial 6 months of treatment, participants will attend weekly in-person intervention sessions. During months 7–12, participants will attend in-person sessions on the 1st and 3rd week of the month and will receive a brief (<10 minutes in duration) telephone contact on the 2nd and 4th week of the month. This will facilitate weekly contact throughout the 12-month intervention. Each group visit will focus on a specific behavioral topic related to weight loss, eating behaviors, or exercise behaviors. Participants are provided written materials to supplement the in-person and telephone interactions with the weight loss counselor. Participants will monitor body weight, eating behaviors, and exercise behaviors. Body weight will be measured at each in-person meeting and participants will also be encouraged to measure their body weight on their own during weeks when no in-person visits are scheduled (e.g., months 7–12). Participants will be encouraged to self-monitor their eating and exercise behaviors and will be provided with a weekly diary to record eating and exercise patterns. Participants will return the completed diary to the intervention staff at each in-person visit for review, and the intervention staff will provide written feedback on the diary prior to it being returned to the participant. All subjects will be prescribed an energy restricted dietary intervention that has been shown to effectively reduce body weight by 8–10% within the initial 6 months of treatment. This will include reducing energy intake to 1200 to 1800 kcal/d based on initial body weight. To facilitate the adoption of the dietary recommendations, individuals will be provided with meal plans that will allow them to plan for modifications in their daily and weekly meal plans, and a calorie counter book. To further facilitate the compliance with the dietary recommendations and to enhance weight loss we propose to provide meal replacements (Slim Fast or Glucerna products) to participants in the LWLI group. Participants will be prescribed exercise that is consistent with data that have shown that higher levels of exercise may be important for preventing weight regain.20,24 Specifically, subjects will be instructed to engage in moderate intensity exercise 5 days per week. The total duration per day will begin at 20 minutes per day and will gradually progress to at least 60 minutes per day. Exercise will be progressed in a gradual manner (5-10 min/d in 4 week intervals) in an attempt to maximize adherence and minimize the onset of musculoskeletal injury. Exercise intensity will be set at 55-70% of age-predicted maximal heart rate. The overall management of the participant's diabetes will be the responsibility of their primary care physician (PCP) or endocrinologist with additional oversight by the study endocrinologist, Dr. Toledo. Therefore prior to initiating the intervention all participants in the LWLI group will be taught how to monitor their blood glucose, and if they do not have a home blood glucose monitor they will be referred to their primary care physician or a study associated diabetes nurse to facilitate the attainment of a home glucose monitor. Participants will also be provided with information regarding symptoms and signs of hypoglycemia and instructions on treating hypoglycemia. During periods of weight loss, participants in the LWLI group may need reductions in diabetes medication(s) to reduce their risk of hypoglycemia. The medical team associated with this study will be responsible for medication adjustment in cooperation with the participant’s PCP/endocrinologist, and this information will be communicated to the intervention staff.

2.6.1 Will blood samples be obtained as part of this research study?

* yes

If Yes, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:

All subjects will have blood drawn at baseline and 12-month follow-up visits. The blood collected during these timepoints will be processed in Dr. Goodpaster's laboratory for the purposes of assaying fasting glucose, insulin, lipid profiles, and markers of inflammation. A maximum of 50 mL (3.4 Tablespoons) will be required for the blood draws at these time points.

The subset of 15 participants will undergo a frequently sampled intravenous glucose tolerance test (FS-IVGTT) at baseline and 12-month follow-up visits. This test will require a volume of approximately 12 tablespoons at each timepoint, or a total volume of approximately 24 tablespoons during the course of the study.

Additionally, the 40 subjects in the SWLI treatment arm will be required to undergo standard laboratory studies for bariatric surgical candidates to determine eligibility for surgery. This will be a one time blood draw and will not require more than 20mL of blood.
2.7 Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* yes

Detailed procedures listed in the textbox below:

Among the SWLI participants, RNY patients will undergo follow-up assessments at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months which is consistent with current clinical practice. GB patients will follow-up post operatively at 2 weeks, and 2, 4, 6, 8, 10, and 12 months with the first band adjustment at approximately 2 months and at 60% of the follow-up visits, as needed for clinically appropriate gastric restriction. Measure of weight on a Tanita scale will be captured at each follow-up visit. SWLI patients will be counseled on a diet program consistent with post bariatric surgery, progressing from clear liquids for 1 to 2 weeks, soft foods for 2 to 4 weeks and then stabilizing at 6 weeks to 3 small, solid protein-rich meals and one healthy snack per day. Participants will be encouraged to exercise a minimum of 3-4 times per week and to focus on weight-bearing, aerobic exercise options. Diabetes management will be overseen by Dr. Toledo, the study endocrinologist, and will be coordinated between the surgeon follow-up visits and close communication with the subject’s family physician or endocrinologist as adjustment of diabetic medications is routine following weight loss surgery interventions.

In addition to the previously noted intervention-specific follow-up procedures, all 60 participants will be seen at 6- and 12-months post-intervention. Both time points will involve a detailed medical assessment by Dr. Courcoulas that includes medication assessment, comorbidity status, height, weight, percent body fat, waist circumference, blood pressure, complication assessment, documentation of health care utilization, and completion of the five psychosocial correlates of change in body weight and behavior questionnaires. The 12-month follow-up time point will also include a visit to the EMRC where, under the direction of Dr. Goodpaster, the body fatness (DXA), physical activity measures, and blood draw/assays will be repeated in the same manners as the baseline visit. The subset of 15 participants who completed IVGTT testing at baseline will undergo repeated testing at the 12-month follow-up timepoint in the UPMC Montefiore CTRC under the direction of Dr. Goodpaster.

2.8 Does this research study involve the use of any questionnaires or survey instruments?

* yes

Upload a copy of all unpublished surveys/questionnaires. Also upload any published materials that may include questions, images, video, or sound recordings that may be especially disturbing to subjects:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triabetes WELS 10.29.2009.doc</td>
<td>12/23/2009 8:34 AM</td>
</tr>
</tbody>
</table>
List the name and publisher for commercially available materials (Note: these materials do not need to be uploaded):

2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?

* yes

If Yes, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:
Fasting blood glucose levels will be used to determine type 2 diabetes (T2DM) status in participants. This laboratory value will have most likely been obtained prior to a participant's enrollment by their PCP and will be used as a screening parameter.

2.10 The blood sample question was moved to 2.6.1.

2.11 What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?

* 12-15 months

2.12 Does this research study involve any type of planned deception?

If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* no

2.13 Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?

* no

2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* yes

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in...
the medical records.

Preoperative testing including blood work, upper GI, electrocardiogram, and chest radiograph in addition to records pertaining to the operation and hospital stay will be placed in the patient's medical records.

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* no

I, Anita Courcoulas, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed HIPAA Researchers Privacy Requirements (Formerly RPF Module 6) training. The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

* yes

2.14.2 Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI from a UPMC/Pitt covered entity? Note that the University of Pittsburgh IRB cannot grant a HIPAA waiver for entities outside of UPMC/Pitt.

* no

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* no

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* no

2.17 What are the main outcome variables that will be evaluated in this study?

Prior to analysis of major outcomes, we will describe study participants and compare the intervention groups on variables of interest (age, BMI, etc) to assess the effectiveness of the randomization in creating groups that are similar pre-intervention. We will control for any unforeseen important differences between the groups in multivariable analyses. We will also do a similar comparison of completers and non-completers (drop-outs) to determine whether completers are representative of the baseline cohort. To examine feasibility (Specific Aim 1) and to inform a larger-scale trial we will collect and analyze data related to the following parameters: 1) recruitment, 2) willingness of subjects to undergo randomization to the proposed treatment arms, 3) retention of subjects across the 12 month study in all arms, 4) compliance with the interventions (i.e., attendance at required sessions, etc.). For Specific Aim 2 and Specific Aim 3, the primary outcome measures are continuous variables (e.g. weight loss, insulin sensitivity, insulin secretion, physical fitness, physical activity, lipid profiles etc.) and the principal analytic goal is to assess the magnitude of change in the specified outcome parameters associated with the assigned intervention groups. Initially, crude (univariate) change scores (from baseline to 12 months post intervention) in the outcome parameters of interest will be plotted graphically by treatment assignment.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:
To examine Specific Aims 2 and 3 we will use a mixed model approach for the analysis of the data to determine if the interventions are successful in changing outcome. For data missing completely at random appropriate statistical analytical methods can be employed. Other options include imputing data or creating indicator variables (generally the least desired approach) to identify missing data. Dropout or censoring will often be informative so the missing outcome data may be "non-ignorable." An exploratory approach used to assess the extent of potential bias and its effect on analysis is to compare characteristics of patients with available data to those with missing data. For data missing completely at random (does not depend on observed outcome; MCAR) linear mixed model analysis provides unbiased results. However, in other cases where the dropout depends on observed outcome and/or covariates (missing at random, MAR) or unobserved outcome and/or covariates (missing not at random, MNAR), we will use selection models such as MNAR Dale model and Diggle-Kenward model. These models often require strong assumptions on the dropout mechanism which are primarily unverifiable based on the observed data. We will conduct sensitivity analyses to investigate the sensitivity of our conclusion to possible violation of such assumptions. We will also fit MCAR, MAR and MNAR and compare the model fits using log-likelihoods. We will consider other approaches to analyzing longitudinal data with informative censoring including modeling the censoring process jointly with the fitted model of interest and weighted estimating equations using inverse probability of missingness to account for the potential bias that arises due to the missing outcomes.

2.19 Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* no

2.21 Will this research study be conducted within a nursing home located in Pennsylvania?

* no

Section 3 - Human Subjects

3.1 What is the age range of the subject population?

Subjects between the ages of 25 and 55 will be enrolled into this research study.

3.2 What is their gender?

* Both males and females

Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?

* no

If Yes, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* yes
3.5 **Participation of Children:** Will children less than 18 years of age be studied?

* no

If **No**, provide a justification for excluding children:

Children will not be included in the proposed study for a number of reasons. The first of which is that it is not standard clinical practice to perform weight loss surgery in children under 18 years of age and remains experimental among children and adolescents in this age range. Additionally, some of the knowledge being sought in this research is being investigated in another ongoing study at our department, TeenLABS, which aims to facilitate coordinated clinical, epidemiological and behavioral research in the field of adolescent bariatric surgery.

[reviewer notes¬]

3.6 **Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?**

* no

[reviewer notes¬]

3.7 **Will pregnant women be knowingly and purposely included in this research study?**

* no

[reviewer notes¬]

3.8 **Does this research study involve neonates?**

* no

[reviewer notes¬]

3.9 **Fetal Tissues: Does this research involve the use of fetal tissues or organs?**

* no

[reviewer notes¬]

3.10 **What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?**

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 150

3.11 **Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.**

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number to undergo research procedures</th>
<th>Number to undergo screening procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1288</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1289</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1290</td>
<td></td>
</tr>
</tbody>
</table>

[reviewer notes¬]
3.12 **Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.**

* Described below:

This is a feasibility trial with an expected 60 patients randomized into three treatment arms and is intended to function as a pilot study for a larger scale trial. We do not anticipate having power to determine the statistical significance of the outcomes in this trial.

3.13 **Inclusion Criteria: List the specific criteria for inclusion of potential subjects.**

- Age 25 to 55 years
- Mild to moderate obesity with a BMI between 30 and 40 kg/m²
- For potential subjects with BMI 35 to 40 kg/m²: T2DM confirmed by either a documented fasting blood glucose > 126 mg/dl OR treatment with an anti-diabetic medication
- For potential subjects with BMI 30 to 35 kg/m²: T2DM that is difficult to control medically and is recommended for the study by the subject's endocrinologist AND treatment with an anti-diabetic medication
- Willingness to be randomized to a surgical intervention

3.14 **Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.**

- Prior bariatric or foregut surgery
- Poor overall general health
- Impaired mental status
- Drug and/or alcohol addiction
- Current smoking
- Pregnant or plans to become pregnant
- Type 1 Diabetes Mellitus
- Portal hypertension and/or Cirrhosis
- Failed study-related nutrition or psychological assessment
- Current participation in any other research study
- Inability to provide informed consent
- Unlikely to comply with study protocol
- Unable to communicate with study staff
- Unable to exercise (walk a city block or a flight of stairs)

3.15 **Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?**

* no

If **Yes**, provide a justification:

---

**4.1 Select all recruitment methods to be used to identify potential subjects:**

- Advertisements
- Recruitment Letters and/or Scripts
- Other Strategies: Described below

**Advertisements**
4.2 Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:

Subjects will be initially contact by both a recruitment letter (registry patients) and by telephone (those responding to advertisements and flyers).

[reviewer notes→]

4.6 Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document, such as with phone screening. This is not a waiver to obtain consent.

* yes

4.6.1 Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form. 

Addressed below:

If not all, identify the specific procedures and/or subject populations for which you are requesting a waiver:

We request a waiver for requirement to obtain a signed, written informed consent form for phone screening interviews, attendance at orientation sessions (described in section and completion of the baseline screening assessment forms only. When eligibility has been determined and the patient is seen in-person by the investigator, signed, written informed consent will be obtained.

This will apply to all subjects recruited through advertising techniques. Those patients identified in the clinic by Dr. Courcolas will not require this waiver because we will be able to evaluate the patient's eligibility based on the investigators review of clinical information and the signed informed consent can be obtained at that time.

4.6.2 Indicate which of the following regulatory criteria is applicable to your request for a
waiver of the requirement to obtain a signed consent form.

45 CFR 46.117(c)(2)

45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

4.6.2.1 Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form present no more than minimal risk of harm to the research subjects:

The waiver of informed consent that we request for the purposes of phone screening presents no more than minimal risk of harm to the research subject because it involves no more than is typically asked of a patient when scheduling a doctor's appointment. Minimal risk of harm applies to all of the questions on the phone screening.

4.6.2.2 Justify why the research listed in 4.6.1 involves no procedures for which written informed consent is normally required outside of the research context:

Outside of the research context, information similar to what is asked in the phone screening is routinely collected and asked at the time of patient entrance into the bariatric surgery program in this department. None of the questions in the phone screening script require informed consent outside of the research context.

4.6.3 Address the procedures that will be used and the information that will be provided (i.e., script) in obtaining and documenting the subjects' verbal informed consent for study participation:

In response to incoming calls from interested potential research participants, study staff will read a brief screening script (attached in other attachments section) describing the study in detail to the patient, documenting their authorization to this screening process with a signature, and asking questions to ascertain eligibility.

Upload Scripts:
Name Modified Date

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* no

4.7.1 If Yes, select the reason(s) for your request:
There are no items to display

[reviewer notes→]
4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

**Note:** This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* no

4.9 Upload all written informed consent documents.

Draft Consent Forms for editing:
- **Name**
- **Modified Date**
  - **Consent Form** 1/21/2010 3:29 PM

Approved Consent Form(s):
- **Name**
- **Modified Date**
  - **Consent Form** 1/21/2010 3:29 PM

4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

* Yes

4.11 At what point will you obtain the informed consent of potential research subjects or their authorized representative?

After performing certain of the screening procedures, but prior to performing any of the research interventions/interactions

4.11.1 Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed.

We believe we meet the criteria that the respective research procedures present not more than minimal risk of harm to the involved participants. We believe that, encompassed in recruitment procedures and screening documents, participants will become fully informed about the study.

We believe the information being obtained from the telephone screening script and orientation screening assessment form is the same type of information that would be collected from patients during a regular doctor's appointment. Please see script and form attached. If the subject does not meet inclusion criteria, all the information collected during the screening process will be retained without any identifiers, and the patient will be notified of this procedure. In addition, written informed consent will be obtained by the investigator prior to any research activities.

In addition to the benefits of allowing the subject sufficient time to make his/her decision and minimizing the possibility of coercion or undue influence, the opportunity to defer obtaining written informed consent until after the screening procedures have been performed will limit...
patient burden that would be incurred in requiring patients to come in for a one-on-one surgeon visit that do not meet the very basic eligibility requirements (BMI, age, Diabetes status).

4.11.2 Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Assessing patient eligibility by telephone and conducting group orientation sessions will ensure that the subject has sufficient time and knowledge to make an informed decision of his/her participation in this study prior to signing the informed consent document. In addition to information collected during the brief telephone interview and during the group orientation session, the participant will have the opportunity to meet with the investigator one-on-one at the end of the orientation session to pose any unanswered questions. Only after the patient has been given ample opportunity to ask questions and has expressed full understanding of the research procedures and protocol will the informed consent be obtained. The process of introducing the patient to the study over the course of three contact time points with the investigator and/or her designee prior to obtaining informed consent will provide the subject with sufficient time to make his/her decision and will minimize the possibility of coercion or undue influence.

[reviewer notes—]

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:
This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

Recruitment materials such as flyers, informed physician referrals, screening scripts, and group orientation sessions contain the elements of informed consent necessary to fully inform participants about the study prior to obtaining any information about them. Individuals who inquire about this study will be asked to complete a brief telephone interview conducted by the research coordinator to assess initial eligibility and eligible participants will be invited to attend a group orientation session. At the orientation session, the investigators (Dr. Courcoulas and Dr. Jakicic) will provide a detailed description of the study and potential subjects will be encouraged to ask any questions regarding their participation in this study. Individuals who remain interested at the orientation session after review of a completed screening assessment will attend an individual appointment with the principal investigator and the research coordinator. The principal investigator and research coordinator will review any additional questions with the eligible participant and informed consent will be obtained by the physician investigator prior to performing any research activities.

4.13 Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a listed physician investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a listed investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* no

If Yes, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14 Will you inform research subjects about the outcome of this research study

https://www.osiris.pitt.edu/...F42844113482999E9EE][&PrintBySection=true&PrintHeaderView=true&PrintHeaderInfo=true&PrintLogo=true[1/6/2015 1:17:18 PM]
following its completion?

* no

If Yes, describe the process to inform subjects of the results:

### Section: Section 5 - Potential Risks and Benefits

**5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:**

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Common Risks</th>
<th>Infrequent Risks</th>
<th>Other Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Sampling</td>
<td>Experimental Interventions: - Occurring in 1% to 25% of people are risks that include bleeding, bruising, dizziness, fainting and soreness. Follow up Procedures: - Occurring in 1% to 25% of people are risks that include bleeding, bruising, dizziness, fainting and soreness.</td>
<td>Experimental Interventions: - Infection (less than 1%) Follow up Procedures: - Infection (less than 1%)</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>iDXA Scanning</td>
<td>No Value Entered</td>
<td>No Value Entered</td>
<td></td>
</tr>
<tr>
<td>IV-GTT</td>
<td>Experimental Interventions: - Discomfort due to wearing a hospital gown and being asked to remove all jewelry, hairpins, etc. Follow up Procedures: - Discomfort due to wearing a hospital gown and being asked to remove all jewelry, hairpins, etc.</td>
<td>Experimental Interventions: Exposure to small amount of radiation (comparable to 1.25% that of a chest x-ray) Follow up Procedures: Exposure to small amounts of radiation (comparable to 1.25% that of a chest x-ray)</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Laparoscopic Adjustable Gastric Banding</td>
<td>No Value Entered</td>
<td>No Value Entered</td>
<td></td>
</tr>
<tr>
<td>Lifestyle Weight Loss Intervention</td>
<td>Intolerance to meal replacements - Hypoglycemia - Exercise induced risks such as serious cardiac event (e.g., heart attack which occurs in less than 1% or 1 out of 100 people) - Musculoskeletal injury</td>
<td>No Value Entered</td>
<td></td>
</tr>
</tbody>
</table>

View

[reviewer notes—]
<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Common Risks</th>
<th>Infrequent Risks</th>
<th>Other Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional and Psychological Evaluations</td>
<td>No Value Entered</td>
<td>Screening Procedures: Distress or anxiety due to the nature of the questions asked during these evaluations</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Obtaining and Storing Identifiable Information</td>
<td>No Value Entered</td>
<td>Screening Procedures: Breach of confidentiality Experimental Interventions: Breach of confidentiality Follow up Procedures: Breach of Confidentiality</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Psychosocial Questionnaires</td>
<td>No Value Entered</td>
<td>Experimental Interventions: -Distress or anxiety due to the nature of the questions Follow up Procedures: -Distress or anxiety due to the nature of the questions</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Roux-en-Y Gastric Bypass Surgery</td>
<td>Experimental Interventions: Mild Post-operative Dehydration</td>
<td>Experimental Interventions: - Anesthesia related complications, wound infection, incisional and internal hernias, urinary tract infection, persistent nausea/vomiting -Major Surgical Complication (1-2%) including bleeding, deep venous thrombosis, pulmonary embolism, anatomic leak, regional abdominal organ trauma, bowel obstruction, atelectasis, pneumonia, cardiac dysrhythmia -Long term complications including anemia, vitamin or mineral deficiency, neurologic complications such as peripheral neuropathy and encephalopathy, adhesive bowel obstruction, and possible effect on bone density</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Screening Questions</td>
<td>No Value Entered</td>
<td>Screening Procedures: Patient becoming distressed due to the nature of the questions (i.e., regarding birth control)</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>SenseWear Pro Armband</td>
<td>No Value Entered</td>
<td>Experimental Interventions: -Minor skin irriation and/or discomfort resulting when the electrode sites are prepared and electrodes placed</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

**Screening Procedures:**

To prevent or minimize the above noted screening risks, all records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant’s name.

Additionally, participants will not be required to answer any question asked solely for the
purpose of research that they find particularly upsetting and may choose to discontinue participation at any time.

Experimental Interventions:

Precaution will be taken to ensure limited physical harm to human subjects. All study related activities will be supervised by investigators and their designees and/or trained CTRC technicians and staff. Risks associated with surgery will be minimized due to the bariatric center’s participation and compliance with National Centers of Excellence requirements, expertise of the surgeon, and the experience of the nursing and medical support staff at Magee-Womens Hospital.

Participants randomized to the surgical weight loss groups, and especially the RNY group, will be counseled extensively on the importance of lifetime supplementation of vitamins and minerals which, if compliant, will greatly decrease the risk of developing a neurological complication due to nutritional deficiencies. Prescriptions for vitamins and minerals (i.e. B12 injections) will be ordered for all patients in the RNY group.

An experienced CTRC phlebotomist and nursing staff will be responsible for the technical aspects of the blood sampling and IV-GTT. Tests will be stopped immediately if any adverse symptoms occur.

Participants will not be required to answer upsetting questions and may choose to discontinue participation at any time.

All records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant’s name.

To minimize risk associated with wearing the SenseWear Pro Armband, the sensing unit will be wiped with rubbing alcohol and dried thoroughly before each use.

To minimize risk associated with increased exercise and activity, participants will be extensively counseled on proper exercise techniques and will be progressed in a gradual manner. This will minimize the onset of musculoskeletal injury.

Prior to initiation of any intervention, participants will be taught how to monitor their blood glucose, be provided with symptoms and signs of hypoglycemia and instruction on how to treat hypoglycemia. This will minimize the risk and occurrence of hypoglycemic incidents that may occur with weight loss and subsequent reductions in blood glucose.

Follow up Procedures:

As always, precaution will be taken to ensure limited physical harm to human subjects. All study related activities will be supervised by investigators and their designees and/or trained CTRC technicians and staff.

An experienced CTRC phlebotomist and nursing staff will be responsible for the technical aspects of the blood sampling and IV-GTT. Tests will be stopped immediately if any adverse symptoms occur.

Participants will not be required to answer upsetting chestions and may choose to discontinue participation at any time. All records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant’s name.

To minimize risk associated with wearing the SenseWear Pro Armband, the sensing unit will be wiped with rubbing alcohol and dried thoroughly before each use.

5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

* Addressed below:

As is current practice in the Department of Minimally Invasive Bariatric and General Surgery,
participants found to have a clinically significant, unexpected disease or condition during the course of screening will be referred to their primary care physician (PCP) or an appropriate specialist for further evaluation and treatment.

5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes¬]

5.4 Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* yes

5.4.1 List the research procedures that pose a risk to pregnant women or fetuses:

Small risk of significant exposure to ionizing radiation during the pre-operative upper GI series and chest radiograph; General anesthesia required of the surgical procedures could pose risk to a pregnant woman or fetus

5.4.2 Describe the steps that will be taken to rule out pregnancy prior to exposing women of child-bearing potential to the research procedures that pose a risk to pregnant women or fetuses:

All women of child-bearing potential will be required to undergo urine hCG pregnancy testing prior to pre-operative testing and prior to any surgical procedure.

5.4.3 Describe the measures to prevent pregnancy, and their required duration of use, that will be discussed with women of child-bearing potential during and following exposure to research procedures:

There are no risks of becoming pregnant following the research procedures that pose a risk to pregnant women pre-procedure. Because pregnancy will mostly likely decrease the weight loss effects observed post-intervention, all women will be counseled on the importance of abstaining from pregnancy in the 12-month post-intervention period.

[reviewer notes¬]

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[reviewer notes¬]

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Yes - Describe below:

If Yes, describe in detail:
Standard treatments for Type 2 diabetes include lifestyle modification with diet and exercise as well as medical treatment with oral and/or injectable agents. Patients are not prohibited from using these other treatments during study intervention and will be counseled extensively on these issues no matter the treatment arm to which the patient is randomly assigned. We expect that most participants in all three treatment arms will experience improvements in their T2DM greater than would have been experienced without undergoing one of the interventions.

[reviewer notes¬]

5.7 Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject’s failure to follow study procedures) that will result in discontinuing a subject’s participation?

* Describe below:
Prior to the beginning of the interventions, participants may be removed from participation if they are determined to no longer meet eligibility criteria or if it is determined that it would be unsafe for the participant to proceed to surgery. Additionally, participants could be withdrawn from participation if they become unable or unwilling to participate. In this situation, participants in one of the surgery arms would be strongly encouraged to continue clinical follow-up with the surgeon outside of the realm of the study.

5.8 Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* no

5.9 Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* no

5.10 Question has been moved to 5.17

5.11 Question has been moved to 5.16

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

No - Describe the general benefits to society (e.g., increased knowledge; improved safety; better health; technological advancement) that may result from the conduct of this research study.

Describe the benefit:
Participants may benefit from participating in the assessments and/or the reductions in weight that may be associated with participating in the study. Bariatric surgery, weight loss, and regular exercise have been associated with improvements in health risks such as blood cholesterol, blood pressure, and Type 2 Diabetes. However, there is no promise that participants will receive any benefits from participation in this study and such benefits cannot be guaranteed.

This research study will help to determine the effectiveness of two dominant bariatric surgery procedures versus an intensive lifestyle intervention to induce weight loss in patients and promote improvements in Type 2 diabetes. We want to learn about resolution of diabetes, glucose control, medication usage, insulin resistance, beta cell function, body composition, measures of physical activity, and psychosocial changes. Through participation by subjects, we may learn more about how these various interventions can help others with Type 2 diabetes.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

The data safety monitoring plan for this trial will be supplemented with a Data Safety Monitoring Board (DSMB) to monitor patient safety and evaluate the efficacy of the intervention. Close monitoring by the PI (Dr. Courcoulas) in conjunction with a DSMB and prompt reporting of adverse events to the NIH and the University of Pittsburgh IRB will ensure data accuracy and patient safety.

A full copy of the DSMP and DSMP Charter is attached in the supporting documentation section.

Section 5 - Potential Risks and Benefits of Study Participation
5.14 **What precautions will be used to ensure subject privacy is respected?** (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

All medical evaluations, nutritional, and psychological evaluations will be conducted in a private clinic room. All research related activities will be conducted in semi-private rooms in either the MUH CTRC or the EMRC.

Additionally, the collection of sensitive information about subjects has been limited in this study and only what is necessary to achieve the aims of research and ensure patient safety is being collected.

5.15 **What precautions will be used to maintain the confidentiality of identifiable information?** (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

All information collected for this research study will be kept confidential and steps will be taken to minimize the risk of a breach of confidentiality. Participants’ names will be used only for the informed consent form and contact information. Participants will be given unique study identifiers, which will be written on all data collection forms. In addition, data collection forms will be kept in a locked file cabinet or locked room and a secure database that can only be accessed by the investigators (and their research staff) listed on the consent form. There will be close communication between the PI, the data entry personnel and the clinic and research staff to ensure the quality and accuracy of the data collected. Each member of the study team will meet with the PI and review confidentiality issues, prior to having contact with research subjects.

5.16 **If the subject withdraws from the study, describe what, if anything, will happen to the subject’s research data or biological specimens.**

If a participant chooses to withdraw from study participation, all linkage codes will be destroyed and the collected data rendered anonymous. At this time, any unprocessed samples would be destroyed. Because samples will not be stored as part of this study the likelihood of having to destroy biological specimens is low.

5.17 **Following the required data retention period, describe the procedures utilized to protect subject confidentiality.** (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

All data files and consents will be stored as previously described until the study ends or until after the retention period at which time documents will be destroyed in a manner which prohibits retrieval of data. Any electronic files with linkage code information will be deleted.

6.1 **Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?**
6.2 Will subjects be compensated in any way for their participation in this research study?
* no

7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Anita P. Courcoulas M.D., M.P.H., F.A.C.S, Principal Investigator: Dr. Courcoulas is an Associate Professor of Surgery at the University of Pittsburgh and Director of Minimally Invasive Bariatric and General Surgery for the University of Pittsburgh Medical Centers (UPMC). She performs the bariatric surgery and sees patients pre- and post-operatively. She has published numerous research articles relating to health outcomes especially comorbidity reduction following bariatric surgery. She is the Principal Investigator of the University of Pittsburgh clinical center of multi-institutional Longitudinal Assessment of Bariatric Surgery (LABS) study. In addition, she is the Principal Investigator on two FDA randomized clinical device trials which focus on different weight loss procedures. She is the Principal Investigator and will be responsible for the management of this study.

John M. Jakicic, Ph.D., Co-Investigator: Dr. Jakicic will be responsible for supervising the development of the lifestyle weight loss intervention at the Physical Activity and Weight Management Research Center. Dr. Jakicic has performed this duty for the multi-center Look AHEAD Study and currently remains a member of the Weight Loss Intervention Group for that study. Dr. Jakicic will also be influential in the inclusion of objective monitoring of physical activity within the scope of this study. He has extensive experience with the activity monitors proposed for this study and has closely supervised the development of the data analysis software that will be used to examine these data in this study.

Melissa Kalarchian, Ph.D., Co-Investigator: Dr. Kalarchian has considerable experience in the development and implementation of cognitive-behavioral lifestyle interventions and clinical research. She is the Principal Investigator on the NIDDK funded "Behavioral Intervention for Weight Loss Failure after Bariatric Surgery” and the randomized controlled trial “Preoperative Lifestyle Intervention in Bariatric Surgery”. She brings a strong background in conducting patient-oriented research in bariatric surgery, in research on adapting obesity treatments for special populations and psychosocial assessment in the obese and bariatric surgical populations.

Bret Goodpaster, Ph.D., Co-investigator: Dr. Goodpaster serves as the Director of the Exercise Physiology Laboratory and served as the Core Director of the Metabolism Core of the Obesity and Nutrition Research Center. He has gained national and international prominence in the clinical investigation of obesity, and has more than 12 years of experience in this area, including the use of glucose clamps and tolerance tests, exercise testing and body composition assessment. He will have overall responsibility for the successful completion of the metabolic testing and protocols and for the preparation of scientific reports, abstracts and publications. He will have the primary responsibility for the IV Glucose Tolerance Tests, exercise tests and body composition assessments.

Frederico Toledo, MD. Co-investigator: Dr. Toledo has worked with Dr. Goodpaster for more than four years examining the effects of weight loss and physical activity on insulin resistance in obesity and type 2 diabetes. Dr. Toledo has collaborated with Dr. Goodpaster on clinical investigation of obesity, including weight loss and exercise interventions. In addition, he has collaborated with Dr. Courcoulas and Dr. Eid on other metabolic related pilot and feasibility studies. Dr. Toledo will be the study endocrinologist primarily responsible for overseeing the IV Glucose Tolerance testing and for providing guidance, supervision and diabetes management of the subjects.
7.2 Indicate all sources of support for this research study.

* 

Selections

Federal: Upload a copy of the entire grant application (including the cover sheet) if our site is the awardee institution; for federal contracts, upload a copy of the research plan.

<table>
<thead>
<tr>
<th>Year</th>
<th>Grant Title</th>
<th>Grant Number</th>
<th>Institution</th>
<th>Sponsor</th>
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<td>1991</td>
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If Federal support, provide the sponsor information and level of support:

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name Modified Date

If Industry support, provide the sponsor information and level of support:

If Foundation support, provide the sponsor information:

If Other support, provide the support information and level of support:

7.3 Is this study funded in part or whole by a PHS Agency? (click here for list of PHS Agencies)

* 

[reviewer notes~]  

Other Attachments (e.g., Reference List)

Additional documents:

<table>
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Provide a short title for this study (200 characters or less):

**The Triabetes Study**

**T1.0 Select the type of application:**
New Research Study

**T2.0 Is the proposed research study limited to the inclusion of deceased individuals?**

* no

**T2.1 Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?**

* no

**T3.0 What is the anticipated risk to the research participants?**

Greater Than Minimal Risk

**CS1.0 What is the reason for this submission?**

New Research Protocol Submission

**CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?**

* no

**CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?**

* no

**CS2.0 Title of Research Study:**

A Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes

**CS2.1 Research Protocol Abstract:**
There has been a dramatic increase in the number of bariatric procedures performed in the last decade and bariatric surgery has been reported to result in significant changes in glucose metabolism in T2DM that often results in complete resolution of diabetes in many patients. Yet there remain many unanswered questions that require well-controlled studies to more completely inform health care decision making and clinical practice in this area. For example, it is not clear, whether diabetes is influenced by the type of surgery or by the amount of weight lost or if bariatric surgery is more effective than non-surgical weight loss induced by diet and physical activity in T2DM patients with more moderate BMIs (Class I and Class II obesity). Finally comparing the improvements in cardiovascular risk factors such as insulin resistance, cardio-respiratory fitness, hypertension and inflammation between surgical to non-surgical weight loss has not been well investigated.

Subjects between the ages of 25 and 55 years of age with T2DM confirmed by either a documented fasting blood glucose > 126 mg/dl or treatment with an anti-diabetic medication and mild to moderate obesity with a BMI between 30 and 40 kg/m2, upon successful completion of screening procedures, will be randomized to one of three treatment arms; gastric bypass, gastric banding, or a structured weight loss program. All participants will undergo detailed medical, psychological, and nutritional evaluation in addition to assessments of body composition, physical activity, and psychosocial correlates of change in body weight and behavior. A subset of patients will undergo intravenous glucose tolerance testing. Post-intervention, patients will follow intervention-specific protocols for a period of 12-months. Additionally, to obtain longer-term follow-up, and in an effort to achieve weight maintenance, a structured low level lifestyle intervention will be employed during years 2 and 3 of follow up with the outcomes of interest that were measured at one year follow-up extended to subsequent annual visits over 3 years. After completion of the 3 year annual visit, the low level lifestyle intervention will be modified to include once monthly contact and participants will be followed at annual follow-up time points to assess outcomes over the longer term.

The primary aim of this study is to determine the feasibility of performing a randomized trial comparing two major types of bariatric surgery, gastric bypass and gastric banding, versus a structured weight loss program induced by diet and increased physical activity in patients with Class I and II obesity and T2DM. A secondary aim is to obtain preliminary information regarding the effectiveness of various bariatric surgery procedures versus an intensive behavioral intervention to induce weight loss with diet and increased physical activity. Finally, we will explore the feasibility, methods for, and implementation of a range of early outcome measures including; resolution of diabetes, beta cell function, change in metabolic parameters, body composition, physical activity, and several psychosocial measures. The importance of this pilot study will be to provide crucial information necessary to plan a larger, more comprehensive and more long-term multi-center trial to further address critical unanswered questions in this emerging area.

[reviewer notes]

CS3.0 Name of the Principal Investigator:
Anita Courcoulas

CS3.1 Affiliation of Principal Investigator:
UPitt faculty member
If you chose any of the Pitt options, please indicate the specific campus:
Main Campus - Pittsburgh

If you chose the UPitt faculty member option, provide the PI’s University Faculty Title:
Professor of Surgery

CS3.2 Address of Principal Investigator:
3380 Boulevard of the Allies, Suite 390
Pittsburgh, PA 15213

CS3.3 Recorded Primary Affiliation of the Principal Investigator:
U of Pgh | School of Medicine | Surgery

CS3.4 Identify the School, Department, Division or Center which is responsible for oversight of this research study:
CS3.5 Telephone Number of Principal Investigator:
(412) 641-3678

CS3.6 Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:
courcoulasap@msx.upmc.edu

CS3.7 Fax Number:
(412) 641-3640

CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?
* no

CS3.9 Is this your first submission, as PI, to the Pitt IRB?
* no

CS4.0 List of Co-Investigators:

<table>
<thead>
<tr>
<th>Last</th>
<th>First</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delany</td>
<td>James</td>
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<tr>
<td>Jakicic</td>
<td>John</td>
<td>U of Pgh</td>
</tr>
<tr>
<td>Kalarchian</td>
<td>Melissa</td>
<td>U of Pgh</td>
</tr>
</tbody>
</table>

CS5.0 Name of Primary Research Coordinator:
Emily Eagleton

CS5.1 Address of Primary Research Coordinator:
3380 Boulevard of the Allies, Suite 390
Pittsburgh, PA 15213

CS5.2 Telephone Number of Primary Research Coordinator:
(412) 641-3743

CS6.0 Name of Secondary Research Coordinator:
William Gourash

CS6.1 Address of Secondary Research Coordinator:
3380 Boulevard of the Allies, Suite 390
Pittsburgh, PA 15213

CS6.2 Telephone Number of Secondary Research Coordinator:
(412) 641-3646

CS6.3 Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):
There are no items to display
CS7.0  Will this research study use any Pediatric PittNet or Clinical and Translational Research Center (CTRC) resources?

yes

CS7.1  Please select the sites you intend to use:

CTRC - Montefiore Hospital Clinical and Translational Research Center

CS8.0  Select the entity responsible for scientific review.

External Scientific Review Completed – The scientific merit of this research protocol has been confirmed by an external scientific review committee as a condition of funding.

CS9.0  Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?

* no

CS10.0  Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

* no

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.o3is.pitt.edu).

CS11.0  Use the 'Add' button to upload one or more of the following:

- the sponsor protocol (including investigator initiated studies) and/or other brochures
- the multi-center protocol and consent form template, if applicable

CS12.0  Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* yes
REQUIREMENTS FOR THE REVIEW OF HUMAN SUBJECT RESEARCH PROTOCOLS BY THE
HUMAN USE SUBCOMMITTEE (HUSC), RADIATION SAFETY COMMITTEE

For Research Protocols Involving the Evaluation of Use of Diagnostic Procedures that Emit Ionizing Radiation:

Formal HUSC review/approval is required if the research protocol involves any of the following:

1. The use or evaluation of a radioactive agent or procedure that is not currently approved (i.e., for any clinical indication) by the FDA
2. The evaluation (i.e., for safety and/or effectiveness) of a FDA-approved radiopharmaceutical or procedure for an “off label” indication; or the use of a FDA-approved radiopharmaceutical or procedure for an “off label” indication if such use is experimental (i.e., not routinely performed in clinical practice).
3. Individuals (e.g., healthy volunteers) who would not be undergoing the procedure in association with the diagnosis or treatment of a disease or condition

Formal HUSC review/approval is not required if the diagnostic procedure is being performed, in a standard clinical manner and frequency, for screening or to evaluate the outcome of a treatment regimen. This would include diagnostic procedures for off-label uses that are routinely performed in clinical practice. 2,3

For Research Studies Involving the Use or Evaluation of Therapeutic Procedures that Emit Ionizing Radiation:

Formal HUSC review/approval is required if parameters (e.g., total radiation dose, dose fractionation scheme, etc.) of the radiation therapy procedure(s) are defined by the research protocol.

1 An “off-label” indication is a clinical indication which is not currently specified in the FDA-approved product labeling.
2 The risks of radiation exposure associated with the diagnostic procedure must continue to be addressed in the protocol and consent form using the HUSC-accepted wording.
3 The University of Pittsburgh IRB, at its discretion, may request formal HUSC review of the research protocol.

For any questions related to these requirements or their application, contact the Chair of the HUSC (412-383-1399) or the University’s Radiation Safety Office (412-624-2728)

CS12.1 After reviewing the HUSC guidance above, does your research protocol require HUSC review? (Note: University of Pittsburgh’s Radiation Safety Committee oversight is limited UPMC Presbyterian-Shadyside, Magee Women’s Hospital of UPMC, Children’s Hospital of Pittsburgh-UPMC, and Hillman Cancer Center. If other sites, you will be required to obtain approval from your radiation safety officer. Please contact askirb@pitt.edu for more information.)

no

Upload Radiation Forms:
Name Modified Date

CS13.0 Does this research study involve the deliberate transfer of recombinant DNA (rDNA) or DNA or RNA derived from rDNA into human subjects?

* no

Upload Appendix M of NIH Guidelines:
Name Modified Date

CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* yes
If Yes, upload completed Research Fiscal Review Form:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
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[reviewer notes¬]

**CS15.0** Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use Other to include sites not listed:

Sites: 
- University of Pittsburgh
- UPMC

**University of Pittsburgh**

*Campus:*
- Main Campus - Pittsburgh

List university owned off-campus research sites if applicable:

**UPMC**

Sites: 
- UPMC Presbyterian
- UPMC Magee Women’s Hospital
- UPMC Montefiore

If you selected School, International or Other, list the sites:

*For non Pitt or UPMC entities, upload documents granting permission to conduct research at that site:

| Name               | Modified Date   |

CS15.1 Have you, Anita Courcoulas, verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

* Facilities & Other Resources
The University of Pittsburgh has both the facilities and resources necessary and readily available to perform the proposed effort. All participant recruitment, clinical care and follow-up, and research related assessments will occur at the following university facilities: Magee-Womens Hospital of UPMC, Montefiore University Hospital, and the Physical Activity and Weight Management Research Center (PAWMRC).

Laboratory:
The University of Pittsburgh Montefiore Clinical & Translational Research Center (MUH-CTRC) is located on the 6th floor of Montefiore University Hospital in a new state-of-the-art facility. Infrastructure support to investigators includes facilities, equipment and personnel for conducting clinical research. The MUH-CTRC facility is available 24 hours a day, 7 days a week and is comprised of 5 inpatient private rooms, 3 outpatient private rooms, an outpatient suite that includes 3 beds and 3 treatment chairs, 6 outpatient examination rooms, a metabolic kitchen, a DEXA...
scanner, a bariatric bed, and a sample-processing laboratory. Personnel include specialized research nurses, a bionutritionist, and support staff, all of whom have completed the University's on-line training required of individuals engaging in human subject research. The MUH-CTRC will be utilized in the proposed project to conduct the follow-up visits. The Endocrinology & Metabolism Research Center (EMRC), also housed within Monefiore University Hospital and located in close proximity to the MUH-CTRC, will be utilized in the proposed study. The EMRC houses the GE Lunar iDXA dual-energy x-ray absorptiometer that will be used to assess body composition at annual follow-up visits. The University of Pittsburgh Obesity and Nutrition Research Center (ONRC) and its affiliate, The Physical Activity and Weight Management Research Center (PAWMRC), houses a multidisciplinary intervention team that specializes in individual and intensive non-surgical weight loss interventions and that is also very experienced in large clinical trials.

Clinical:
The Division of Minimally Invasive Bariatric and General Surgery (MIBGS) at Magee-Womens Hospital of the University of Pittsburgh Medical Center (UPMC) is one of the oldest, largest, and most high-volume academic bariatric surgical centers in the United States. The Division is staffed by 6 academic surgeons and 39 research, clinical, and administrative staff which includes a clinical business operations director, a pre- and post-bariatric surgery coordinator, 5 physicians assistants/nurse practitioners trained in bariatric surgery, 7 nurses dedicated to the group and a host of clinical administrative support staff. All of these administrative and clinical team members interact readily and daily with the research team to keep them abreast of patient visits, scheduling, and other important subject issues. Magee-Women’s Hospital of the UPMC Health System provides a 284-bed modern hospital facility with 5 specialized minimally invasive operating rooms, a spacious bariatric surgical clinic, and a dedicated and experienced unit with nursing and medical support staff for bariatric surgical patients. The hospital has equipped the entire facility to accommodate morbidly obese patients and is an ASMBS Designated Center of Excellence in Bariatric Surgery. In addition, the hospital’s long history of bariatric surgery care has helped to develop a broad range of sub-specialists experienced in the care of morbidly obese bariatric surgical patients (e.g. anesthesiologists, cardiologists, pulmonologists, and endocrinologists).

Computer:
Database accessible computers are available in the offices, clinics, CTRC, and PAWMRC of Magee-Womens Hospital and Montefiore University Hospital. All of these computers are networked in such a way to allow access to study resources from any computer in a secured, monitored fashion. This has greatly increased the productivity and organization of past and ongoing research study operations. The existing resources of ONRC and PAWMRC will provide the initial database, randomization schemes, study-specific data form modifications, development of data collection and double entry guidelines, and development of an initial data analysis plan.

Office:
The Division of Minimally Invasive Bariatric and General Surgery (MIBGS) is a well-organized academic bariatric surgery practice and has both ample staff and office facilities needed to support its patient care, education, and research activities. The Division provides an administrative office with 6,500 square feet of office space for its staff. The division research staff is located at this same site with adequate work stations, computer and software access, clerical supplies and equipment, conference rooms, and file storage to carry out the proposed protocol. This shared office space for clinical and research staff enhances the close working relationship to simplify both clinical and research activities.

Other:
All of the facilities at the University of Pittsburgh are readily available to the investigators and research associates for both clinical and research activities related to the care and recruitment of patients for this study.
The University of Pittsburgh Clinical and Translational Science Institute (CTSI) provides investigators a key source of valuable information about support services, policies, procedures, and regulations related to the conduct of research. In addition, all patients at the University of Pittsburgh have full access to resources of the hospitals which are attached to the clinical and research spaces.

CS16.0 Special Research Subject Populations:

| Categories | None |

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* no 2560
* no 2561

Section: Section 1 - Objective, Aims, Background and Significance

1.1 **Objective: What is the overall purpose of this research study?** (Limit response to 1-2 sentences.)

The proposed project will address the lack of randomized controlled studies and comparative effectiveness research in bariatric surgery by utilizing a three arm randomized trial to compare surgical and non-surgical treatments for Type 2 diabetes in obese subjects. Understanding more clearly the impact of bariatric surgery compared to a non-surgical, intensive lifestyle intervention for the treatment of diabetes in the setting of obesity will have a major impact on both the science and public health for the communities of obese and diabetic patients in this country and worldwide.

1.2 **Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).**

The Specific Aims of the first phase of the study (RC1DK086037) are as follows:

Aim 1. To determine the feasibility of performing a randomized trial comparing two major types of bariatric surgery, Laparoscopic Roux en Y Gastric Bypass (RNY) and Laparoscopic Adjustable Gastric Banding (GB) versus a lifestyle weight loss intervention (LWLI) induced by diet and increased physical activity in moderately obese patients (Class I and II obesity) with T2DM. We hypothesize that: 1) A randomized design with both surgical and non-surgical arms will be both feasible and acceptable to participants and to providers 2) There will be no difference in retention rates between the LWLI and surgical arms (RNY, GB) of the study and it will provide estimates of overall retention for future studies.

Aim 2. To obtain preliminary information regarding the effectiveness of two dominant bariatric surgery procedures versus an intensive lifestyle intervention to induce weight loss with diet and increased physical activity. We hypothesize that: 1) RNY will be superior to GB and LWLI in weight lost in 12 months.

Aim 3. To explore the feasibility, methods for, and implementation of a range of early outcome measures including; resolution of diabetes, glucose control, medication usage, insulin resistance, beta cell function, body composition, objective measures of physical activity, and several psychosocial measures. We hypothesize that: 1) Participants will be willing to undergo a range of early outcome testing measures to assess metabolic change, body composition alterations, objective physical activity, and psychosocial factors. 2) Measures of T2DM improvement including an intravenous glucose tolerance test (IVGTT) will be feasible in a subset of participants in each study arm and RNY will be superior to both GB and LWLI for the clinical and metabolic improvement of T2DM. 3) The LWLI group will show improvements in physical activity compared to RNY and GB.

The specific aims of the extension phase of the study (R01DK095128) are as follows:

Aim 1. The primary aim of this proposal is to continue longer-term follow up of outcomes in a unique cohort of 60 total randomized subjects with Class I and II obesity and T2DM that...
underwent intervention in one of three arms; Laparoscopic Roux en Y Gastric Bypass (RNY), Laparoscopic Adjustable Gastric Banding (GB), or a lifestyle weight loss intervention (LWLI) induced by diet and increased physical activity. The outcomes of interest are measured at one year follow-up in the originally funded study, and will be extended to subsequent annual visits over 3 years. These measures include evaluation of weight loss, diabetes resolution, change in metabolic parameters, body composition, physical activity, and several psychosocial measures. We hypothesize that: 1) T2DM resolution rates will be highest in the RNY group at 2 years post intervention compared to the two other (GB, LWLI) treatment groups 2) Weight loss will be equivalent in the two surgical arms at 3 years post intervention and will exceed total weight loss in the LWLI group 3) The LWLI group will show improvements in physical activity compared to RNY and GB.

Aim 2. A secondary aim is to investigate the feasibility and importance of the initiation of a structured low level lifestyle intervention (LLLI) administered to all three treatment groups on weight maintenance over the longer-term follow up. We hypothesize that: 1) There will be no difference in retention rates between the LWLI and surgical arms (RNY, GB) of the study during both the initiation and completion of the LLLI 2) Retention rates of the subjects in the surgical arms (RNY, GB) will be enhanced by initiation of the LLLI when compared to historically reported rates of follow-up among surgical subjects with usual care 3) The LWLI group (nonsurgical intervention), with initiation of the LLLI, will maintain weight loss and some other health improvements from the first year in the subsequent longer-term 3 year follow-up period.

Longer-term data from this proposed extension of the first randomized cohort comparing surgical to nonsurgical treatment for T2DM in Class I and II obesity will both fill an important knowledge gap and also help to guide future studies in this important and emerging area.

### 1.3 Background

**BARIATRIC SURGERY AND THE TREATMENT OF TYPE 2 DIABETES:**

One of the key questions in the scientific, medical and lay communities is whether or not bariatric surgery represents a long-term effective treatment for T2DM. Type 2 diabetes mellitus (T2DM) is a worldwide epidemic, and it is currently the 6th cause of death in the US and a major cause of kidney failure, blindness, amputations, heart attack and others vascular and gastro-intestinal dysfunctions. It is estimated that there will be 380 million affected individuals worldwide by 2025. The pathogenesis of T2DM is regarded as a combination of impaired insulin secretion and insulin resistance (IR). Traditionally, treatments include intensive lifestyle modification with or without glucose lowering agents. Neither treatment alone, or in combination, results in complete amelioration of diabetes and its potential long-term complications.

Operations for morbid obesity range from purely restrictive procedures such as vertical banded gastroplasty (VBG) and adjustable gastric banding (GB) to gastrointestinal bypass procedures such as Roux-en-Y gastric bypass (RNY) and the biliopancreatic diversion (BPD). The two dominant procedures currently in use in the United States are the Roux-en-Y gastric bypass and the adjustable gastric band and they are the subject of this investigation. Dramatic improvements in glycemic control have been observed in subjects with T2DM specifically after RNY and BPD. The remarkable resolution of diabetes after these two procedures typically occurs rapidly and prior to significant weight loss, suggesting that these operations may have a direct and profound impact on glucose homeostasis. Clinical resolution, usually defined as independence from all anti-diabetic medications, was reported to occur in 47%-70% of patients after restrictive procedures (currently only the GB is in use), 80-98% after RNY and 92.5 to 100% after BPDs. Long-term (up to 16 years) control of glycemia after RYGB have been documented in the severely obese. Furthermore, mortality risk from diabetes over a 10-year follow-up was reduced after RNY compared to patients with T2DM matched for age, weight, and BMI who did not undergo operation (1.0% versus 4.5% for every year of follow-up).

Although data are sparse, there is also compelling evidence that bariatric surgery can result in dramatic improvements or complete resolution of diabetes even in the non-morbidly obese. Because of this growing literature demonstrating improvements in T2DM following bariatric surgery and the fact that weight loss involving calorie restriction and physical activity is difficult for most obese patients, there is much interest by both patients and providers in offering ‘metabolic’ surgery to patients with Class I and II obesity (mild and moderate obesity) for control of T2DM. The Diabetes Surgery Symposium held in Rome, Italy in 2007 indicated as a major point of consensus that “gastrointestinal surgery may be appropriate for the treatment of T2DM in patients who are good surgical candidates with BMI
of 30 to 35 who are inadequately controlled by lifestyle and medical therapy”. However, despite these recommendations, the role of a non-operative comparison cohort for diabetes treatment has not been sufficiently addressed by current available research. A recent study by Dixon et al. demonstrated that the reduction in diabetes risk following gastric banding (GB) compared to a randomized control, non-surgical treatment group of patients with BMIs 30-40 kg/m2 was due to the amount of weight loss.13 The medical weight loss program in this study resulted in <2 kg weight loss at one year. An earlier study by Dixon et al. saw greater improvement in metabolic syndrome in those patients with a BMI of 30 to 40 kg/m2 randomized to an intensive medical management program but the improvements were still less than those in the GB group.14 In contrast, the multi-center Look AHEAD Study has shown an 8.6% weight loss and reduction in A1C from 7.3% to 6.6% at 12 months in response to an intensive lifestyle intervention. This argues that a randomized trial that includes an effective and intensive one-on-one behavioral weight loss program is urgently needed to better objectively inform practitioners as well as patients with T2DM how various surgical options compare to an effective behavioral weight loss program.

Randomization of participants into three treatment arms, as proposed in this study, will begin to answer some of these questions and is justified due to the gap in knowledge of most effective therapy for patients with T2DM in addition to the safety and risk/benefit ratio being roughly equal across all three treatment arms. A recent publication in the New England Journal of Medicine by the LABS Consortium has demonstrated a low overall risk of death and other adverse outcomes following bariatric surgery. In this study, the 30-day rate of death among the 4,776 patients who underwent RNY or GB was 0.3%. Additionally, a significant association between BMI and increased risk of mortality and adverse event rates was observed.21 Similarly, AHRQ data published in 2007 revealed a 0.19% rate of inpatient death among 121,055 bariatric surgery patients.22 Non-surgical diabetes treatment is not without risk. Seven studies published between 2002 and 2007 revealed annual mortality rates from 2.0-8.7% in patients with T2DM due to diabetic complications.23-28

In summary, there still remain many unanswered questions about the relative utility of surgical and medical treatment for the BMI strata of 30-35 and 35-40 kg/m2 that will require well-controlled studies to more completely inform health care decision making and clinical practice in diabetes treatment. For example, it is not clear, whether diabetes is influenced by the type of surgery or by the amount of weight lost or if bariatric surgery is more effective than non-surgical weight loss induced by diet and physical activity in T2DM patients with more moderate BMIs (Class I and Class II obesity). Finally comparing the improvements in cardiovascular risk factors such as insulin resistance, cardio-respiratory fitness, hypertension and inflammation between surgical and non-surgical weight loss has not been well documented. This study will begin to address, in a systematic way, these important and yet unanswered questions.

1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

GAPS IN BARIATRIC SURGICAL RESEARCH:
Despite tremendous growth in the use of bariatric surgical procedures, research on these interventions continues, until recently, to be reported primarily through the case series of experienced practitioners and has focused only on selected outcomes. As a result, there is a gap between the proliferation of these procedures and the evidence base needed to understand key components of their use. This gap includes an assessment of the effectiveness of bariatric surgery in the population at large, the total impact of bariatric surgery on patients and the health care system, identification of which patients are best suited for specific surgical procedures, and the physiological mechanisms that promote sustained weight loss after surgery. Understanding the circumstances that have limited research in bariatric surgery should help direct future investigators to the challenges that need to be addressed when studying the important and increasingly performed group of weight loss procedures.1 Some of these perceived and identified barriers to furthering objective evidence gathering in bariatric surgery are particularly relevant to this study. The first and one of the most important, is a lack of randomized trials in bariatric surgery and especially the lack of randomized comparisons between operative and best available non-operative treatments for weight loss. In addition, there is a lack of generalizability of bariatric surgical interventions, there is only short-term and incomplete longitudinal follow-up of bariatric surgical subjects in most studies, there is considerable difficulty in the evaluation of safety for elective bariatric procedures where serious adverse outcomes are rare, and there are problems in addressing the broad range and multiple domains of outcomes following bariatric surgery that require a very comprehensive approach to prospective research. Finally, a significant challenge for the future of bariatric surgical research is funding of high quality...
comparative effectiveness studies in this field. This study will address the first and last of these aforementioned barriers; lack of randomized studies and the funding of comparative effectiveness research in bariatric surgery.

The NIH-NIDDK funded LABS Consortium (U01 DK066585) is an ongoing multi-institutional, prospective and comprehensive evaluation of the safety, efficacy, and some mechanisms in bariatric surgery and will certainly begin to address some of these identified knowledge gaps such as generalizability, evaluation of safety, longitudinal outcome evaluations, and the prospective assessment of the range of outcome domains. It will not, however, provide a control group for comparison or be able to evaluate, in a randomized way, the differences between operative and non-operative treatments for weight control. The LABS phase 3 study of diabetes; "Mechanisms for Improving Type 2 Diabetes Following Bariatric Surgery" is sub study currently underway within LABS to study diabetic patients undergoing gastric bypass and to investigate mechanisms of diabetes improvement following gastric bypass versus a control, non-operated group.

THE IMPACT ON PUBLIC HEALTH:
Most current bariatric surgery patients are severely obese (BMI > 40) or moderately obese (BMI 35 – 40) with high-risk, obesity-related medical co-morbid conditions such as T2DM or severe sleep apnea. The prevalence of clinically severe obesity (BMI > 40) is 4.8%, and obesity (BMI > 30) is 32.2% among U.S. adults.15 The number of weight loss surgery patients is growing not only due to increases in the prevalence of moderate and severe obesity and its complications, but also to advances in surgical technique and the mounting evidence demonstrating the benefits of bariatric surgery. Gastric bypass remains the most common procedure in the U.S. with the number of gastric banding (GB) procedures growing approximately 20-25% per year. The number of bariatric surgical procedures in the U.S. increased from 13,000 in 1998, to over 100,000 in 2003.15 and the American Society for Metabolic and Bariatric Surgery (ASMBs) estimates that 250,000 bariatric surgery procedures were performed in 2008. The number of bariatric surgery patients will continue to increase as patients with severe obesity and moderate obesity with co-morbid conditions such as T2DM demand access to effective treatment. For example, in 2002 bariatric surgical procedures were performed on only 0.6 percent of the 11.5 million clinically eligible U.S. adults in 2002.17 Although bariatric surgery is expanding dramatically to meet the global epidemic of severe obesity, currently only 1% of eligible patients are undergoing procedures worldwide.18 Furthermore, the criteria for surgery are expanding to include a wider range of patients; including both older and younger patients, as well as patients with lower BMIs (30-35 kg/m2) and T2DM. Well-designed and well-controlled clinical studies are necessary to further define the potential role of surgical options for the treatment of diabetes in this population.

Diabetes is the most costly disease in the United States, consuming one out of every 7 health care dollars and accounting for 137 billion dollars of cost annually including both medical care costs and lost wages and productivity. Diabetes is a leading cause of death and increases the risk for heart disease six fold and multiplies the risk of stroke by four.19 Diabetes-related conditions are severe and disabling and include; amputations, loss of eyesight, and end stage renal disease. The projected U.S. diabetic population, alone, in 2012 is 22.7 million.20 Understanding more clearly the impact of bariatric surgery compared to a non-surgical intensive lifestyle intervention for the treatment of T2DM will have a major impact on both the science and the public health for the communities of both obese and diabetic patients in this country and worldwide.

### 2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

* no

### 2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* no
2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

Comparative Effectiveness Research, Feasibility, Descriptive and Evaluative, Randomized, Active Treatment Controlled

2.3.1 Does this research study involve a placebo-controlled arm?
* no

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?
* no

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?
* yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

Individuals who inquire about this study will be asked to complete a brief telephone interview to assess initial eligibility, with eligible participants invited to attend a group orientation. The investigators will provide a detailed description of the study at this orientation, and subjects will be encouraged to have all of their questions regarding their participation in this study answered. Individuals who remain interested at the orientation session, will complete a screening assessment that will be reviewed by the investigators. If a patient is deemed ineligible based on review of the screening assessment, the document will be destroyed. Potential participants with BMI between 30 and 35 kg/m² will be required to provide a note from their endocrinologist approving their participation in the study and documenting the difficult to control nature of their T2DM. If deemed eligible, individuals will be scheduled to meet with the surgeon (Dr. Courcoulas) where detailed written informed consent will be obtained and for a complete medical evaluation. Women of child bearing potential will be required to give a urine sample at this time for a pregnancy test. Subjects will then be scheduled to meet with the clinical psychologist and nutritionist to evaluate their appropriateness for this study and to determine if there are any factors that may negatively impact compliance with the surgical, medical, and/or lifestyle aspects of this study. Similar screening procedures to those described here are already in place for both surgical and non-surgical subjects at this site and they will both be adapted conform to the common flow shown in the attached flow chart. Upon successful completion of all screening procedures, individuals who remain eligible will be randomized to one of three treatment arms; one of two bariatric surgery procedures RNY or GB (Surgical Weight Loss Intervention-SWLI) or the lifestyle weight loss intervention (LWLI).

All SWLI patients will undergo further preoperative surgical testing including; blood work, upper GI to assess foregut anatomy, electrocardiogram, and chest radiograph.
2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- all research activities
- personnel (by role) performing the procedures
- location of procedures
- duration of procedures
- timeline of study procedures

Pre-intervention, participants who meet the inclusion criteria will be enrolled into the study and undergo detailed medical evaluation at Magee-Womens Hospital of UPMC with Dr. Courcoulas. Included in this assessment are collection of demographic information, medication assessment, comorbidity status, height, weight, percent body fat, waist circumference, and blood pressure. Subjects who continue to meet study inclusion criteria will then be scheduled to meet with the clinical psychologist, Linda Ewing, RN, PhD and a Magee-Womens Hospital dietician for standard psychological and nutritional evaluation for bariatric surgical/diabetic candidates. These evaluations will evaluate appropriateness for the study and will determine if there are any factors that may negatively impact compliance with the surgical, medical and/or lifestyle aspects of this study.

Randomization will be by random assignment so that each participant has an equal chance of being assigned to each of the three treatments. Randomly permuted block sizes stratified by BMI will be used to ensure that representative groups are entered into all three study treatment groups. The randomization schema will be provided by the data managers of the ONRC/PAWMRC and randomization envelopes will be used to ensure allocation concealment.

Following randomization, the 40 patients assigned to the Surgical Weight Loss Intervention (SWLI) will undergo further preoperative testing including blood work, upper GI to assess foregut anatomy, electrocardiogram, and chest radiograph. All preoperative testing will take place at Magee-Womens Hospital facilities within 3 months of surgical intervention.

All 60 participants will attend a baseline research visit in the Endocrinology and Metabolism Research Center (EMRC) under the direction of Dr. Goodpaster. This visit will include assessments of body fatness, physical activity, psychosocial correlates of change in body weight and behavior, and a baseline blood draw. Body composition (fat mass, lean body mass, bone mineral content, bone mineral density, and percent body fat) will be assessed using a GE Lunar iDXA dual-energy x-ray absorptiometer (Lunar, Inc., Madison, WI). Subjects will be clothed in a lightweight hospital gown and will be instructed to remove all jewelry, hairpins, etc. that would potentially affect the accuracy of this measurement. The scanner will be calibrated each day according to the guidelines specified by the manufacturer. To assess physical activity, participants will wear the SenseWear Pro Armband (BodyMedia, Inc.) for 9 to 11 consecutive days prior to undergoing intervention. Psychosocial correlates of change in body weight and behavior will be assessed at this timepoint through administration of six questionnaires: (1 & 2)Self-Efficacy for Weight Loss and Physical Activity: Self-efficacy for weight loss will be assessed using the questionnaire developed by Clark et al. (1991) Self-efficacy for exercise will be assessed using the questionnaire by Marcus et al. (1992); (3) Outcome Expectations: The questionnaire developed by Steinhardt and Dishman (1989) will be used to assess outcome expectations for physical activity with modifications specific to eating behavior and weight loss; (4) Perceived Barriers: The questionnaire developed by Steinhardt and Dishman (1989) will be used to assess perceived barriers for physical activity with modifications specific to eating behavior and weight loss; (5) Beck Depression Inventory (BDI): The Beck Depression Inventory (BDI) is a series of 21 questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric diagnoses; (6) SF-36: The SF-36 is a multi-purpose, short-form health survey with 36 questions which yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. In addition to the above questionnaires, patients will be asked to fill out the following forms in order to capture the information detailed below (Table 1) and in the more detailed chart attached in the 'Supporting Documentation' section: Treatment Preference Questionnaire which will be used to gauge willingness to be randomized to all three interventions and can be retrospectively correlated unwillingness to be randomized and drop-out rates; Eating and Weight History Questionnaire to assess past attempts at weight loss and weight status of the patient and the patient's...
family: Measure of Weight Loss Goals; Diabetes History Questionnaire; Diabetic Medication Log; Additional Treatments Questionnaire; and Physical Activity Armband Diary. Total time for completion of these questionnaires will be 30-45 minutes. Blood assays including fasting glucose, HgbA1C, insulin, lipid profiles, C-peptide, and markers of inflammation will be drawn and measured in Dr. Goodpaster’s laboratory.

Table 1. Study Measures and Assessments
Contact Time Points
Baseline 6-Month 12-Month
Follow-Up Follow-Up

Demographic Information x x
Medication Assessment x x x
Comorbidity Status x x x
Height, Weight, % Body Fat, x x x
Waist Circumference,
Blood Pressure

Complications and Health x x
Care Utilization

IVGTT x x
(on subset of 15 patients)

Blood Assays (glucose, x x
HgbA1c, lipids,
inflammatory markers)

iDXA x x

Physical Activity Armband x x

Psychosocial Correlates of x x x
Change in Body Weight and Behavior

Pre-intervention, a subset of 18 participants (6 from each of 3 treatment arms- gastric bypass, gastric banding, and lifestyle) will undergo frequently sampled intravenous glucose tolerance testing (FS-IVGTT) at the University of Pittsburgh Montefiore CTRC under the direction of Dr. Goodpaster. This measure will examine the effect of each of the 3 study interventions on the acute insulin response (AIRglucose) and insulin sensitivity (Si) before and after treatment. Subjects taking exogenous insulin will not be eligible for this subset outcome measure. Patients with diabetes on oral medications who enter this study will be asked to stop their medications for 5 days before metabolic testing. During this time, the participants will monitor their blood glucoses twice a day, before their morning and evening meals. If the patient obtains a fasting blood glucose value of 300 mg/dl or more they will be required to contact study staff, will be withdrawn from the IVGTT portion of the study and will be instructed on how to resume diabetic medications. Six patients from each treatment group will be admitted for an overnight stay at the CTRC between 5-7 PM and fed a standard meal of 7kcal/kg. Following the meal, patients will remain fasting (except water) until completion of all study procedures the following day. After a 12 hour fast, intravenous catheters will be placed in both antecubital veins. After fasting samples are obtained, 50% dextrose and insulin will be given in dosages calculated on the basis of body surface area due to the high body mass of obese subjects. Blood samples will be obtained at minutes -15, -10, -5, +2, +3, +4, +5, +6, +8, +10, +12, +14, +16, +19, +22, +23, +24, +25, +27, +30, +40, +50, +60, +70, +80, +90, +100, +120, +120, +140, +160, +180 for determination of insulin sensitivity and insulin secretion.

All 40 of the participants randomized to the SWLI will undergo surgery performed by Dr. Courcoulas at Magee-Womens Hospital under general anesthesia and will receive DVT prophylaxis with subcutaneous heparin and sequential compression devices on the lower limbs. On the morning of surgery, women of child bearing age will be required to undergo urine hCG testing to determine pregnancy status. Half of the participants randomized to the SWLI will undergo laparoscopic Roux-en-Y Gastric Bypass (RNY) and half will undergo laparoscopic Gastric Banding (GB). The RNY will be performed with a standard retrocolic, retrogastric technique, using a linear stapled and hand sewn gastrojejunal anastomosis.
GB will be performed using the Allergan 10 Lap Band with suture securing of the gastric cardia to prevent slippage and placement of the infusion port on the anterior rectus muscle. Post-operative length of hospital stay will be 48 hours for the RNY participants and 24 hours for the GB participants. All SWLI participants will undergo upper GI radiography prior to discharge to rule out any anastomotic leaks or obstructions.

The 20 participants randomized to the Lifestyle Weight Loss Intervention (LWLI) will receive a standard behavioral weight control program that will be delivered in an in-person format under the direction of Dr. Jakicic at the PAWMRC located in Birmingham Towers. This intervention is based on the intervention developed for the Diabetes Prevention Program (DPP) and the Look AHEAD Study (a multi-center study of adults with T2DM). Dr. Jakicic and colleagues have adapted these intervention materials into an ongoing 12-month intervention for weight loss to treat class II and III obesity. During the initial 6 months of treatment, participants will attend weekly in-person intervention sessions. During months 7-12, participants will attend in-person sessions on the 1st and 3rd week of the month and will receive a brief (<10 minutes in duration) telephone contact on the 2nd and 4th week of the month. This will facilitate weekly contact throughout the 12-month intervention. Each group visit will focus on a specific behavioral topic related to weight loss, eating behaviors, or exercise behaviors. Participants are provided written materials to supplement the in-person and telephone interactions with the weight loss counselor. Participants will monitor body weight, eating behaviors, and exercise behaviors. Body weight will be measured at each in-person meeting and participants will also be encouraged to measure their body weight on their own during weeks when no in-person visits are scheduled (e.g., months 7-12). Participants will be encouraged to self-monitor their eating and exercise behaviors and will be provided with a weekly diary to record eating and exercise patterns. Participants will return the completed diary to the intervention staff at each in-person visit for review, and the intervention staff will provide written feedback on the diary prior to it being returned to the participant. All subjects will be prescribed an energy restricted dietary intervention that has been shown to effectively reduce body weight by 8-10% within the initial 6 months of treatment. This will include reducing energy intake to 1200 to 1800 kcal/d based on initial body weight. To facilitate the adoption of the dietary recommendations, individuals will be provided with meal plans that will allow them to plan for modifications in their daily and weekly meal plans, and a calorie counter book. To further facilitate the compliance with the dietary recommendations and to enhance weight loss we propose to provide meal replacements (Slim Fast or Glucerna products) to participants in the LWLI group. Participants will be prescribed exercise that is consistent with data that have shown that higher levels of exercise may be important for preventing weight regain.20,24 Specifically, subjects will be instructed to engage in moderate intensity exercise 5 days per week. The total duration per day will begin at 20 minutes per day and will gradually progress to at least 60 minutes per day. Exercise will be progressed in a gradual manner (5-10 min/d in 4 week intervals) in an attempt to maximize adherence and minimize the onset of musculoskeletal injury. Exercise intensity will be set at 55-70% of age-predicted maximal heart rate. The overall management of the participant’s diabetes will be the responsibility of their primary care physician (PCP) or endocrinologist with additional oversight by the study endocrinologist, Dr. Toledo. Therefore prior to initiating the intervention all participants in the LWLI group will be taught how to monitor their blood glucose, and if they do not have a home blood glucose monitor they will be referred to their primary care physician or a study associated diabetes nurse to facilitate the attainment of a home glucose monitor. Participants will also be provided with information regarding symptoms and signs of hypoglycemia and instructions on treating hypoglycemia. During periods of weight loss, participants in the LWLI group may need reductions in diabetes medication(s) to reduce their risk of hypoglycemia. The medical team associated with this study will be responsible for medication adjustment in cooperation with the participant’s PCP/endocrinologist, and this information will be communicated to the intervention staff.

After completion of the first year of study treatment, participants will be approached for re-consent to participate in an extension to the study meant to sustain achieved weight loss and allow for longer-term follow-up of the cohort. Additionally, after completion of the third year of study treatment, participants will again be approached for re-consent for longer term participation. The "Extension Flow Chart", attached, describes the flow of participants as they undergo 2 years of the low level lifestyle intervention (LLLLI) and complete annual follow-up visits for a total of three-year follow-up. Details of the LLLLLI and annual visits are further explained in Section 2.7.

2.6.1 Will blood samples be obtained as part of this research study?

* Yes

If Yes, address the frequency, volume per withdrawal, the total volume per visit, and the
qualifications of the individual performing the procedure:
All subjects will have blood drawn at baseline and 12-month follow-up visits. The blood collected during these timepoints will be processed in the Montefiore CTRC, in the EMRC laboratory, and at the CLSI for the purposes of assaying fasting glucose, insulin, lipid profiles, and markers of inflammation. Samples will be sent to the CLSI for immediate same day processing (Comprehensive Metabolic Panel, Lipid Panel, CBC, TSH, and HbA1c). Serum and plasma processed in the CTRC will be stored in the EMRC laboratory for batch specimen processing of insulin and metabolic markers at study conclusion. A maximum of 50 mL (3.4 Tablespoons) will be required for the blood draws at these time points.

The subset of 15 participants will undergo a frequently sampled intravenous glucose tolerance test (FS-IVGTT) at baseline and 12-month follow-up visits. This test will require a volume of approximately 12 tablespoons at each timepoint, or a total volume of approximately 24 tablespoons during the course of the study.

Additionally, the 40 subjects in the SWLI treatment arm will be required to undergo standard laboratory studies for bariatric surgical candidates to determine eligibility for surgery. This will be a one time blood draw and will not require more than 20mL of blood.

Those participants that agree to participate in the study extensions will have blood drawn at 24- and 36-month visits and annually thereafter. The blood collected during these timepoints will be processed in the Montefiore CTRC, the EMRC laboratory, and the CLSI for the purposes of assaying fasting glucose, insulin, lipid profiles, and markers of inflammation. Samples will be sent to the CLSI for immediate same day processing (Comprehensive Metabolic Panel, Lipid Panel, CBC, TSH, and HbA1c). Serum and plasma processed in the CTRC will be stored in the EMRC laboratory for batch specimen processing of insulin and metabolic markers at study conclusion. A maximum of 50 mL (3.4 Tablespoons) will be required for the blood draws at these time points.

**Study Flow Chart:**

<table>
<thead>
<tr>
<th>Name</th>
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</thead>
<tbody>
<tr>
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<td>5/1/2013 12:35 PM</td>
</tr>
</tbody>
</table>

[reviewer notes¬]

2.7  
**Will follow-up procedures be performed specifically for research purposes?** Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* yes

Detailed procedures listed in the textbox below:

Among the SWLI participants, RNY patients will undergo follow-up assessments at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months which is consistent with current clinical practice. GB patients will follow-up post operatively at 2 weeks, and 2, 4, 6, 8, 10, and 12 months with the first band adjustment at approximately 2 months and at 60% of the follow-up visits, as needed for clinically appropriate gastric restriction. Measure of weight on a Tanita scale will be captured at each follow-up visit. SWLI patients will be counseled on a diet program consistent with post bariatric surgery, progressing from clear liquids for 1 to 2 weeks, soft foods for 2 to 4 weeks and then stabilizing at 6 weeks to 3 small, solid protein-rich meals and one healthy snack per day. Participants will be encouraged to exercise a minimum of 3-4 times per week and to focus on weight-bearing, aerobic exercise options. In follow-up year 1, diabetes management will be overseen by Dr. Toledo, the study endocrinologist, and will be coordinated between the surgeon follow-up visits and close communication with the subject’s family physician or endocrinologist as adjustment of diabetic medications is routine following weight loss surgery interventions.

In addition to the previously noted intervention-specific follow-up procedures, all 60 participants will be seen at 6- and 12-months post-intervention. Both time points will involve a visit with Dr. Courcoulas and the study coordinator during which Dr. Courcoulas will assess comorbidity status and complications, the coordinator will document medication usage and health care utilization, and the participant will complete the five psychosocial correlates of...
change in body weight and the demographic and behavior questionnaires. Included among these self-assessment questionnaires is the Beck Depression Inventory (BDI) which will be administered by the study coordinator according to the BDI Intervention Protocol (see Other Attachments section). The 12-month follow-up time point will also include a visit to the Montefiore CTRC and EMRC where, under the direction of Dr. Goodpaster, vital signs and anthropometric measures (height, weight, percent body fat, waist circumference, blood pressure, temperature) will be taken and the body fatness (DXA), physical activity measures, and blood draw/assays will be repeated in the same manners as the baseline visit.

Additionally, all participants will undergo resting energy expenditure consisting of gas exchange measurements to measure resting energy expenditure. To quantify carbohydrate oxidation, systemic indirect calorimetry using an open canopy system (Parvomedics, Salt Lake City, UT) will be performed. This test will take approximately 30 minutes. The subset of 15 participants who completed IVGTT testing at baseline will undergo repeated testing at the 12-month follow-up timepoint in the UPMC Montefiore CTRC under the direction of Dr. Goodpaster.

After completion of the first year of study treatment, participants will be approached for re-consent to participate in an extension to the study meant to sustain achieved weight loss and allow for longer-term follow-up of the cohort. After completion of the 3 year annual visit, participants will again be approached for re-consent to continue with the LLLI and be followed at annual follow-up time points to assess outcomes over the longer term. The "Extension Flow Chart", in section 2.6, describes the flow of participants as they undergo the low level lifestyle intervention (LLLI) and complete annual follow-up visits.

The follow-up LLLI in this study will be similar for both SWLI and LWLI group. During months 13-36 of the intervention, the LLLI will require attendance at one in-person session per month (~30-45 minutes in duration) and one brief (<10 minutes in duration) telephone contact per month. After re-consent has been obtained at 36 months, the LLLI will be modified to include one contact per month (28-31 day period) that can be completed either in-person or over the telephone for each contact. At each in-person session participants are weighed, self-monitoring records are reviewed, and a new lesson is presented, following a standardized treatment protocol that will be the same for all treatment arms. During months 13-36 of the intervention, participants will be asked to monitor their blood glucose values for one week per month and to document the values on a Blood Glucose Log. Blood glucose logs will be collected by the interventionists at the monthly in-person sessions if the subject completes the log as they were asked to do. The interventionists will complete the "For Staff Use" section of the Blood Glucose Log and will fax the log to Dr. Courcoulas for review. Dr. Courcoulas will review the values and indicate her recommendation and the completed log will be faxed back to the interventionist to be retained in the participant file. To facilitate transportation to these sessions and to enhance retention over the intervention period free parking is provided and an extensive mass transit system is available to participants. To facilitate transportation to these sessions and to enhance retention over the intervention period free parking is provided and an extensive mass transit system is available to participants. To facilitate the telephone intervention contact the staff will pre-schedule the time with the participant and send a reminder postcard prior to the call, which is similar to the procedure that we have successfully implemented in other intervention studies. Each intervention visit will focus on a specific behavioral topic related to weight loss, eating behaviors, or exercise behaviors, and will also involve problem solving and relapse prevention strategies to address ongoing or anticipated barriers to optimal adherence. Participants are provided written materials to supplement the in-person discussion. Moreover, behavioral and lifestyle "tip sheets" are mailed to participants on the weeks that they do not attend an in-person session to further enhance compliance to the lifestyle intervention. Attempts are made to schedule make-up sessions when an individual misses an in-person session, and in the event that this is not possible, participants are mailed all intervention materials and are to review them prior to the next in-person or telephone intervention contact. During months 13-36, if a participant becomes unable to attend monthly LLLI sessions in-person, he/she may be contacted by the intervention team for phone calls in place of the in-person visits and, if this occurs, the participant will be considered to be receiving "alternate intervention". Should a participant that is placed on "alternate intervention" wish to resume in-person LLLI sessions, they may be allowed to do so. Detailed records on the method by which the intervention contacts are delivered each month (i.e. in-person or via phone) will be kept. After re-consent at the 36-month time point, the LLLI will begin to implement lifestyle campaigns. During each 12 month period there will be an opportunity for subjects to engage several prize-based point systems.

During each of these periods the subject will earn points based on their ability to achieve a goal that is consistent with the recommended lifestyle intervention (e.g. completion of intervention contacts, achieving the recommended physical activity goal, self-reporting of eating behaviors or weight, meeting a recommended nutrition goal that is consistent with healthy weight loss or weight loss maintenance, etc.). During each campaign each subject will receive a small gift (t-shirt, umbrella, lunch bag, $10 WePay card etc.) for earning a pre-specified number of points during the campaign period. Participants will also have the opportunity to take part in a drawing for an additional gift.
An initial group session will be held for both surgical arms (RNY, GB) to provide a lesson on behavioral weight control to orient them to the skills and strategies that were learned and developed for the intensive lifestyle intervention group. This orientation is not an attempt to implement the intensive lifestyle intervention for the surgical patients, after the fact, but to prepare them for the LLLI. To follow, a variety of group session and activities will be developed under the direction of all of the investigators and research staff that are specific to each arm of treatment (LWLI, GB, RNY). These will include small support groups conducted by a trained staff member and other group activities intended to both enhance learning and foster retention among study subjects. Group sessions such as these were held during the original intensive LWLI and gave participants an opportunity to meet and interact with other participants from the same intervention group while partaking in an informative and instructional activity. Such examples of these group sessions and activities were a group exercise session and a session in which participants were taught how to exercise with resistance bands. A schedule of monthly group sessions and themes will be developed. Each group session theme will be similar across treatment arms but will be modified slightly to address the issues and obstacles specific to the particular treatment arm. The sessions will be conducted by behavior group leaders and will include presentations by the interventionists, investigators, study staff, and also will incorporate an array of guest speakers knowledgeable and experienced in the session’s theme. The regular monthly optional group sessions (as specified in the Follow-up Consent) have been modified as of January 2013. Group sessions similar to those held during the original intensive LWLI may still be held for subjects undergoing the LLLI for the purposes described above. Additionally, other group session events to encourage retention and keep participants engaged may be held throughout the year.

All participants who consent to the extension of the study will be seen at 24- and 36-months (+/- 90 days) post-intervention and annually thereafter (+/- 90 days) (Table 2). All annual follow-up time points will involve a visit with Dr. Courcoulas and the study coordinator during which Dr. Courcoulas will assess comorbidity status and complications, the coordinator will document medication usage and health care utilization, and the participant will complete the five psychosocial correlates of change in body weight and the demographic and behavior questionnaires. Included among these self-assessment questionnaires is the Beck Depression Inventory (BDI) which will be administered by the study coordinator according to the BDI Intervention Protocol (see Other Attachments section). Dr. Courcoulas may assess the participant’s comorbidity status by phone as necessary. The follow-up time points will also include a visit to the Montefiore CTRC and EMRC where, under the direction of Dr. DeLany (formerly Dr. Goodpaster), vital signs and anthropometric measures (height, weight, percent body fat, waist circumference, blood pressure, temperature) will be taken and the body fatness (DXA), physical activity measures, resting energy expenditure, and blood draw assays will be repeated in the same manners as the 12-month visit. As of May 1, 2014, the resting energy expenditure test will no longer be performed on subjects.

Due to the number of visits associated with this study, it is expected that, on occasion, a subject may fail to report for his/her scheduled visit as specified in the research protocol due to holidays, vacations, illnesses, or other unforeseen events. The PI and her study staff will implement a “SHORT” form to be reviewed with any Triabetes participant at the PI/coordinator’s discretion. The "SHORT" form will be a mechanism to avoid a complete missed visit and to collect minimal data from a participant as needed. Subjects who fail to report for a scheduled study visit within the window specified in the research protocol will be contacted, by telephone, for evaluation of their safety, and such missed visits will be tracked by the research team. If a subject demonstrates significant difficulties complying with the scheduled visit protocol requirements, we will consider removing the subject from the study. If a subject fails to report for his/her scheduled visit and we are not able to contact the subject for assessment of safety, an event report will be submitted to the IRB.

Due to the extended follow-up with this study, it is expected that over time, a participant’s contact information may change. As a last resort, if all other reasonable avenues to locate a participant in the Triabetes Study have failed, a search engine will be employed (e.g., Transunion, CLEAR, Experian, LexisNexis Accurint) to assist in ascertaining new contact information (address, phone number) for any participants whose phone numbers and addresses have become obsolete. Demographic information (e.g. name, DOB, or SSN) collected from the medical record or provided by the participant at the time of study enrollment or at annual follow-up visits may be used to perform a search to locate participants whose contact information has changed or who are lost to follow-up. This information will only be used on a one-off look up basis and will not be stored outside the university. Use of this retention contingency will be kept to a minimum and only used when all other methods of contact have failed. Accurate records which reflect the frequency of use of this contingency will be kept and can be reported to the IRB on an annual basis, upon
request. Once reached, participants will be reminded that they are voluntarily participating and can choose to not participate if they wish.

In an effort to obtain long-term health and weight outcomes information from all treated participants, the PI, Dr. Courcoulas, and her study staff will attempt to reach out to any participants who were or who may become lost to follow up or inactivated during the Triabetes Study.

The study team will attempt to contact these participants. Once reached, Dr. Courcoulas or her study staff will explain to the participant that he/she is being contacted because of his/her prior involvement in the study. Dr. Courcoulas or her study team will review the waiver to document informed consent to collect health information over the phone (e.g. SHORT) and will then assess the participant’s willingness to continue participating in the study. Continued participation for these participants will consist of an annual follow-up assessment. Ideally, participants will attend an in-person annual study assessment and will be asked to complete the annual study measures as outlined in Table 2. However, because of the extended follow-up and the nature of the participants being approached for study participation (previously discontinued participation), it is expected that some participants will not be willing to attend annual follow-up visits. Given that this is a randomized controlled trial involving a surgical procedure, it is important to continue to follow-up with a participant’s health status and important to retain the participant in the study. For those reasons, if a participant is unwilling to complete the annual study assessment in-person, an abbreviated assessment will be completed with the participant over the telephone and through the mail as appropriate and convenient for the participant. The abbreviated assessment will count as a “minimal data” visit and may consist of a brief interview (5-10 minutes) during which the participant may be asked about his/her demographic information, medications, comorbidity status, psychosocial, and physical measures. Additionally, given the study is a randomized control trial, it is important to assess participants willing to re-consent to the study as soon as possible. If a participant re-consents to the study, he or she will be seen as soon as possible. Ideally, this will occur within the participant’s time point window (+/- 90 days from treatment start); however, if the visit cannot occur at that time, the participant may still be seen outside of his or her window and the visit will then count toward the closest time point window. All subsequent time point visits will occur within the specified window.

Table 2. Complete Study Measures/Assessments Contact Time Points (+/- 90 days) 24-Month 36-Month Annual Follow-Up

| Demographic Information | x | x | x |
| Treatment Preference Assessment | x | x | x |
| Medication Assessment | x | x | x |
| Comorbidity Status | x | x | x |
| Complications and Health Care Utilization | x | x | x |
| Anthropometrics and Vital Measurements | x | x | x |
| Blood Assays (Glucose, HbA1c, Lipids, Inflamm. Markers) | x | x | x |
| iDXA | x | x | x |
| Resting Energy Expenditure (RMR) | x | x | x |
| Physical Activity Armband | x | x | x |
| Psychosocial Correlates of Change in Body Weight & Behavior | x | x | x |

*As of May 1, 2014, the resting energy expenditure test will no longer be performed on subjects. This coincides with subjects being between the 36 and 48 month time points.

2.8 Does this research study involve the use of any questionnaires or survey instruments?

* yes

Upload a copy of all unpublished surveys/questionnaires. Also upload any published materials that may include questions, images, video, or sound recordings that may be especially disturbing to subjects:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
</table>
List the name and publisher for commercially available materials (Note: these materials do not need to be uploaded):

2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?

* yes

If Yes, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:
Fasting blood glucose levels will be used to determine type 2 diabetes (T2DM) status in participants. This laboratory value will have most likely been obtained prior to a participant's enrollment by their PCP and will be used as a screening parameter.

2.10 The blood sample question was moved to 2.6.1.

2.11 What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?

* 12-15 months for initial phase of study. If participant agrees to study extension, duration will be extended 24 months. If subject agrees to the extension beyond 36 months, participation will be extended indefinitely until funding ceases/outcomes reached

2.12 Does this research study involve any type of planned deception?

If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* no

2.13 Does this research study involve the use of UPMC/Pitt protected health information
that will be de-identified by an IRB approved "honest broker" system?
* no

[reviewer notes¬]

2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?
* yes

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

Preoperative testing including blood work, upper GI, electrocardiogram, and chest radiograph in addition to records pertaining to the operation and hospital stay will be placed in the patient's medical records. Additionally, follow-up blood work obtained for research purposes and processed in a UPMC laboratory will be included in the patient's medical records, as is practice at UPMC facilities.

Additionally, if signed informed consent has been obtained to do so, the PI and her study staff may review the participant's electronic medical records for information on physical measures (e.g. weight, blood pressure), diagnosis of T2DM, laboratory values, medication usage, and comorbid conditions.

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?
* yes

If Yes, describe how the HIPAA requirements will be met:
If signed informed consent has been obtained to do so, the PI and her study staff may contact the participant's PCP for information on physical measures (e.g. weight, blood pressure), diagnosis of T2DM, laboratory values, medication usage, and comorbid conditions.

I, Anita Courcoulas, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed HIPAA Researchers Privacy Requirements (Formerly RPF Module 6) training. The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.
* yes

2.14.2 Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI from a UPMC/Pitt covered entity? Note that the University of Pittsburgh IRB cannot grant a HIPAA waiver for entities outside of UPMC/Pitt.
* no

[reviewer notes¬]

2.15 Does this research study involve the long-term storage (banking) of biological specimens?
* no

[reviewer notes¬]
2.16 Will research participants be asked to provide information about their family members or acquaintances?
* no

[reviewer notes¬]

2.17 What are the main outcome variables that will be evaluated in this study?

For the first phase of the study (RC1DK086037):

Prior to analysis of major outcomes, we will describe study participants and compare the intervention groups on variables of interest (age, BMI, etc) to assess the effectiveness of the randomization in creating groups that are similar pre-intervention. We will control for any unforeseen important differences between the groups in multivariable analyses. We will also do a similar comparison of completers and non-completers (drop-outs) to determine whether completers are representative of the baseline cohort. To examine feasibility (Specific Aim 1) and to inform a larger-scale trial we will collect and analyze data related to the following parameters: 1) recruitment, 2) willingness of subjects to undergo randomization to the proposed treatment arms, 3) retention of subjects across the 12 month study in all arms, 4) compliance with the interventions (i.e., attendance at required sessions, etc.). For Specific Aim 2 and Specific Aim 3, the primary outcome measures are continuous variables (e.g., weight loss, insulin sensitivity, insulin secretion, physical fitness, physical activity, lipid profiles etc.) and the principal analytic goal is to assess the magnitude of change in the specified outcome parameters associated with the assigned intervention groups. Initially, crude (univariate) change scores (from baseline to 12 months post intervention) in the outcome parameters of interest will be plotted graphically by treatment assignment.

For the second phase of the study (R01DK095128):

The primary outcome measures are continuous variables (e.g. weight loss, HbA1c, physical fitness, physical activity, lipid profiles etc.) and the principal analytic goal is to assess the magnitude of change in the specified outcome parameters associated with the assigned intervention groups. Initially, crude (univariate) change scores (from baseline to annual visits post intervention) in the outcome parameters of interest will be plotted graphically by treatment assignment. (Specific Aim 1)

To examine the feasibility aims and to inform a larger-scale trial we will collect and analyze data related to the following parameters: 1) willingness of subjects to undergo the LLLI by treatment arm, 2) retention of subjects for 36 months in all arms, 3) compliance with the interventions (i.e., attendance at required sessions, etc.). As this is an extension of a pilot study, several aims are exploratory and we may not have enough power to examine all putative moderators and mediators. Instead we will explore their potential roles in subjects’ responses to intervention. (Specific Aim 2)

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

To examine RC1DK086037 Specific Aims 2 and 3 and to examine R01DK095128 Specific Aim 1 we will use a mixed model approach for the analysis of the data to determine if the interventions are successful in changing outcome. For data missing completely at random appropriate statistical analytical methods can be employed. Other options include imputing data or creating indicator variables (generally the least desired approach) to identify missing data. Dropout or censoring will often be informative so the missing outcome data may be "non-ignorable." An exploratory approach used to assess the extent of potential bias and its effect on analysis is to compare characteristics of patients with available data to those with missing data. For data missing completely at random (does not depend on observed outcome; MCAR) linear mixed model analysis provides unbiased results. However, in other cases where the dropout depends on observed outcome and/or covariates (missing at random, MAR) or unobserved outcome and/or covariates (missing not at random, MNAR), we will use selection models such as MNAR Dale model and Diggle-Kenward model. These models often require strong assumptions on the dropout mechanism which are primarily unverifiable based on the observed data. We will conduct sensitivity analyses to investigate the sensitivity of our conclusion to possible violation of such assumptions. We will also fit MCAR, MAR and MNAR and compare the model fits using log-likelihoods. We will consider other approaches to analyzing longitudinal data with informative censoring including modeling the censoring.
process jointly with the fitted model of interest and weighted estimating equations using inverse probability of missingness to account for the potential bias that arises due to the missing outcomes.

2.19 Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?
* no

2.21 Will this research study be conducted within a nursing home located in Pennsylvania?
* no

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Section 3 - Human Subjects

3.1 What is the age range of the subject population?
Subjects between the ages of 25 and 55 will be enrolled into this research study.

3.2 What is their gender?
* Both males and females
Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?
* no
If Yes, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?
* yes

3.5 Participation of Children: Will children less than 18 years of age be studied?
* no
If No, provide a justification for excluding children:
Children will not be included in the proposed study for a number of reasons. The first of which is that it is not standard clinical practice to perform weight loss surgery in children under 18 years of age and remains experimental among children and adolescents in this age range. Additionally, some of the knowledge being sought in this research is being investigated in another ongoing study at in our department, TeenLABS, which aims to facilitate coordinated clinical, epidemiological and behavioral research in the field of adolescent bariatric surgery.

3.6 Does this research study involve prisoners, or is it anticipated that the research
study may involve prisoners?
* no

[reviewer notes¬]

3.7 Will pregnant women be knowingly and purposely included in this research study?
* no

[reviewer notes¬]

3.8 Does this research study involve neonates?
* no

[reviewer notes¬]

3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?
* no

[reviewer notes¬]

3.10 What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 150

3.11 Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.

* 3686

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<tr>
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</tr>
<tr>
<td>View Group</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

3.12 Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.

* Described below:

This is a feasibility trial with an expected 60 patients randomized into three treatment arms and is intended to function as a pilot study for a larger scale trial. We do not anticipate
having power to determine the statistical significance of the outcomes in this trial.

[reviewer notes¬]

3.13 **Inclusion Criteria: List the specific criteria for inclusion of potential subjects.**

- Age 25 to 55 years
- Mild to moderate obesity with a BMI between 30 and 40 kg/m²
- For potential subjects with BMI 35 to 40 kg/m²: T2DM confirmed by either a documented fasting blood glucose > 126 mg/dl OR treatment with an anti-diabetic medication
- For potential subjects with BMI 30 to 35 kg/m²: T2DM that is difficult to control medically and is recommended for the study by the subject's endocrinologist AND treatment with an anti-diabetic medication
- Willingness to be randomized to a surgical intervention

3.14 **Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.**

- Prior bariatric or foregut surgery
- Poor overall general health
- Impaired mental status
- Drug and/or alcohol addiction
- Current smoking
- Pregnant or plans to become pregnant
- Type 1 Diabetes Mellitus
- Portal hypertension and/or Cirrhosis
- Failed study-related nutrition or psychological assessment
- Current participation in any other research study
- Inability to provide informed consent
- Unable to communicate with study staff
- Unable to exercise (walk a city block or a flight of stairs)

3.15 **Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?**

* no

If **Yes**, provide a justification:

3747 **Section: Section 4 - Recruitment and Informed Consent Procedures**

[reviewer notes¬]

4.1 Select all recruitment methods to be used to identify potential subjects:

- Advertisements
- Recruitment Letters and/or Scripts
- Other Strategies: Described below

### Advertisements

Upload the advertisements for review:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Flyer-Triabetes 9.11.09 Modified 1.6.2010.doc</td>
<td>1/6/2010 2:01 PM</td>
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<tr>
<td>Newspaper Ad Triabetes BMI 30-35.doc</td>
<td>7/15/2010 4:19 PM</td>
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<td>11/9/2010 2:04 PM</td>
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<tr>
<td>Newspaper Ad Triabetes 1.13.2010.doc</td>
<td>1/13/2010 11:33 AM</td>
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<tr>
<td>Study Brochure-Triabetes 9.11.09 Modified 1.6.2010.doc</td>
<td>1/6/2010 2:07 PM</td>
</tr>
<tr>
<td>Study Flyer with Tear Aways-Triabetes 11.19.09 Modified 1.6.2010.doc</td>
<td>1/6/2010 2:05 PM</td>
</tr>
</tbody>
</table>
4.2 Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:

Subjects will be initially contact by both a recruitment letter (registry patients) and by telephone (those responding to advertisements and flyers).

As a retention tool, at monthly group sessions we will hold retention raffles in which a small prize (gift cards, pedometers, and similar items) will be raffled to participants that attend the sessions. Participants will be notified about raffles either at the time of their individual in-person monthly sessions or during their monthly telephone conversations with the study interventionists. Participants will also be invited to the optional, monthly group sessions, as they are scheduled, via telephone or during individual in-person sessions and informed that a raffle will be held during the group sessions. Reminders of group session dates and times may be sent via mail or email or handed out during in-person sessions or annual follow-up visits and will include mention of a raffle in addition to mention of the focus of the group session (to be held through the year after January 2013, see Section 2.7).

4.6 Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document, such as with phone screening. This is not a waiver to obtain consent.

* yes

4.6.1 Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form.

Addressed below:

If not all, identify the specific procedures and/or subject populations for which you are requesting a waiver:

We request a waiver for requirement to obtain a signed, written informed consent form for phone screening interviews, attendance at orientation sessions (described in section 2.5.1) and completion of the baseline screening assessment forms only. When eligibility has been determined and the patient is seen in-person by the investigator, signed, written informed consent will be obtained.

This will apply to all subjects recruited through advertising techniques. Those patients identified in the clinic by Dr. Courcoulas will not require this waiver because we will be able to evaluate the patient’s eligibility based on the investigators review of clinical information and the signed informed consent can be obtained at that time.

Additionally, we request a waiver of the requirement to document signed informed consent for the purposes of contacting participants who are/were treated in the Triabetes Study but have not consented to study extension or who may become lost to follow up before reconsenting to extension. These participants will be contacted in an effort to reengage them in the study. The waiver to informed consent (Triabetes Telephone Script) will be administered at the beginning of the call, will explain the purpose for the call, and will contain information about becoming reengaged in the study. The script will be used to obtain permission to collect

[reviewer notes¬]
health information over the phone. It contains the information necessary to obtain informed consent from participants to do so. The script will be read by a study team member and the outcome of the informed consent discussion will be documented.

4.6.2 Indicate which of the following regulatory criteria is applicable to your request for a waiver of the requirement to obtain a signed consent form.

45 CFR 46.117(c)(2)

45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

4.6.2.1 Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form present no more than minimal risk of harm to the research subjects:

The waiver of informed consent that we request for the purposes of phone screening presents no more than minimal risk of harm to the research subject because it involves no more than is typically asked of a patient when scheduling a doctor's appointment. Minimal risk of harm applies to all of the questions on the phone screening.

The waiver of informed consent that we request for the purposes of contacting the lost to follow up or inactivated participants presents no more than minimal risk of harm to the participant because the collection of health information over the phone does not place the participant at any greater risk of harm or discomfort.

4.6.2.2 Justify why the research listed in 4.6.1 involves no procedures for which written informed consent is normally required outside of the research context:

Outside of the research context, information similar to what is asked in the phone screening is routinely collected and asked at the time of patient entrance into the bariatric surgery program in this department. None of the questions in the phone screening script require informed consent outside of the research context.

Additionally, questions asked to the lost to follow up/inactivated participants are similar to what would be asked by a physician's office.

4.6.3 Address the procedures that will be used and the information that will be provided (i.e., script) in obtaining and documenting the subjects' verbal informed consent for study participation:

In response to incoming calls from interested potential research participants, study staff will read a brief screening script (attached in other attachments section) describing the study in detail to the patient, documenting their authorization to this screening process with a signature, and asking questions to ascertain eligibility.

The participants who have not consented to study extension will be contacted and the Triabetes Telephone Script will be read and reviewed with the participant. The participant's verbal response will be clearly documented on the telephone script and the process will be validated by a study team member's signature.

Upload Scripts:

Name | Modified Date
---|---
Triabetes Telephone Script | 8/13/2013 7:08 PM

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?
4.7.1 If Yes, select the reason(s) for your request:
There are no items to display

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an ‘emergency’ procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* no

4.9 Upload all written informed consent documents.

Draft Consent Forms for editing:

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Form</td>
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</tr>
<tr>
<td><strong>Extension Consent for Discontinued Participants</strong></td>
<td>4/23/2014 9:54 AM</td>
</tr>
<tr>
<td><strong>Follow-Up Consent.doc</strong></td>
<td>2/10/2011 11:13 AM</td>
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<tr>
<td><strong>Addendum Follow-Up Consent with PCP</strong></td>
<td>4/23/2014 9:55 AM</td>
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</table>

Approved Consent Form(s):

<table>
<thead>
<tr>
<th>Name</th>
<th>Modified Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extension Consent for Discontinued Participants</strong></td>
<td>4/23/2014 9:54 AM</td>
</tr>
<tr>
<td><strong>Addendum Follow-Up Consent with PCP</strong></td>
<td>4/23/2014 9:55 AM</td>
</tr>
</tbody>
</table>

4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

* Yes

4.11 At what point will you obtain the informed consent of potential research subjects or their authorized representative?

After performing certain of the screening procedures, but prior to performing any of the
4.11.1 Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed.

We believe we meet the criteria that the respective research procedures present not more than minimal risk to the involved participants. We believe, that, encompassed in recruitment procedures and screening documents, participants will become fully informed about the study.

We believe the information being obtained from the telephone screening script and orientation screening assessment form is the same type of information that would be collected from patients during a regular doctor’s appointment. Please see script and form attached. If the subject does not meet inclusion criteria, all the information collected during the screening process will be retained without any identifiers, and the patient will be notified of this procedure. In addition, written informed consent will be obtained by the investigator prior to any research activities.

In addition to the benefits of allowing the subject sufficient time to make his/her decision and minimizing the possibility of coercion or undue influence, the opportunity to defer obtaining written informed consent until after the screening procedures have been performed will limit patient burden that would be incurred in requiring patients to come in for a one-on-one surgeon visit that do not meet the very basic eligibility requirements (BMI, age, Diabetes status).

4.11.2 Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Assessing patient eligibility by telephone and conducting group orientation sessions will ensure that the subject has sufficient time and knowledge to make an informed decision of his/her participation in this study prior to signing the informed consent document. In addition to information collected during the brief telephone interview and during the group orientation session, the participant will have the opportunity to meet with the investigator one-on-one at the end of the orientation session to pose any unanswered questions. Only after the patient has been given ample opportunity to ask questions and has expressed full understanding of the research procedures and protocol will the informed consent be obtained. The process of introducing the patient to the study over the course of three contact time points with the investigator and/or her designee prior to obtaining informed consent will provide the subject with sufficient time to make his/her decision and will minimize the possibility of coercion or undue influence.

[reviewer notes->]

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:
This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent.

Recruitment materials such as flyers, informed physician referrals, screening scripts, and group orientation sessions contain the elements of informed consent necessary to fully inform participants about the study prior to obtaining any information about them. Individuals who inquire about this study will be asked to complete a brief telephone interview conducted by the research coordinator to assess initial eligibility and eligible participants will be invited to attend a group orientation session. At the orientation session, the investigators (Dr. Courcoulas and Dr. Jakicic) will provide a detailed description of the study and potential
subjects will be encouraged to ask any questions regarding their participation in this study. Individuals who remain interested at the orientation session after review of a completed screening assessment will attend an individual appointment with the principal investigator and the research coordinator. The principal investigator and research coordinator will review any additional questions with the eligible participant and informed consent will be obtained by the physician investigator prior to performing any research activities.

Addendum consent- through 36-month follow-up:
Subjects will be approached for re-consent at or after the 12 month time point (see Extension Flow, Section 2.6). The re-consent process will begin during in-person follow-up visits, via telephone conversations, and through the mail, as necessary. The PI and her study staff will be involved in the re-consent process and the participant will be given adequate time to review, discuss, ask questions, and verbalize understanding of the new elements contained within the extension/addendum informed consent document prior to signing.

Addendum consent- extended follow-up annually beyond 36 months:
Subjects will be approached for consent to extended follow-up at or after their 36-month time point. The re-consent process will be completed through in-person follow-up visits, via telephone conversations, and through the mail, as necessary. The process through which a participant has been consented (in-person or via mail) will be clearly documented. Consent may be obtained by the Principal Investigator or by the research coordinator, as specified on the delegation of authority log. The participant will be given adequate time to review, discuss, ask questions, and verbalize understanding of the new elements contained within the extension/addendum informed consent document prior to signing. The Principal Investigator, who is a listed physician, will be available to answer any questions the subject may have about the extended follow-up.

Lost-to-follow-up/inactivated - extended follow-up annually:
Participants who were/are treated in the Triabetes study but subsequently became/may become lost to follow up, inactivated, or who did not initially consent to extension in the Triabetes Study will be approached for re-consent to an extended follow-up in the study. The participant will initially be contacted via telephone, email, or postal mail depending on the available information. The re-consent process will then be completed via telephone conversations, through the mail, and in-person as necessary. The process through which a participant has been consented (in-person or via mail) will be clearly documented. Consent may be obtained by the Principal Investigator or by the research coordinator, as specified on the delegation of authority log. The participant will be given adequate time to review, discuss, ask questions, and verbalize understanding of the new elements contained within the extension/addendum informed consent document prior to signing. The Principal Investigator, who is a listed physician, will be available to answer any questions the subject may have about the extended follow-up.

4.13 Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a listed physician investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a listed investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* yes

If Yes, provide a justification and describe the qualifications of the individual who will obtain consent:
After 36-months participation, participants will be approached for consent to study continuation for the purposes of following outcomes over the longer term. Study continuation will include participation in a low level lifestyle program and annual study visits as described in section 2.7. Likewise, lost to follow up/ inactivated participants will be contacted for resumed, extended participation in the study. Resumed participation will consist of annual assessments as described in section 2.7. The follow-up procedures in the study continuation do not involve a drug, device, or surgical procedure and thus should not require consent by a listed physician. Consent may be obtained by the principal investigator, who is a listed physician, or by the study coordinator, as specified on the delegation of authority log. The responsibility of administering informed consent will be added to the study coordinator’s responsibilities on the delegation of authority log, and the study coordinator will be a trained personnel on all aspects of administering informed consent per the IRB policy and department SOPs.
4.14 Will you inform research subjects about the outcome of this research study following its completion?
* no

If Yes, describe the process to inform subjects of the results:

Section: Section 5 - Potential Risks and Benefits

[reviewer notes~]

5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

* 

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Blood Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks</td>
<td>Experimental Interventions: -Occurring in 1% to 25% of people are risks that include bleeding, bruising, dizziness, fainting and soreness</td>
</tr>
<tr>
<td>Infrequent Risks</td>
<td>Follow up Procedures: -Occurring 1% to 25% of people are risks that include bleeding, bruising, dizziness, fainting and soreness</td>
</tr>
<tr>
<td>Other Risks</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>iDXA Scanning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Infrequent Risks</td>
<td>Experimental Interventions: Discomfort due to wearing hospital gown and being asked to remove all jewelry, hairpins, etc. Follow up Procedures: Discomfort due to wearing hospital gown and being asked to remove all jewelry, hairpins, etc.</td>
</tr>
<tr>
<td>Other Risks</td>
<td>Experiment Interventions: Exposure to small amount of radiation (comparable to 1.25% that of a chest x-ray) Follow up Procedures: Exposure to small amounts of radiation (comparable to 1.25% that of a chest x-ray)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>IV-GTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks</td>
<td>Experimental Interventions: -Discomfort, bleeding, and bruising at the site of the needle insertion Follow up Procedures: -Discomfort, bleeding, and bruising at the site of the needle insertion</td>
</tr>
<tr>
<td>Infrequent Risks</td>
<td>Experimental Interventions: -Infiltration, fainting, phlebitis -Infection -Rarely, exposure to insulin injection and 50% dextrose injection could cause hypoglycemia that, if severe, could case rare instances of coma, seizure, and death Follow up Procedures: -Infiltration, fainting, phlebitis -Infection -Rarely, exposure to insulin injection and 50% dextrose injection could cause hypoglycemia that, if severe, could case rare instances of coma, seizure, and death</td>
</tr>
<tr>
<td>Other Risks</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Laparoscopic Adjustable Gastric Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Infrequent Risks</td>
<td>Experimental Interventions: -2% risk of device malfunction which includes band slippage, band erosion, and band or port malfunction or breakage -Anesthesia related complications, wound infection, incisional hernias, urinary tract infection, persistent nausea/vomiting, and dehydration</td>
</tr>
<tr>
<td>Other Risks</td>
<td>No Value Entered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Lifestyle Weight Loss Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Risks</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Infrequent Risks</td>
<td>Experimental Interventions: -Intolerance to meal replacements - Hypoglycemia -Exercise induced risks such as serious cardiac event (e.g., heart attack which occurs in less than 1% or 1 out of 100 people) -Musculoskeletal injury</td>
</tr>
</tbody>
</table>

https://www.osiris.pitt.edu/...true&Project=com.webridge.entity.Entity%5BOID%5B01CD6645DDC3DE45B51260D6A6C3A96E6%5D%5D[1/7/2015 2:30:37 PM]
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<tr>
<th>Research Activity</th>
<th>Common Risks</th>
<th>Infrequent Risks</th>
<th>Other Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SenseWear Pro Armband</td>
<td>No Value Entered</td>
<td>-Hypoglycemia -Exercise induced risks such as serious cardiac event (e.g., heart attack which occurs in less than 1% or 1 out of 100 people) -Musculoskeletal injury</td>
<td>No Value Entered</td>
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<td>Low Level Lifestyle Intervention</td>
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<td></td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Nutritional and Psychological Evaluations</td>
<td>No Value Entered</td>
<td>Screening Procedures: Distress or anxiety due to the nature of the questions asked during these evaluations</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Obtaining and Storing Identifiable Information</td>
<td>No Value Entered</td>
<td>Screening Procedures: Breach of confidentiality Experimental Interventions: Breach of confidentiality Follow up Procedures: Breach of Confidentiality</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Psychosocial Questionnaires</td>
<td>No Value Entered</td>
<td>Experimental Interventions: -Distress or anxiety due to the nature of the questions Follow up Procedures: -Distress or anxiety due to the nature of the questions</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Resting Energy Expenditure</td>
<td>No Value Entered</td>
<td>The risk of anxiety due to the canopy being placed over the head during the indirect calorimetry test is rare (occurs in less than 1% of people). All subjects will have procedures explained to them. The subjects will be informed that they may abort the study at any time.</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Roux-en-Y Gastric Bypass Surgery</td>
<td>Experimental Interventions: Mild Post-operative Dehydration</td>
<td>Experimental Interventions: - Anesthesia related complications, wound infection, incisional and internal hernias, urinary tract infection, persistent nausea/vomiting -Major Surgical Complication (1-2%) including bleeding, deep venous thrombosis, pulmonary embolism, anatomic leak, regional abdominal organ trauma, bowel obstruction, atelectasis, pneumonia, cardiac dysrhythmia -Long term complications including anemia, vitamin or mineral deficiency, neurologic complications such as peripheral neuropathy and encephalopathy, adhesive bowel obstruction, and possible effect on bone density</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>Screening Questions</td>
<td>No Value Entered</td>
<td>Screening Procedures: Patient becoming distressed due to the nature of the questions (i.e., regarding birth control)</td>
<td>No Value Entered</td>
</tr>
<tr>
<td>SenseWear Pro Armband</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Risks:</td>
<td>No Value Entered</td>
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<td>--------------</td>
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<tr>
<td>Infrequent Risks:</td>
<td>Experimental Interventions: -Minor skin irritation and/or discomfort resulting when the electrode sites are prepared and electrodes placed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Risks:</td>
<td>No Value Entered</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

Screening Procedures:

To prevent or minimize the above noted screening risks, all records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant's name.

Additionally, participants will not be required to answer any question asked solely for the purpose of research that they find particularly upsetting and may choose to discontinue participation at any time.

Experimental Interventions:

Precaution will be taken to ensure limited physical harm to human subjects. All study related activities will be supervised by investigators and their designees and/or trained CTRC technicians and staff. Risks associated with surgery will be minimized due to the bariatric center's participation and compliance with National Centers of Excellence requirements, expertise of the surgeon, and the experience of the nursing and medical support staff at Magee-Womens Hospital.

Participants randomized to the surgical weight loss groups, and especially the RNY group, will be counseled extensively on the importance of lifetime supplementation of vitamins and minerals which, if compliant, will greatly decrease the risk of developing a neurological complication due to nutritional deficiencies. Prescriptions for vitamins and minerals (i.e. B12 injections) will be ordered for all patients in the RNY group.

An experienced CTRC phlebotomist and nursing staff will be responsible for the technical aspects of the blood sampling and IV-GTT. Tests will be stopped immediately if any adverse symptoms occur.

Participants will not be required to answer upsetting questions and may choose to discontinue participation at any time.

All records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant's name.

To minimize risk associated with wearing the SenseWear Pro Armband, the sensing unit will be wiped with rubbing alcohol and dried thoroughly before each use.

To minimize risk associated with increased exercise and activity, participants will be extensively counseled on proper exercise techniques and will be progressed in a gradual manner. This will minimize the onset of musculoskeletal injury.

Prior to initiation of any intervention, participants will be taught how to monitor their blood glucose, be provided with symptoms and signs of hypoglycemia and instruction on how to treat hypoglycemia. This will minimize the risk and occurrence of hypoglycemic incidents that may occur with weight loss and subsequent reductions in blood glucose.

Follow up Procedures:

As always, precaution will be taken to ensure limited physical harm to human subjects. All study related activities will be supervised by investigators and their designees and/or trained CTRC technicians and staff.

An experienced CTRC phlebotomist and nursing staff will be responsible for the technical...
aspects of the blood sampling and IV-GTT. Tests will be stopped immediately if any adverse symptoms occur.

Participants will not be required to answer upsetting chestions and may choose to discontinue participation at any time. All records and information will be kept locked in the research facility. Computers that contain confidential and identifying information will be password protected. All data will be stored with an identification number that will be used in place of the participant's name.

To minimize risk associated with wearing the SenseWear Pro Armband, the sensing unit will be wiped with rubbing alcohol and dried thoroughly before each use.

5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

* Addressed below:

As is current practice in the Department of Minimally Invasive Bariatric and General Surgery, participants found to have a clinically significant, unexpected disease or condition during the course of screening will be referred to their primary care physician (PCP) or an appropriate specialist for further evaluation and treatment.

5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes¬]

5.4 Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* yes

5.4.1 List the research procedures that pose a risk to pregnant women or fetuses:

Small risk of significant exposure to ionizing radiation during the pre-operative upper GI series and chest radiograph; General anesthesia required of the surgical procedures could pose risk to a pregnant women or fetus

5.4.2 Describe the steps that will be taken to rule out pregnancy prior to exposing women of child-bearing potential to the research procedures that pose a risk to pregnant women or fetuses:

All women of child-bearing potential will be required to undergo urine hCG pregnancy testing prior to pre-operative testing and prior to any surgical procedure.

5.4.3 Describe the measures to prevent pregnancy, and their required duration of use, that will be discussed with women of child-bearing potential during and following exposure to research procedures:

There are no risks of becoming pregnant following the research procedures that pose a risk to pregnant women pre-procedure. Because pregnancy will mostly likely decrease the weight loss effects observed post-intervention, all women will be counseled on the importance of abstaining from pregnancy in the 12-month post-intervention period.

[reviewer notes¬]

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[reviewer notes¬]

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

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* Yes - Describe below:

If **Yes**, describe in detail:

Standard treatments for Type 2 diabetes include lifestyle modification with diet and exercise as well as medical treatment with oral and/or injectable agents. Patients are not prohibited from using these other treatments during study intervention and will be counseled extensively on these issues no matter the treatment arm to which the patient is randomly assigned. We expect that most participants in all three treatment arms will experience improvements in their T2DM greater than would have been experienced without undergoing one of the interventions.

[reviewer notes¬]

**5.7** Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject’s failure to follow study procedures) that will result in discontinuing a subject’s participation?

* Describe below:

Prior to the beginning of the interventions, participants may be removed from participation if they are determined to no longer meet eligibility criteria or if it is determined that it would be unsafe for the participant to proceed to surgery. Additionally, participants could be withdrawn from participation if they become unable or unwilling to participate. In this situation, participants in one of the surgery arms would be strongly encouraged to continue clinical follow-up with the surgeon outside of the realm of the study. Serious or excessive failure by a subject to follow study procedures or attend study follow-up visits will be addressed on a case-by-case basis and the decision regarding removal of the subject from the study will be thoroughly documented.

[reviewer notes¬]

**5.8** Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* no

**5.9** Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* no

**5.10** Question has been moved to 5.17

**5.11** Question has been moved to 5.16

[reviewer notes¬]

**5.12** Does participation in this research study offer the potential for **direct benefit** to the research subjects?

No - Describe the general benefits to society (e.g., increased knowledge; improved safety; better health; technological advancement) that may result from the conduct of this research study.

Describe the benefit: Participants may benefit from participating in the assessments and/or the reductions in weight that may be associated with participating in the study. Bariatric surgery, weight loss, and regular exercise have been associated with improvements in health risk such as blood cholesterol, blood pressure, and Type 2 Diabetes. However, there is no promise that participants will receive any benefits from participation in this study and such benefits cannot be guaranteed.
This research study will help to determine the effectiveness of two dominant bariatric surgery procedures versus an intensive lifestyle intervention to induce weight loss in patients and promote improvements in Type 2 diabetes. We want to learn about resolution of diabetes, glucose control, medication usage, insulin resistance, beta cell function, body composition, measures of physical activity, and psychosocial changes. Through participation by subjects, we may learn more about how these various interventions can help others with Type 2 diabetes.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

The data safety monitoring plan for this trial will be supplemented with a Data Safety Monitoring Board (DSMB) to monitor patient safety and evaluate the efficacy of the intervention. Close monitoring by the PI (Dr. Courcoulas) in conjunction with a DSMB and prompt reporting of adverse events to the NIH and the University of Pittsburgh IRB will ensure data accuracy and patient safety. As of October 2012, a regular review schedule was formally put into place for the extension part of the study to assure adequate review and supervision of all research-related activities (see Study Activities Review Schedule and Log in Other Attachments). As part of this review schedule, and also contained in the study’s DSMP, a monitoring program to oversee study activities at each University site has been implemented.

A full copy of the DSMP and DSMP Charter is attached in the supporting documentation section.

Section 5 - Potential Risks and Benefits of Study Participation

5.14 What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

All medical evaluations, nutritional, and psychological evaluations will be conducted in a private clinic room. All research related activities will be conducted in semi-private rooms in either the MUH CTRC or the EMRC.

Additionally, the collection of sensitive information about subjects has been limited in this study and only what is necessary to achieve the aims of research and ensure patient safety is being collected.

In the event that a search engine (e.g. CLEAR, Lexis-Nexis) is used (as described in 2.7), participant information such as name, birthdate, or social security number may be entered into the search engine. However, this will only be done on a one-off look up basis, and will not be stored or shared with any outside individuals. The security of these systems were reviewed and approved by Information Security Officer, Sean Sweeney (written approval attached in References and Other Attachments).

5.15 What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

All information collected for this research study will be kept confidential and steps will be taken to minimize the risk of a breach of confidentiality. Participants’ names will be used only for the informed consent form and contact information. Participants will be given unique study identifiers, which will be written on all data collection forms. In addition, data collection forms will be kept in a locked...
The participant will be paid a total of $350 if all parts of this study are completed through the 36 month time point. After completion of the 24-month visit the participant will receive $150, after completion of the 36-month visit, remuneration will be increased and the participant will receive $200. In addition, at annual follow-up visits after 36 months, participants will receive $200 for completion of the complete in-person assessment. Any parking fees associated with the study will be paid for by the study.

5.16 If the subject withdraws from the study, describe what, if anything, will happen to the subject’s research data or biological specimens.

If a participant chooses to withdraw from study participation, and does so formally and in writing as is specified in the consent form, all linkage codes will be destroyed and the collected data rendered anonymous. At this time, any unprocessed samples would be destroyed. Because samples will not be stored as part of this study the likelihood of having to destroy biological specimens is low.

5.17 Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

All data files and consents will be stored as previously described until the study ends or until after the retention period at which time documents will be destroyed in a manner which prohibits retrieval of data. Any electronic files with linkage code information will be deleted.

6.1 Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?

* No

6.2 Will subjects be compensated in any way for their participation in this research study?

* yes

6.2.1 Describe the amount of payment or other remuneration offered for complete participation in this research study.

The participant will be paid a total of $350 if all parts of this study are completed through the 36 month time point. After completion of the 24-month visit the participant will receive $150, after completion of the 36-month visit, remuneration will be increased and the participant will receive $200. In addition, at annual follow-up visits after 36 months, participants will receive $200 for completion of the complete in-person assessment. Any parking fees associated with the study will be paid for by the study.

Additionally, at group sessions we will hold retention raffles in which a small prize (gift cards, pedometers, and similar items) will be raffled to participants that attend the sessions.

After re-consent at the 36-month time point, the LLLI will begin to implement lifestyle campaigns as described in 2.7. Participants may receive a small gift (t-shirt, umbrella, lunch bag, $10 WePay card, etc.) for participation in the campaign. In addition, participants may be entered into a drawing for a gift basket that will include items that can be used to support weight loss, diet, or physical activity efforts.

6.2.2 Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.

Partial payment ($25) will be given to participants who complete the annual assessment over
the phone, and an additional $25 will be given to these participants if they also complete the questionnaire assessments.

A subject will be provided the full $200 remuneration for the annual follow-up visit if the annual visit is completed in full (regardless of LLLI attendance).

Section: Section 7 - Qualifications and Source(s) of Support

7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Anita P. Courcoulas M.D., M.P.H., F.A.C.S, Principal Investigator: Dr. Courcoulas is a Professor of Surgery at the University of Pittsburgh and Director of Minimally Invasive Bariatric and General Surgery for the University of Pittsburgh Medical Centers (UPMC). She performs the bariatric surgery and sees patients pre- and post-operatively. She has published numerous research articles relating to health outcomes especially comorbidity reduction following bariatric surgery. She is the Principal Investigator of the University of Pittsburgh clinical center of multi-institutional Longitudinal Assessment of Bariatric Surgery (LABS) study. In addition, she is the Principal Investigator on two FDA randomized clinical device trials which focus on different weight loss procedures. She is the Principal Investigator and will be responsible for the management of this study.

John M. Jakicic, Ph.D., Co-Investigator: Dr. Jakicic will be responsible for supervising the development of the lifestyle weight loss intervention at the Physical Activity and Weight Management Research Center. Dr. Jakicic has performed this duty for the multi-center Look AHEAD Study and currently remains a member of the Weight Loss Intervention Group for that study. Dr. Jakicic will also be influential in the inclusion of objective monitoring of physical activity within the scope of this study. He has extensive experience with the activity monitors proposed for this study and has closely supervised the development of the data analysis software that will be used to examine these data in this study.

Melissa Kalarchian, Ph.D., Co-Investigator: Dr. Kalarchian has considerable experience in the development and implementation of cognitive-behavioral lifestyle interventions and clinical research. She is the Principal Investigator on the NIDDK funded "Behavioral Intervention for Weight Loss Failure after Bariatric Surgery" and the randomized controlled trial "Preoperative Lifestyle Intervention in Bariatric Surgery". She brings a strong background in conducting patient-oriented research in bariatric surgery, in research on adapting obesity treatments for special populations and psychosocial assessment in the obese and bariatric surgical populations.

James DeLany, Ph.D., Co-investigator: Dr. DeLany is an Associate Professor of Medicine. As the Director of the Obesity and Nutrition Research Center (ONRC) Stable Isotope Lab, Dr. DeLany has experience with a number of NIH-funded projects in the areas of obesity and nutrition and obesity-related diseases. Dr. DeLany has worked closely with Dr. Jakicic on the assessment of physical activity and energy expenditure, particularly the validity and reliability of the SenseWear Pro Armband. Dr. DeLany will oversee the annual metabolic testing and measurements protocol at Montefiore Hospital. He will have primary responsibility for exercise tests and body composition assessments.

7.2 Indicate all sources of support for this research study.

* Selections

Federal: Upload a copy of the entire grant application (including the cover sheet) if our site is the awardee institution; for federal contracts, upload a copy of the research plan.

Other: Upload a copy of the research plan that was submitted for funding (if applicable).

If Federal support, provide the sponsor information:

<table>
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<tr>
<th>Federal sponsor</th>
<th>Grant Title</th>
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<td>A Randomized Trial to Compare Surgical and</td>
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Is this study funded in part or whole by a PHS Agency? *(click here for list of PHS Agencies)*

* yes

Does any investigator* involved in this study (select all that apply):

** Name

A. Have a financial interest (aggregated value of equity and remuneration** during the past or next twelve months) in a publically-traded entity that either sponsors*** this research or owns the technology being evaluated or developed that exceeds $5,000 but not $10,000?

B. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publically-traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

C. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $5,000 but not $10,000?

D. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

E. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

F. Receive reimbursement or sponsorship of travel expenses (for one trip or a series of trips during the past or next twelve months) by an outside entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $5,000?

G. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?

H. Have an officer or management position**** with a Licensed Start-up Company overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?

I. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?

None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.
**Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.

**such as salary, consulting fees, honoraria, or paid authorship**

***through the provision of funds, drugs, devices, or other support for this research**

****Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).
Summary of Protocol Changes:

Phase 1 (RC1) study:

- Raffles for small prizes (gift cards, pedometers, and similar items) were added and were held at monthly group sessions for participants that attended the sessions.

Protocol Changes were made at the time of study extension from Phase 1 (RC1) to Phase 2 (RO1):

- At the time of study extension from RC1 to RO1 (1 to 3-year follow up) the protocol was modified to include subsequent annual visits and a new consent was added to allow this longer-term follow-up.
- The aims and primary outcome measures of the RO1 extension Phase 2 study were added.
- Low Level Lifestyle Intervention (LLLI) was added after year 1 follow up to all 3 treatment arms in Phase 2.
- Blood draw for the purposes of assaying fasting glucose, insulin, lipid profiles, and markers of inflammation will continue at each annual visit in Phase 2.
- Updated blood glucose log communication forms and processes between study interventionists and PI for review were made.
- The LLLI intervention was modified to include phone contact in place of in-person visits, if needed or requested by/or a participant. Optional group LLLI sessions were added.
- LLLI implemented ‘lifestyle campaigns’ that included a small gift upon completion of the campaign.

Other Protocol Changes:

- A protocol modification was made to allow contact of lost-to-follow up participants from Phase 1 of the study and a lost-to-follow up consent form for participants was added.
- The ‘Comorbidity Status Follow up’ form was modified to be completed by phone, if necessary.
- Compensation increase for longer-term follow-up visits, with the option for partial payment in the case a participant completed forms over the phone.
- A ‘SHORT form’ was added to collect minimal data by phone, for participants felt to be at risk of missing an annual visit.
A ‘Minimal Measurements Form’ was added for subjects that who were lost-to-follow up in the Phase 1 study, and were re-contacted and possibly re-engaged for longer-term follow up.

- The use of search engines (e.g., Transunion, CLEAR, Experian, LexisNexis Accurint) to assist in ascertaining new contact information (address, phone number) for any participants whose phone numbers and addresses have become obsolete was added. Use of this information will be kept to a minimum and only used when all other methods of contact have failed.
- Removal of participant from the study for failure to attend follow-up visits will be addressed on a case-by-case basis and documented.
- Beginning October 2012, a monitoring program to oversee study activities at each of 2 remote sites within the University was implemented.
- Resting Energy Expenditure testing was no longer performed, ending May 2014.

- Personnel Changes:
  - Dr. Goodpaster will continue to cover annual follow-up visits for participants at the Montefiore CTRC and EMRC
  - Sheila Pierson took over for Jessie Eagleton as Study Coordinator and Emily Eagleton added as Secondary Research Coordinator.
  - Emily Eagleton took over for Sheila Pierson as Study Coordinator and William Gourash added as Secondary Research Coordinator.
  - Dr. DeLany replaced Dr. Goodpaster at the Montefiore CTRC and EMRC.
**Initial Statistical Plan:**

To examine RC1DK086037 Specific Aims 2 and 3 and to examine R01DK095128 Specific Aim 1 we will use a mixed model approach for the analysis of the data to determine if the interventions are successful in changing outcome. For data missing completely at random appropriate statistical analytical methods can be employed. Other options include imputing data or creating indicator variables (generally the least desired approach) to identify missing data. Dropout or censoring will often be informative so the missing outcome data may be "non-ignorable." An exploratory approach used to assess the extent of potential bias and its effect on analysis is to compare characteristics of patients with available data to those with missing data. For data missing completely at random (does not depend on observed outcome; MCAR) linear mixed model analysis provides unbiased results. However, in other cases where the dropout depends on observed outcome and/or covariates (missing at random, MAR) or unobserved outcome and/or covariates (missing not at random, MNAR), we will use selection models such as MNAR Dale model and Diggle-Kenward model. These models often require strong assumptions on the dropout mechanism which are primarily unverifiable based on the observed data. We will conduct sensitivity analyses to investigate the sensitivity of our conclusion to possible violation of such assumptions. We will also fit MCAR, MAR and MNAR and compare the model fits using log-likelihoods. We will consider other approaches to analyzing longitudinal data with informative censoring including modeling the censoring process jointly with the fitted model of interest and weighted estimating equations using inverse probability of missingness to account for the potential bias that arises due to the missing outcomes.
Final Statistical Plan:

Statistical analyses were performed using SAS (version 9.3) with the type I error rate fixed at 0.05 (two-tailed). Categorical variables are summarized using frequencies and percentages. Continuous variables with normal distributions are presented as mean (± standard deviation); continuous variables with non-normal distributions are presented as medians and interquartile ranges. Differences in baseline characteristics among the RYGB, LAGB and LWLI groups were examined using the Pearson’s chi-square test or Fisher’s exact test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables.

Changes from baseline to 12-, 24-, and 36-months were analyzed using mixed effects models with covariate adjustment for randomization stratification factors (gender and baseline BMI). Change in weight was adjusted for baseline weight. Inferences focused on the overall treatment effect, time, and treatment by time interaction. Pairwise comparisons were made between treatment groups at 36-months. Least-square means were obtained from the models along with their standard errors. Intent-to-treat analyses were conducted using multiple imputation implemented using SAS procedures PROC MI and PROC MIANALYZE. For each outcome, ten datasets were imputed and results were combined. For categorical data with missing values (e.g. T2DM remission, medication use,), no remission or no improvement for the condition at follow up was imputed. The Fisher’s exact test was used to compare differences between groups for T2DM remission and medication category usage.
Summary of Statistical Plan Changes:

1. We did compare characteristics of patients with complete data (N=53) to those with missing data (N=8) at 3-year. Results show that there are no difference between completers and those with missing 3-year data in terms of ethnicity (Hispanic vs. non-Hispanic, p=1.0), race (African American yes vs. no, p=1.0), gender (p=0.3301), diabetes drug (none vs. Insulin vs. Insulin+other vs. oral/other, p=1.0), hypertension (yes vs. no, p=0.2541), and lipids (yes vs. no, p=0.4198). There is also no significant difference among the three treatment groups in the % of participants with missing 3-year data (p=0.1513). Although these findings were not included in the results section of the paper, we did conduct these analyses per study protocol.

2. The original statistical plan states that we will use selection models such as missing not at random (MNAR) Dale model and Diggle-Kenward model. We did not run these models as the analyses we’ve performed in #1 above did not show any significant difference. Study investigators believe that data we have collected does not warrant MNAR assumption. In a study group call among investigators prior to data analysis, various types of missing data mechanisms were discussed and consensus was reached to treat data as missing at random and run multiple imputation for sensitivity analysis.

3. Within the nested models, the likelihood ratio test was used to compare the models. Because missing completely at random (MCAR) is a special case of missing at random (MAR), we focus our analyses on the mixed effects models which assume MAR. Once again, the MNAR models were not run.

4. The original protocol states that “We will consider other approaches to analyzing longitudinal data with informative censoring including modeling the censoring process jointly with the fitted model of interest and weighted estimating equations using inverse probability of missingness to account for the potential bias that arises due to the missing outcomes”. We have explored the possibility of fitting an inverse probability weighted GEE model. However, due to the small sample size per group as well as small cell frequencies, such model has run into convergence issue. Therefore, we used the Chi-square test or Fisher’s exact test for categorical outcomes.

5. The original protocol does not fully specify the covariates. In the analyses we have performed, the mixed effects models include covariate adjustment for randomization stratification factors (gender and baseline BMI). Furthermore, the analysis examining group difference in weight change also adjusted for baseline weight.

6. While the original protocol does not clearly state the use of intent-to-treat principle, we have conducted analyses using intent-to-treat and have included all randomized participants in the analyses. For continuous outcomes, the mixed effects models along with multiple imputation are used to handle missing data. For categorical data (e.g. T2DM remission, medication use), no remission or no improvement for the condition at follow up was imputed whenever data are missing.