Longitudinal Assessment of Bariatric Surgery (LABS-2)

Version 7 post 6/1/2013

Design Synopsis

Primary Objectives

1. To describe surgical risks and changes in clinical, metabolic, and psychosocial measures among patients undergoing bariatric surgery. Risks and changes occurring within 3 years of surgery will be assessed using standardized techniques and measures in a multi-center cohort of patients.

2. To determine the associations of clinical and demographic patient characteristics, components of the surgical procedure, and peri-operative and post-operative care with post-operative risks and changes in clinical, metabolic, and psychosocial measures.

Secondary Objectives

1. To assess health care utilization of patients undergoing bariatric surgery for treatment of obesity and related co-morbidities.

2. To obtain and store biospecimens (serum, plasma, whole blood) for research related to the aims of this study, and for future research into the pathophysiology and genetics of obesity and obesity related complications.

Type of Study

- Prospective cohort

Inclusion Criteria

- Patients who are at least 18 years of age and undergo bariatric surgery by a LABS certified surgeon
- Selected by algorithm to be included in LABS-2

Exclusion Criteria

- Informed consent not obtained
- Prior bariatric surgery
- Unlikely to comply with follow-up protocol
- Unable to communicate with local study staff

Sample Size

- Approximately 2,400 patients recruited over a 3 year period

Duration of Follow-up

- Up to 7 years following bariatric surgery

Outcomes

- Death
- Complications
- Changes in clinical, metabolic, and psychosocial measures

Data Collection Schedule

- The LABS-2 baseline data will be collected within 30 days prior to bariatric surgery.
- Follow-up assessments will occur approximately 30 days, 6 months and 12 months following date of bariatric surgery and annually thereafter.

1 Introduction

1.1 Background. Obesity has become one of the leading health concerns in the United States (US) (Mokdad 2004). The traditional approach to weight loss consisting of diet, exercise, and medication generally achieves no more than a 5-10% reduction in body weight (Yanovski 2002, McTigue 2003) and regain to or above baseline after such weight loss occurs in more than 90% of people undergoing non-operative therapy within five years (Safer 1991, Wadden 1989).

Bariatric surgical procedures, which restrict stomach size or lead to decreased absorption of nutrients, are being increasingly performed to treat extreme obesity. These procedures often result in substantial weight loss and can have a dramatic effect on co-morbidities associated with obesity, such as improved control of blood sugar or even reversal of type 2 diabetes**.** However, bariatric surgical procedures also carry substantial risks, including death.

Extreme or Class 3 obesity (BMI >40) has dramatically increased in prevalence over the past several decades, now affecting almost 5 percent of the US adult population. Although an increasing number of people with extreme obesity and obesity-related complications are undergoing bariatric surgical procedures, there has been little systematic research to help determine the risks and benefits of bariatric surgery, or to provide guidance on appropriate patient selection. Of the several different types of bariatric procedures performed in the US, the Roux-en-Y gastric bypass (RYGB) (Howard 1995, MacLean 1995, MacLean 1993, Sugerman 1987, Laws 1981, Lechner 1981, Naslund 1986, Naslund 1987, Naslund 1988a, Naslund 1988b, Pories 1982, Hall 1990) is the most commonly performed. The restrictive adjustable gastric band is increasing in use in the US and is the leading procedure performed outside of the US (Johnson 2004). The biliopancreatic diversion (BPD) with or without the duodenal switch (BPD DS) has also grown in use but is performed by a smaller number of practitioners. Growth in the use of any type of bariatric procedure over the last decade has been truly remarkable with over 120,000 procedures performed in 2003 compared to less than 20,000 performed in 1993 (Johnson 2004, Pope 2002). This growth may be related to the reported efficacy of these procedures, the availability of less-invasive laparoscopic procedures, a 10-12% yearly increase in the pool of surgical candidates (as defined by the 1991 National Institutes of Health (NIH) consensus conference criteria), by increased media exposure of celebrity patients who had successful bariatric procedures (Johnson 2004), and the identification of morbid obesity as a life-threatening disease (Calle, 1999; Flegal, 2005).

One of the more challenging issues facing health care providers and patients considering bariatric surgery is a lack of comprehensive and reliable data concerning risk stratification, effectiveness, and global outcomes. To facilitate and accelerate research in this area, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with the support of the NIH Office of Research On Women's Health, established a Bariatric Surgery Clinical Research Consortium, now known as the Longitudinal Assessment of Bariatric Surgery consortium (LABS). LABS is comprised of six clinical centers and a Data Coordinating Center (DCC) working in cooperation with NIDDK scientific staff to plan, develop,

and conduct coordinated clinical, epidemiological, and behavioral research in the field of bariatric surgery.

Investigative centers in LABS include the University of Pittsburgh Medical Center (Pennsylvania), Columbia-Presbyterian Hospital and Cornell University (New York), East Carolina Medical Center (North Carolina), Neuropsychiatric Research Institute (North Dakota), Oregon Health & Science University and Legacy Good Samaritan Hospital (Oregon), and the University of Washington / Virginia Mason (Washington). The Data Coordinating Center is at the University of Pittsburgh, Graduate School of Public Health.

The overarching goal of LABS is to bring together researchers with expertise in bariatric surgery, obesity research, internal medicine, endocrinology, behavioral science, outcomes research, epidemiology, and other relevant fields to plan and conduct studies that will ultimately lead to a better understanding of bariatric surgery and its impact on the health and well-being of patients with obesity and obesity-related diseases. To achieve this goal, LABS will create and implement standardized measures and data collection instruments for patients undergoing bariatric surgery at participating clinical centers. Rigorously collected information on patient characteristics, surgical procedures, clinical and psychosocial outcomes, and health care utilization will ultimately lead to developing rational recommendations for clinical care. LABS is intended to develop evidence-based information regarding the risks and benefits of bariatric surgery. LABS will also submit serum and plasma specimens to the NIDDK-supported biospecimens repository. These specimens will be used to address the research aims of this study, and to be stored for future research into the pathophysiology of obesity and its complications.

LABS has designed a prospective, longitudinal cohort study with three components. LABS-1 includes all patients who are at least 18 years of age and who undergo bariatric surgery by LABS certified surgeons prior to December 31, 2007, with the primary goal of evaluating the short-term **safety** of bariatric surgery. Important adverse outcomes (i.e., death, rehospitalization, reintervention) occurring within 30 days of surgery are recorded to assess the relationship between short-term morbidity and mortality rates and various patient, operative, and post-surgical care characteristics. LABS-2, described in this protocol, will include a subset of patients from the LABS-1 cohort, with the primary goal of evaluating the longer-term **efficacy** of bariatric surgery. More extensive data collection (i.e. demographic, anthropometric, surgical, clinical, and behavioral) and longer follow-up will allow LABS-2 to identify longer-term safety and efficacy (up to 7 years) outcomes, both risks and benefits, and to determine their associations with patient, surgical, and post-surgical care characteristics. Finally, LABS-3, which will be developed in a series of future protocols, will include selected subsets of patients from the LABS-2 cohort to conduct detailed studies of **mechanisms** involved in weight loss and weight gain, energy expenditure, glucose control, and other aspects of the pathophysiology of obesity and obesity-related complications.

This protocol refers specifically to the LABS-2 component (**efficacy**) of LABS. A detailed description of the LABS-1 and LABS-3 components are addressed in separate protocols.

2 Objectives and hypotheses

2.1 Primary Objective

The primary objective of LABS-2 is to use standardized techniques and measures to assess the longer-term safety and efficacy of bariatric surgery by:

1. comparing post-surgical outcomes to pre-operative status
2. examining risks and benefits of surgery.

LABS-2 will determine the associations between clinical/demographic patient characteristics, components of the surgical procedure, and peri-operative and post-operative care with post-operative risks and changes in patient status.

The principal domains of research interest are delineated below and relate to achieving weight loss and changes in clinical and metabolic co-morbidities of obesity, psychosocial parameters, and quality of life. Additionally, post-operative sequelae as a result of undergoing surgery will be examined. These outcomes will be assessed prospectively for up to 7 years across a multi-center cohort of participants.

Weight Loss and Body Composition. The primary intent of bariatric surgery is to induce weight loss. The ability of bariatric surgery to meet this goal will be assessed by maximum weight loss and long-term patterns of weight loss or regain. LABS-2 will examine differences in weight loss, fat mass and fat-free mass, and waist and neck circumferences based on gender (hypothesizing greater weight loss in men (Ballantyne 2003)), diabetes mellitus (hypothesizing less weight loss among patients with diabetes (Perugini 2003, Schauer 2003)), pre-operative and post-operative physical activity level (hypothesizing a direct relationship between activity and weight loss (Boan 2004)), and surgical technique (hypothesizing greater weight loss maintenance with longer length of the bypass limb in gastric bypass surgery (Choban 2002, Brolin 2002)).

Diabetes Mellitus and Insulin Resistance. Type 2 diabetes mellitus (T2DM), the metabolic syndrome, and insulin resistance (IR) are common metabolic co-morbidities of obesity (Curtis 2005). Assessing the longer-term efficacy of bariatric surgery with respect to T2DM will be based on a clinical history of medication use and on serial measurements of HbA1c. Assessing efficacy for metabolic syndrome and IR will be based on changes in fasting glucose, insulin, lipoprotein profiles, resting blood pressure, waist circumference and clinical history of medications for treatment of hyperglycemia, hypertension, and dyslipidemia.

It is hypothesized that improvement of T2DM, metabolic syndrome, and IR will be related to maximal weight loss, maximal loss of fat mass, nadir BMI and physical activity level (Sjostrom 1999, Cummings 2004, Sugerman 2003, Greenway 2002, Orchard 2005).

Cardiovascular and Pulmonary Disease. Obesity is a risk factor for cardiovascular diseases (CVD) and sleep apnea (Guisti 2004, de Leiva 1998, Koch 1999, Valencia-Flores 2004, Vendrell 2004, Infanger 2003, Buchwald 2004). To assess the efficacy of bariatric surgery with respect to CVD, changes in the traditional factors listed above for IR as well as high-sensitivity C - reactive protein (hsCRP), a marker of systemic inflammation, will be measured. It is hypothesized that improvement of

CVD factors will be related to maximal weight loss, maximal loss of fat mass, and nadir BMI post surgery (Christ 2004, Reinehr 2004, Blumenthal 2000, Stefanick 1998, Schotte 1990). In addition, change in cardiac function will be measured by the time to complete a 400 meter corridor walk. It is hypothesized that the time to complete the 400 meter corridor walk will be directly related to age, degree of obesity (body mass index [BMI]), sex (longer in females), physical activity level, measures of diabetes mellitus (DM) and insulin resistance (IR), blood pressure (BP), liver function tests, inflammatory markers, and sleep apnea (Newman 2003). Furthermore, the time to complete the corridor walk is hypothesized to predict future events such that increased time or inability to complete the walk is related to subsequent cardiovascular clinical events and mortality (Miyamoto 2000, Zugck 2000). We will also evaluate the incidence of coronary heart disease, defined as sudden death, myocardial infarction or need for coronary revascularization post surgery. It is hypothesized that patients who are male and patients who have unchanging metabolic profiles associated with diabetes or PCOS will be at higher risk (Talbot 2004, Kannel 1979).

The prevalence of sleep apnea and changes from baseline status will be assessed by self-report via the Berlin Sleep Questionnaire and by use of continuous or bilevel positive airway pressure machines (CPAP or BiPAP). It is hypothesized that weight loss and reductions in neck circumference will be associated with improvements in sleep apnea.

Renal Disease. Obesity causes and complicates diabetes and hypertension, the two most common causes of kidney failure (Wiggens 2005). Furthermore, obesity in its own right can cause renal disease and may accelerate injury in glomerulonephritides (De Jong 2002). The mechanisms for the adverse effects of obesity on the kidney include its hypertensive and diabetogenic effects. Additionally, adipogenic hormones may have direct injurious actions in the kidney (Coresh 2004). Thus, weight loss is likely to improve indices of renal function. However, bariatric surgery itself has been associated with progressive renal disease through a variety of mechanisms (Khurana 2004). Renal function will be measured by serum creatinine and cystatin and urinary albumin and creatinine (spot urine).

It is hypothesized that albuminuria, the most sensitive index of chronic kidney disease, will diminish after successful bariatric surgery and that the renal function as reflected by serum creatinine will remain stable after successful bariatric surgery (Holzwarth 2002).

Liver Function and Size. The apparent increased prevalence of various forms of non-alcoholic fatty liver disease (NAFLD) in the obese population (Haynes 2004), and the growing identification of NAFLD when sought by liver biopsy among patients undergoing bariatric surgical procedures (Abrams, 2004) have both been the subject of recent publications. The limited data available thus far indicate that it would be important to determine the presence of NAFLD and define the prevalence of advanced forms, such as non-alcoholic steatohepatitis (NASH) and cryptogenic cirrhosis, by systematic intra-operative liver biopsy in a well defined bariatric surgical population. When a liver biopsy is taken during surgery as part of the clinical institution's standard practice, a portion will be studied by LABS investigators. The thickness of the left lobe of the liver will be assessed using a standardized measuring technique.

It is hypothesized that the prevalence and severity of the spectrum of non-alcoholic fatty liver disease are underestimated by traditional laboratory parameters, clinical assessment, and intra-operative visual inspection of the liver (Gholam 2002, Spaulding 2003). Additionally, it is hypothesized that severity of

the liver disease detected on intra-operative biopsy will correlate with short-term post-operative morbidity and mortality and that significant steatohepatitis detected on intra-operative biopsy will correlate with clinical and biochemical worsening of liver disease during periods of rapid post-operative weight loss (Capron 1982, Bradbury 2004). It is also hypothesized that hepatic iron accumulation in the fatty liver disease of the bariatric surgery population will be associated with more severe fibrosis (George, 1998). Furthermore, it is hypothesized that the prevalence and severity of fatty liver disease, controlled for age, BMI, and diabetes, will vary across racial and ethnic groups with the prediction that the most severe findings will occur in patients of Hispanic ethnicity, followed by non-Hispanic Caucasians, followed by African Americans, and that a multivariable combination of traditional clinical, demographic and laboratory assessments can be helpful in predicting the severity of NAFLD in obese patients (Ruhl, 2004).

We also hypothesize that increased liver size at the time of operation is associated with a higher rate of failed laparoscopic procedures due to problematic visualization of the gastroesophageal junction, a higher rate of intraoperative bleeding complications and that presurgical weight loss is associated with decreased liver size. To test these hypotheses we will assess the relationship of liver thickness, the rate of failed laparoscopic procedures secondary to visualization, the rate of liver bleeding and repair and pre-operative weight loss.

Behavioral Factors. Evidence suggests that pre-existing psychological and behavioral problems influence the outcomes, both short-term and long-term, of bariatric surgery (Herpertz 2004). In particular, it is hypothesized that subjects who have active untreated problems with alcohol or drug abuse, problems with binge eating, or problems with untreated depression will experience higher rates of surgical post-operative medical complications, less weight loss (Hsu 1998, Hsu 1996, Hsu 1997, Green 2004, Averbukh 2003), and less relative improvement in social functioning, quality of life, depression, and overall psychological status (Green 2004), while those who intentionally lose weight pre-operatively (van de Weijgert 1999) and those with more family/social support (Ray 2003, Hildebrandt 1998) will achieve greater weight loss. Furthermore, it is hypothesized that bariatric surgery will result in substantial improvements in social functioning (Choban 1999), quality of life (Dymek 2001), depression (Dixon 2003, Dymek 2001), and overall psychological status (Hsu 1998). The magnitude of the improvement in these parameters will positively correlate with the degree of weight loss. Additionally, depression that reoccurs or develops post-operatively will be associated with decreased improvement in quality of life (Moore 2005).

Gender Issues. Potential gender differences in longer-term efficacy of bariatric surgery for weight loss, maintenance of weight loss, prevalence of T2DM, parameters of metabolic syndrome, insulin resistance and magnitude of CVD risk factors will be examined. It is hypothesized that baseline insulin resistance severity will be more important than gender as a predictor of efficacy of bariatric surgery for DM and CVD risk factors. LABS-2 will also examine whether changes in sexual functioning are related to weight loss (Larsen 1990, Camps 1996, Trischitta 2003)

Women's Health. Women constitute the majority of patients who undergo bariatric surgery. Obesity is a risk factor for several health conditions specific to, or more common among, women, such as menstrual abnormalities (Norman 2004), infertility (Norman 2004), and urinary incontinence (Kapoor 2004). It is hypothesized that menstrual abnormalities (Crosignani 2003), fertility (Gerrits 2003), symptoms of polycystic ovarian diseases (Crosignani 2003), and urinary incontinence (Sugerman 2001)

will resolve following bariatric surgery. However, menstrual abnormalities may increase or show no improvement in the first 12 months following surgery when weight loss is often rapid (Schuetz 2004).

Risks of Bariatric Surgery. Bariatric surgeries impart potential long-term risks that are not necessarily faced by those who do not undergo such procedures or that differ depending on aspects of the surgical procedure (Deveney 2004). Thus, potential adverse outcomes such as death, outlet obstruction, wound complications, and surgical revisions and re-operations will be tracked. Pre-operative characteristics including demographics (e.g., sex, race), BMI, and co-morbidities will be examined for their relationships with these outcomes (Perugini 2003, Liu 2003, Livingston 2002). Additionally, the occurrence of stomal ulcer, PE/DVT, and dehydration will be examined in relationship to limb length, pouch size, and types of anastomoses used in the gastric bypass procedure. Hypotheses related to surgical risk are that males will have higher mortality than females, wound infections are more common among patients who undergo an open or laparoscopic converted to open bariatric surgery than among patients undergoing a laparoscopic procedure, that nutritional complications, including re-admission to hospital, will be more common in patients undergoing more malabsorptive operations than among those undergoing a more restrictive operation, that total morbidity is higher in males than females and is positively associated with pre-operative BMI, that African-Americans will have lower percent excess weight loss results following bariatric surgery than patients in other racial groups, and that patients who undergo bariatric surgery without any pre-operative thromboembolism prophylaxis will experience a higher deep vein thrombosis or pulmonary embolism rate than patients who do receive pre-operative prophylaxis.

Nutrient Deficiencies. Another potential long-term risk of bariatric surgery is nutrient deficiency (Alvarez-Leite 2004). LABS-2 will investigate micro-nutrient and macro-nutrient deficiencies by surgical procedure, hypothesizing more frequent occurrences with malabsorptive procedures (Brolin 2002, Ortega 2004, Skroubis 2002, Coates 2004, Faintuch 2004) and by various components of surgery (e.g., limb length, pouch size, and type of anastomoses in bypass surgeries (Brolin 2002, Chobin 2002)). Specifically, protein malnutrition secondary to deficient intake or malabsorption is hypothesized to occur from rapid weight loss, clinically important anemias are hypothesized to be due to a deficiency of vitamin B12 or iron, fat soluble vitamin deficiencies are hypothesized to be more frequent in patients undergoing duodenal switch procedures, and deficiencies of micronutrients related to bone health are hypothesized to be more frequent among patients with malabsorptive operative procedures.

Work Productivity and Activity. Obese workers have the highest prevalence of work limitations (6.9% vs. 3.0% among normal-weight workers) (Hertz 2004) and weight reduction interventions appear to increase productivity (Sartorio 2003). Severe obesity increases the number of work loss days and is an important factor in the workplace (Pronk 2004, Bungum 2003). The effects of weight loss surgery on productivity at work, absenteeism and presenteeism have not been well studied. It is hypothesized that patients undergoing bariatric surgery will have fewer days lost to work secondary to obesity compared with presurgery, that productivity at work, as measured by absenteeism and presenteeism, will be improved after surgery, and that the size of these effects will be associated with the extent of weight loss and the degree of initial obesity.

2.2 Secondary Objectives

1. To assess health care utilization of patients undergoing bariatric surgery for treatment of obesity and related co-morbidities.

2. To obtain and store biospecimens (serum, plasma, urine and tissue) for research related to the aims of LABS-2, and for future research into the pathophysiology of obesity and obesity related complications.

Specific hypotheses to be investigated from these secondary objectives are described below:

Health Care Utilization. Patient outcome following bariatric surgery is variable, and hence, so is subsequent use of health services. It is hypothesized that higher levels of BMI pre-surgery will be associated with higher post-surgery health services utilization; hospital readmission rates will be higher for patients who undergo BPD-DS compared to other surgical procedures; and patients who are more physically active following surgery will utilize fewer health services.

Biospecimens. Approximately, 55.5mL of blood and 4.5 of urine will be obtained from LABS-2 participants at pre-specified intervals (see §3.4). Fasting insulin, high sensitive C-reactive protein, lipid profile (HDL, LDL, total cholesterol, triglycerides), HbA1C, serum creatinine, cystatin C, urine creatinine, and urine albumin will be measured at a central laboratory. Aliquots of plasma and serum will be banked for future investigations into parameters such as changes in metabolic parameters and markers of risk. An additional 24mL of whole blood will be drawn to be used for DNA analysis. Additionally, if a liver biopsy is taken during surgery as part of the clinical institution's standard practice, a small portion will be studied by LABS investigators. Non-LABS investigators may access biospecimens through application via the LABS ancillary studies process or a process to be developed by the NIDDK Biospecimens Repository, where the specimens will be stored indefinitely. A spot urine test will be obtained and sent to a central laboratory for creatinine and albumin determinations. Aliquots of urine will be stored at the NIDDK Repository for use in future substudies on nutrition (e.g. – to measure bone markers).

3 Study Design

3.1 Study Summary. The primary goal of LABS-2 is to evaluate the efficacy and safety of bariatric surgery over a longer term than LABS-1, i.e., more than 30 days. Approximately 2,400 patients, will be recruited over 3 years. LABS-2 will include clinical assessments and detailed interviews and questionnaires pre-operatively and at several post-operative time points (30 days, 6 months, 12 months following surgery, and annually thereafter) to assess risks of surgery, and changes in clinical, metabolic, and psychosocial characteristics in patients, and health care utilization following bariatric surgery. Detailed data about the surgical procedure and peri- and post-operative care will also be collected to determine if components of the surgical procedure, and peri-operative and post-operative care as well as clinical/demographic patient characteristics are associated with post-operative risks and changes in patient status. Patients enrolled in LABS-2 will provide blood specimens pre-operatively and post-operatively to address LABS-2 hypotheses and additional samples will be stored at the NIDDK tissue repository for serologic, pathologic and genomic testing of other hypotheses.

3.2 Study Population

3.2.1 Sources of Patients. LABS-2 patients will be selected from people undergoing bariatric surgery at participating sites.

3.2.2 Inclusion Criteria

- Patients at least 18 years of age who undergo bariatric surgery by a LABS-certified surgeon
- Selected by a site-specific sampling algorithm to be approached for inclusion in LABS-2

3.2.3 Exclusion Criteria

- Informed consent not obtained
- Prior bariatric surgery
- Unlikely to comply with follow-up protocol (e.g., travel time from home too long to make visits feasible, unwilling to return for follow-up visits)
- Unable to communicate with local study staff

3.2.4 LABS-certified surgeon

- Performs bariatric surgery at one of the LABS clinical centers
- Has undergone training on the LABS protocol and data collection
- Has successfully completed a certification examination
- Agrees to adhere to LABS protocol and provide required data

3.2.5 Criteria for Study Withdrawal

- Patient withdraws consent
- NIDDK ends the study

3.2.6 Target composition of the database population. LABS-1 (see §1.1) will consist of patients aged 18 years and older undergoing bariatric surgery performed by LABS certified surgeons. Based on current patient demographics and surgeon practices in the participating clinical centers:

- approximately 84% of the patients are expected to be women
- approximately 25% are expected to have a BMI at least 50 kg/m^2
- approximately 18% are expected to be African American
- approximately 15% are expected to be Hispanic or Latino
- approximately 25% are expected to have type 2 diabetes
- approximately 2.5% are expected to undergo bariatric surgery with a BPD
- approximately 5% of patients are expected to have a laparoscopic adjustable gastric band placed
- approximately 20% of patients will have an anastomotic sealant used
- approximately 25% of patients will be prescribed low molecular weight heparin
- approximately 25% of patients will be prescribed subcutaneous heparin and
- approximately 25% will have both low molecular weight heparin and subcutaneous heparin
- approximately 22% will be planned open procedures

The goal of LABS-2 is to accrue 2,400 patients. This goal will provide a large enough sample of patients to detect odds ratios of at least 2.0 for categorical outcomes and small effect sizes for continuous outcomes (see § 4.2.4).

3.3 Study Visits and Database Contents. Pre-operative data will be collected (SITE SPECIFIC)… Patients will be seen 1-30 days prior to surgery for their LABS-2 baseline evaluation. Follow-up data collection will occur at approximately 30 days, 6 months, and 12 months following surgery, and annually. Starting with the 6-year visits, every other year during follow-up, a reduced battery will be collected during a minimal assessment visit in lieu of the standard in-person visit. During the odd years, participants will be asked to come in for the full LABS visit. There will also be data collected about the surgery and at hospital discharge following the bariatric surgery procedure. All data are collected during an in-person visit or via chart review. The tables below indicate the schedule of measures by study visit. A copy of all measures are included in the Appendix (see §10).

3.3.1 Clinical Forms and Biospecimen Collections

Measure/Test	Form Details	Contact time points						
		Pre-surgery/baseline	Pre-surgery/baseline Update	At time of initial discharge	30-days	6-month follow-up	12-months/full visits (odd years beginning Year 6)	Minimal Visits (even years beginning year 6)
Biospecimen collection*	Central (includes blood & urine)	X					X	
	Local	X				X	X	
	Genetics Repository	X					X	

	Biospecimen Repository (includes blood & urine)	X					X	
400 meter corridor walk	400 Meter Eligibility Form	X					X	
	400 meter corridor walk form	X					X	
Medication Collection	Medication form	X	X			X	X	X
Stepwatch Activity Monitor	Stepwatch Activity Diary	X					X	
Surgeon/Clinician Administered Forms	Surgeons/Clinician Medical Assessment	X					X	
	Post-surgical Hospital Discharge Questions			X				
	Post-Operative Evaluation Form				X			
	Health Care Utilization Form**					X	X	X
	6-month Follow-up Form					X		
	Research Coordinator Assessment	X	X				X	X***
	Short Form						X	X
	Minimal Visit Follow-up Form							X
	Events & Complications Form						X****	X
Self Assessment Forms	Demographic Information Questions	X					X	
	Pre-Bariatric Weight Loss Questions	X	X					

* Central Laboratory results will be provided to the DCC electronically and will neither require the completion nor entry of this form by the clinical sites. Local labs, at 6-months, will include ALT and AST only.

** The Health Care Utilization form will be administered if the patient reports being hospitalized or having an out-patient procedure. Protocol Amendment (V.7 / July 1, 2013): As of the local IRB approval date for this amendment, sites will forego the collection of the Health Care Utilization form beyond 48-months. Moving forward, information on events and complications after bariatric surgery will be captured through the Events and Complications (EC) and Short Form.

***The Research Coordinator Assessment Follow-up Form will only be completed if a participant comes in for the visit or there is not participant contact and weight and medications are obtained from medical charts.

**** Protocol Amendment (V.7 / July 1, 2013): As of the local IRB approval date for this amendment, sites will administer the Events & Complications Form.

Form Details	Contact time points						
	Pre-surgery/baseline	Pre-surgery/baseline Update	At time of initial discharge	30-days	6-month followup	12-months/full visits (odd years beginning Year 6)	Minimal Visits (even years beginning year 6)
Selected questions from Goals and Relative Weights Questionnaire (GRWQ)	X	X					
Weight Control Practices	X					X	
Questionnaire on Eating/Weight Patterns (QEWP-R)	X					X	
Weight Loss Practices & Eating Habits (L, AHEAD)	X					X	
Eating Beyond Satiation	X					X	
Tobacco use	X					X	
Alcohol use (AUDIT)	X					X	
Substance Abuse	X					X	
Beck Depression Inventory (BDI)	X				X	X	
Interpersonal Support Evaluation List (ISEL-12)	X					X	
Short Form Health Survey (SF-36)	X				X	X	
Work Productivity and Activity Impairment (WPAI:GH)	X					X	
Psychiatric & Emotional Test Survey	X					X	X
Impact on Weight Questionnaire (IWQOL – Lite)	X					X	
Gastrointestinal Symptoms Response Scale (GSRS)	X					X	
Urinary Incontinence Questionnaire	X					X	
Selected Questions from the Berlin Sleep Questionnaire	X					X	
Sexual Function Questionnaire	X					X	
Reproductive Health Questionnaire	X					X	
Self-assessment Medical Assessment	X					X	
Western Ontario and McMaster's University (WOMAC) Osteoarthritis Index	X					X	

Michigan Neuropathy Screening Instrument	X					X	
Cancer Diagnosis						X	
Excess Skin Questionnaire						X	
Suicide Behavior Questionnaire						X	
Weight Form						X	X
Reproductive Health Pregnancy							X
Cancer Follow-up							X

3.3.2 Surgical forms. Surgical forms will be completed by LABS certified surgeons and study coordinators.

Surgical forms:

- Adjustable Gastric Band
- Roux-en-Y Gastric Bypass
- Biliopancreatic Diversion (BPD)
- Biliopancreatic Diversion with Duodenal Switch (BPD-DS)
- Gastric Sleeve
- Vertical Banded Gastroplasty
- Adjustment to Gastric Sleeve
- Surgeon's Questionnaire

3.3.3 Other forms

- The **Surgeon's Experience Form** will be completed by LABS surgeons following certification.
- When a liver biopsy is taken as part of usual care during surgery, a liver sample will be processed and sent to a pathology laboratory for LABS-2, at which time, a liver **Pathology Evaluation form** will be completed by the central hepatopathologist.
- The **Adjudication Forms** (mortality and unconfirmed cause) will be completed by the Adjudication Committee. The information will include reason(s) for an intervention within 30-days of surgery if the reason could not be confirmed at the site. Criteria for confirmation are provided in the Manual of Operations. The Adjudication Committee will also determine all causes of deaths using information provided by the clinical sites through the Data Coordinating Center.
- The **Off-Protocol Form** will be completed by the study coordinator to report deviation(s) from study protocol (e.g., missed visit, incomplete data collection).
- An **Inactivation Form** will be utilized to report patient drop-outs or inactivations and reason(s) for dropping out or inactivation.
- An **Enrollment Form** will be completed to report those participants who are enrolled into LABS-2. This form reports whether patients provided consent to LABS-2 and whether they provided genetic consent, along with dates of consent. If the patient does not consent, the reason why is reported.

3.3.4 Corridor Walk. After a brief medical screening, eligible participants will be asked to complete a 400 meter corridor walk at their usual walking pace at baseline and annual study visits. Details are outlined in the manual of operations.

3.3.5 Stepwatch Activity Monitor. Participants will be asked to wear a StepWatch Activity Monitor (SAM) during the day for one week following baseline and annual study visits. The SAM is a highly accurate instrument the size of a small pager that is worn on the ankle. Consisting of a sensor, electronics and battery inside a polycarbonate case, the SAM is sealed and requires no adjustment by the wearer. The case is contoured to fit comfortably against the leg and an elastic attachment strap or soft cloth sleeve are used to ensure that the SAM remains securely attached to the ankle without irritating the skin. The SAM will continuously record the number of steps per minute over a week, allowing for a calculation of the amount of low, moderate and vigorous activity performed each day. After wearing the monitor for a week, the monitor will be returned to the study clinic by mail in a pre-addressed stamped envelope. Details are outlined in the manual of operations.

3.3.6 Biospecimens. Serum, plasma and urine will be collected pre-operatively and at scheduled LABS annual follow-up visits. Serum and plasma will be aliquoted into approximately 40 separate cryovials (20 serum and 20 plasma) in volumes of 0.5 mL for storage at the NIDDK repository for future research. Blood and urine will be collected from the pre and post-operative visits for fasting insulin, high sensitive C-reactive protein, lipid profile (HDL, LDL, total cholesterol, triglycerides), HbA1C, serum creatinine, cystatin C, urine creatinine, and urine albumin determinations as well as uncommitted specimens for the repository. Urine will be sent for storage at the NIDDK repository for future research. Also, three 8mL tubes of whole blood will be shipped to the NIDDK Genetics Repository and stored for DNA analysis. Participants in LABS-2 must agree to serum, plasma, and urine collection, but may opt out of specimens for DNA analysis.

Liver biopsies will only be collected as part of standard care at some of the clinical centers participating in LABS and not as a research procedure. Slides will be shipped to the study hepatopathologist for central reading.

3.4 Biospecimens Collection and Transmission to Repository. Samples will be collected and initially stored at the clinical centers. They will be sent in batches to the NIDDK Central Repositories, a research resource supported by the National Institutes of Health. Patients will be asked to provide urine samples and approximately three or four tablespoons of blood. Some samples will be sent to central laboratories and to the clinical institution's laboratory for testing. Other samples will be stored at the NIDDK Central Repository for future evaluation.

4 Data Analysis and Statistical Power

4.1. Data Analysis. The analytic approach to be used in LABS-2 centers principally on evaluating the efficacy of bariatric surgery across a broad range of patient outcomes, both short- (within 30 days) and longer-term (31 days-3 years), and within varying surgical procedures and specific patient subgroups. Given this wide scope of analysis, as exemplified by the large number of study hypotheses (section 2.1) and variety of anticipated data sources and data types, a broad range of statistical models shall be

utilized. The final analytic approach for a given hypothesis or area of investigation will be what is most appropriate given the nature of the data.

4.1.1. Data Description and Exploration. Descriptive and exploratory data techniques will form a critical first stage of the analytic process, illuminating data patterns, guiding further modeling, and aiding in data quality control. For both collected (raw) and created variables, graphical techniques such as histograms and boxplots will be examined to assess distributional forms, variability, and extent of outliers. Change over time (e.g., extent of weight loss), and bivariate relationships will be examined by scatter plots, side-by-side boxplots, or contingency tables depending on the types of variables.

4.1.2. Summary of Primary Statistical Methods. The LABS-2 longitudinal study design proposed, coupled with the time-varying nature of both predictor (e.g., eating patterns) and outcome (e.g., comorbidity resolution) permits analysis of study hypotheses at both a patient- and visit-level of analysis. Table 4.1 defines the primary statistical methods to be used to evaluate the wide range of LABS-2 hypotheses.

Table 4.1. Primary Analytic Methods Used to Evaluate LABS-2 Hypotheses

Outcome Variable	Measurement	Predictor Variable(s)	Measurement	Unit of Analysis	Primary Method(s) Of Analysis
Weight Loss and Body Composition:					
Max. weight loss	Continuous	Gender, diabetes, surgical technique	Categorical	Patient	Analysis of covariance (ANCOVA)
Max. Δ in fat mass	Continuous			Patient	
Max. Δ in fat free mass	Continuous			Patient	
Max. Δ in waist circumference	Continuous	Physical activity level (pre-op and post-op)	Continuous	Patient	Linear regression
Max. Δ in neck circumference	Continuous			Patient	
Patterns of weight loss	Continuous	SAME AS ABOVE	SAME AS ABOVE	Visit	Linear mixed models, piece-wise linear mixed models, non-linear hierarchical models
Pattern of weight regain	Continuous			Visit	
Diabetes Mellitus & Insulin Resistance:					
Reduction in diabetes	Categorical	Maximal weight loss, maximal loss of fat mass, nadir BMI	Continuous	Patient/Visit	Logistic regression, Discrete-time proportional hazards (pooled logistic regression)
Reduction in met. syndrome	Categorical			Patient/Visit	
Δ in insulin resistance	Continuous			Patient/Visit	Spearman correlation, linear regression, linear mixed models
CVD and Pulmonary Disease:					
Corridor walk time	Continuous	Age, BMI, insulin resistance, blood pressure, liver function, inflammatory markers	Continuous	Patient	Spearman correlation, linear regression
Corridor walk time	Continuous	Gender, diabetes, sleep apnea	Categorical	Patient	ANCOVA
Incident CVD, mortality	Categorical	Corridor walk time	Continuous	Patient	Survival analysis, Cox regression
Renal Disease:					
Δ in albuminuria	Continuous	Pre/post bariatric surgery	Continuous	Patient	Paired t-tests or analogous non-parametric methods
Δ in GFR	Continuous	Pre/post bariatric surgery	Continuous	Patient	

Table 4.1. (continued). Primary Analytic Methods Used to Evaluate LABS-2 Hypotheses

Outcome Variable	Measurement	Predictor Variable(s)	Measurement	Unit of Analysis	Primary Method(s) Of Analysis
Liver Function:					
Prevalence/severity of non-alcoholic fatty liver disease (NAFLD) (based on histology)	Categorical	Traditional assessment of NAFLD (labs, clinical assessment, visual inspection)	Categorical	Patient	Kappa statistic, predictive value negative
		Race/ethnicity, traditional demographic, clinical, and laboratory assessments	Categorical and continuous	Patient	Binomial and ordinal logistic regression
Short-term post-operative morbidity and mortality	Categorical	Severity of liver disease (biopsy)	Categorical	Patient	Poisson regression
Δ in liver disease (clinical and biochemical)	Continuous	Steatohepatitis (detected on biopsy), weight loss	Categorical	Patient/visit	Linear regression / linear mixed models
Liver fibrosis severity	Categorical	Hepatic iron accumulation	Continuous	Patient	Ordinal logistic regression
Behavioral Factors:					
Surgical post-discharge medical complications	Categorical	Pre-op untreated alcohol/drug abuse, binge eating, untreated depression	Categorical	Patient	Logistic regression
Δ in body weight	Continuous			Patient/Visit	ANCOVA, linear mixed models,
Δ in social functioning	Continuous			Patient/Visit	piece-wise linear mixed models,
Δ in quality of life	Continuous	Time since surgery, degree of	Continuous	Patient/Visit	non-linear hierarchical models
Δ in psychological status	Categorical	weight loss		Patient/Visit	Logistic regression, generalized estimating equations (GEE)
Δ in body weight	Continuous	Intentional pre-op weight loss	Continuous	Patient/Visit	Linear regression, linear mixed
		Extent of family/social support	Continuous	Patient/Visit	models, piece-wise linear mixed models, non-linear hierarchical models
Δ in quality of life	Continuous	Re-occur/post-op depression	Categorical	Patient/Visit	ANCOVA, linear mixed models
Gender Issues:					
Reduction in diabetes	Categorical	Gender	Categorical	Patient/Visit	Logistic regression, GEE
Δ in CVD risk factors	Categorical	Insulin resistance severity	Continuous	Patient/Visit	
Δ in sexual functioning	Continuous	Weight loss	Continuous	Patient/Visit	Linear regression / mixed models
Urinary incontinence	Categorical				Logistic regression / GEE

Table 4.1. (continued). Primary Analytic Methods Used to Evaluate LABS-2 Hypotheses

Outcome Variable	Measurement	Predictor Variable(s)	Measurement	Unit of Analysis	Primary Method(s) Of Analysis
Women's Health:					
PCOS, menstrual abnormalities, infertilty	Categorical	Time: PCOS, menstrual abnormalities, and infertility status before surgery and during follow-up after surgery	Categorical	Patient	McNemar's chi-square test
Risks of Bariatric Surgery:					
Complications – death, outlet obstruction, wound complications, surgical revision, re-operation	Categorical	Sex, race, pre-op comorbidities Pre-op BMI	Categorical Continuous	Patient	Survival analysis, Cox regression
Stomal ulcer, PE/DVT, dehydration	Categorical	Type of anastomoses used, limb length, pouch size	Categorical Continuous	Patient	Survival analysis, Cox regression
Nutrient Deficiencies:					
Protein malnutrition (albumin)	Categorical	Δ in body weight	Continuous	Patient	Logistic regression, GEE
Anemia	Categorical	Limb length, pouch size	Continuous	Patient	
Fat soluble vitamin deficiency	Categorical	Type of surgical procedure	Categorical	Patient	
Micronutrient deficiency related to bone health	Categorical	Type of anastomoses used	Categorical	Patient	
Health Care Utilization:					
Post-surgery health services utilization	Continuous	BMI pre-surgery Physical activity post-surgery	Continuous Continuous	Patient Patient	Linear regression
Hospital readmission rates	Categorical	BPD-DS versus other surgery	Categorical	Patient	Poisson regression

4.1.3. Analytic Issues. Given the large volume and wide range of data to be collected in LABS-2, coupled with repeated measurements over time, several analytic issues are germane to insuring valid assessment of the efficacy of bariatric surgery.

4.1.3.1. Assessment and Control of Confounding. Most, if not all, of the comparisons of efficacy will be based on non-randomized comparisons of patients with certain characteristics, specific operative techniques, or both. Hence, there will invariably be imbalances in characteristics predictive of outcome between the comparator groups of interest that must be adjusted for statistically to obtain valid estimates of effect. In general, the primary strategy to identify potential confounding variables will be to fit an initial basic predictor/outcome model (e.g., type of surgery performed and extent of long-term weight loss achieved) and then add individual covariates (potential confounders) singly in separate models to assess the relative change in the parameter estimate of interest (e.g., beta coefficient). If $\geq$10% change in the parameter estimate is observed for a particular covariate, this suggests the presence of appreciable confounding and need for statistical adjustment (Mickey 1989). This approach is favored since it is relatively invariant to sample size, a feature not present in standard stepwise selection procedures.

4.1.3.2 Assessment of Effect Modification. Many analyses anticipated will involve subgroup comparisons of the efficacy of bariatric surgery – in other words, do all patients achieve the same degree of benefit from weight loss surgery? To assess whether the effect of bariatric surgery is modified by specific patient characteristics, two primary approaches will be employed. These include stratified analyses to compare estimates of effect across levels of patient characteristics, and more formal tests of interaction. Formal tests of interaction are not selected as the primary analytic approach for the simple reason that they are heavily influenced by the sample size of the subgroups involved, and hence, often underpowered to detect meaningful interactions.

4.1.3.3. Loss to Follow-up and Missing Data. In LABS-2, as with many longitudinal studies, participant dropout or censoring, as well as missing data points, will likely be informative. For example, sicker patients and those with sub-optimal or conversely excellent post-surgery results may opt to discontinue participating or providing particular samples or questionnaire responses. Thus, the probability of missing outcome data may be dependent on covariate data and, hence, "non-ignorable" (Rubin 1976, Laird 1988). In circumstances when missing covariate and outcome data are missing completely at random (MCAR), the principle net effect of conducting a complete case analysis is loss of precision, whereas with other types of missing data, biased effect estimates may result. To assess the probable type of missing data, baseline covariates among patients with and without missing data will be compared. If missing data are judged as MCAR, the typical strategy will be to conduct a complete case analysis, recognizing a loss of precision. The exception to this strategy will be when considerable data (i.e. >15%) are missing on a particular covariate that is judged to be critical for inclusion in the analysis. In this instance, imputation will be considered (see below). This may be accomplished by unconditional or conditional mean imputation; these relatively simple approaches perform well when the overall percentage of missing data is low (Barzi 2004). In unexpected rare instances when the percentage of missing data is not low (i.e. >15%), more sophisticated multiple imputation methods may be employed (Rubin 1987. Strategies to account for missing outcome data will also be considered. For example, participants who drop out may be more likely to have weight

gain than those who return for all visits. One possible analytical approach would be to impute 0 weight loss for these individuals. When imputation schemes are employed, sensitivity analyses will be conducted to assess the robustness of findings to various imputation schemes and strategies for handling missing data.

4.2. Sample Size Estimates. As listed in Section 2.1, LABS-2 will evaluate the efficacy of bariatric surgery using a wide range of patient outcomes with various scales of measurement and across many scientific disciplines. Moreover, additional hypotheses regarding the efficacy of bariatric surgery will be developed and evaluated during the course of the study. For these reasons, sample size calculations have been provided for both binary and continuous outcome measures, assuming either single or repeated measurements, and assuming varying proportions of patients within subgroups to be compared. For simplicity, patient and surgical characteristics to be compared are based on two-group comparisons, recognizing that some characteristics may be evaluated using more than two groups and with alternative statistical methods, such as linear tests of trend. Finally, to be conservative, all calculations are based on desired power of at least 90% and two-sided alpha of 0.05.

4.2.1. Comparisons of Proportions Based on Single Outcome Measurement. Table 4.2.2 presents odds ratios detectable at 90% power for comparing binomial proportions of outcome occurrence given various sample sizes, event rates in the reference (control) group, and percentage of all subjects as controls. As seen, with an effective sample size ranging from 1200 to 3200 patients, detectable odds ratios range from 1.32 to 3.10. With the goal of having sufficient statistical power to detect odds ratios of 2.0 or higher, an effective sample size of 2000 patients is sufficient for all conditions with the exception of when a low event rate of 5% is observed in the reference subgroup coupled with a highly imbalanced design in which 90% of all subjects reside within the reference subgroup. Of note, these binomial comparisons of event rates and detectable odds ratios are conservative with respect to the frequent anticipated use of alternative survival analysis methods, when appropriate.

Table 4.2.2. Odds Ratios Detectable at 90% Power Given Various Sample Sizes, Event Rates in Control Subjects (Reference Group) and Proportions of Subject in Reference Group*

Sample Size	5% event rate in reference group			10% event rate in reference group			20% event rate in reference group		
% of reference group →	50%	75%	90%	50%	75%	90%	50%	75%	90%
1200	2.13	2.33	3.10	1.78	1.91	2.44	1.57	1.67	2.05
1400	2.03	2.21	2.90	1.71	1.83	2.30	1.52	1.61	1.95
1600	1.95	2.11	2.74	1.65	1.77	2.19	1.48	1.56	1.88
1800	1.88	2.03	2.61	1.61	1.71	2.11	1.45	1.53	1.81
2000	1.83	1.97	2.50	1.57	1.67	2.04	1.42	1.49	1.76
2200	1.78	1.91	2.41	1.54	1.63	1.98	1.40	1.47	1.72
2400	1.74	1.86	2.34	1.52	1.60	1.93	1.38	1.44	1.68
2600	1.71	1.82	2.27	1.49	1.58	1.88	1.36	1.42	1.65
2800	1.67	1.79	2.21	1.47	1.55	1.84	1.35	1.41	1.62
3000	1.65	1.76	2.16	1.45	1.53	1.81	1.33	1.39	1.60
3200	1.62	1.73	2.12	1.44	1.51	1.78	1.32	1.38	1.57

*Based on chi-square test with continuity correct and assuming 2-sided alpha of 0.05.

4.2.3. Comparisons of Proportions Based on Repeated Outcome Measurements. Table 4.2.4 presents odds ratios detectable at 90% power for comparing binomial proportions of repeated outcome measurements given various sample sizes, event rates in the reference group, and correlations between repeated measurements. These estimates illustrate the increase in variance that occurs (and hence required sample size) with correlated observations over time. The impact of this within-person correlation on the odds ratio that is detectable for a given sample size is illustrated in the formula below, as described by Diggle (2002).

$$m = \frac{\{z_\alpha(2p^*q^*)^{1/2} + z_Q(p_Aq_A+p_Bq_B)^{1/2}\}^2 (1+(n-1)\rho)}{nd^2}$$

where m = number of subjects needed per group
α = type I error rate
p = binomial proportion in each group (A, B), $p^* = (p_A + p_B) / 2$
$q = 1 - p$, $q^* = 1 - p^*$
$Q = 1$ – desired power (proportion)
n = number of repeated observations per person
ρ = correlation among repeated observations
d = smallest meaningful difference to be detected between groups A and B

All of the above estimates assume equal distribution of patients in the two groups being compared and four repeated outcome measurements. As seen, with an effective sample size ranging from 1200 to 3200 patients, detectable odds ratios range from 1.22 to 1.99. By way of comparison with single outcome measurements and equal distribution of patients in the two groups being compared (previous table 4.2), corresponding detectable odds ratios range from 1.32 to 2.13, indicating the gain in power achieved by use of repeated measurements.

Table 4.2.4. Odds Ratios Detectable at 90% Power Given Various Sample Sizes, Event Rates in Control Subjects (Reference Group), and Correlations Between Repeated Measurements*

Sample Size	5% event rate in reference group			10% event rate in reference group			20% event rate in reference group		
Correlation→	0.2	0.4	0.6	0.2	0.4	0.6	0.2	0.4	0.6
1200	1.71	1.86	1.99	1.50	1.60	1.69	1.37	1.44	1.51
1400	1.65	1.79	1.89	1.46	1.55	1.63	1.34	1.41	1.46
1600	1.61	1.72	1.84	1.43	1.51	1.58	1.32	1.38	1.43
1800	1.56	1.68	1.78	1.40	1.48	1.55	1.30	1.35	1.40
2000	1.53	1.64	1.73	1.38	1.45	1.51	1.28	1.33	1.38
2200	1.51	1.60	1.69	1.36	1.43	1.49	1.27	1.32	1.36
2400	1.48	1.57	1.66	1.34	1.41	1.47	1.25	1.30	1.34
2600	1.46	1.55	1.63	1.33	1.39	1.44	1.24	1.29	1.33
2800	1.44	1.53	1.61	1.31	1.37	1.43	1.23	1.28	1.32
3000	1.42	1.51	1.58	1.30	1.36	1.41	1.22	1.27	1.30
3200	1.41	1.49	1.56	1.29	1.35	1.40	1.22	1.26	1.29

*Assuming 2-sided alpha of 0.05, equal number of subjects in the two groups being compared, and a total of four outcome measurements per subject. The Correlation row in the table indicates the within subject correlation between repeated outcome measurements.

4.3. Comparisons of Continuous Outcome Variables Based on Single Outcome Measurement. Table 4.4 presents effect sizes (difference in mean scores between the 2 groups being compared / common standard deviation) detectable at 90% power given various sample sizes and proportion of all subjects in the control (reference) group. As seen, with an effective sample size ranging from 1200 to 3200 patients, detectable effect sizes range from 0.11 to 0.31. In general, effect sizes less than 0.2 are considered "small" and those from 0.2 to <0.5 are considered "medium" (Cohen 1988). Thus, an effective sample size of 1800 subjects will be sufficiently powered to detect "small" effect sizes under all conditions with the exception of a highly imbalanced design in which 90% of all subjects reside within the reference subgroup.

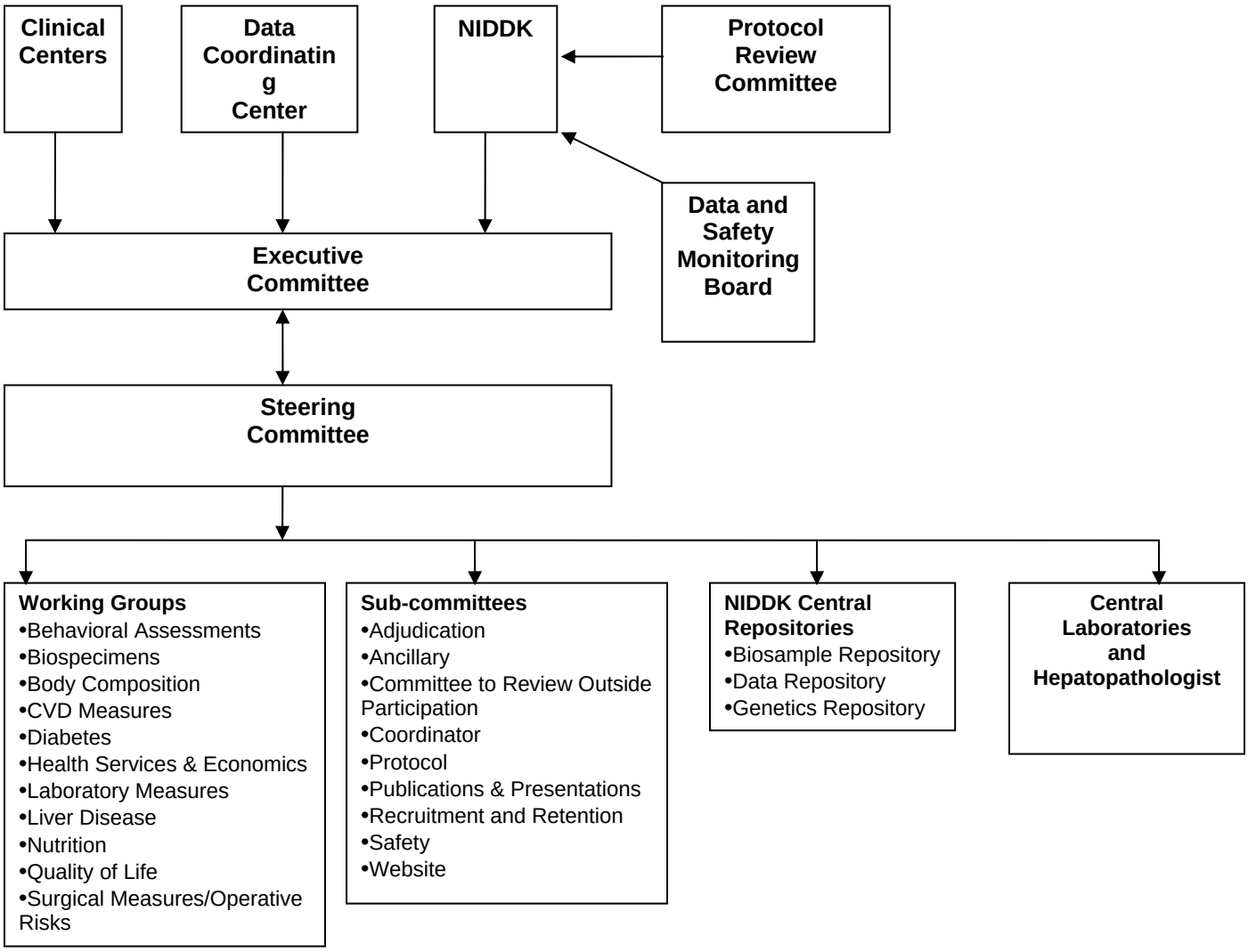
Table 4.4. Effect Sizes for Continuous Outcome Measures Detectable at 90% Power Given Various Sample Sizes and Proportions of Subjects in the Reference Group*

	% of All Subjects in Reference Group				
Sample Size	**50%**	**60%**	**70%**	**80%**	**90%**
1200	0.19	0.19	0.20	0.23	0.31
1400	0.17	0.18	0.19	0.22	0.29
1600	0.16	0.17	0.18	0.20	0.27
1800	0.15	0.16	0.17	0.19	0.25
2000	0.15	0.15	0.16	0.18	0.24
2200	0.14	0.14	0.15	0.17	0.23
2400	0.13	0.14	0.14	0.17	0.22
2600	0.13	0.13	0.14	0.16	0.21
2800	0.12	0.13	0.13	0.15	0.20
3000	0.12	0.12	0.13	0.15	0.20
3200	0.11	0.12	0.13	0.14	0.19

*Based on Student's *t* test and assuming 2-sided alpha of 0.05.

4.4.1. Target Sample Size. Based on the above sample size calculations and the desire to be able to detect odds ratios of at least 2.0 for categorical outcomes and "small" effect sizes for continuous outcomes, a target sample size of 2,400 patients is proposed. This exceeds the estimates of 2,000 patients for discrete outcomes under most circumstances (table 4.2) and 1800 patients for continuous outcomes (table 4.4) so as to conservatively allow for loss to follow-up ranging from approximately 16% to 25%.

5 Study Organization



5.1 Sites

Clinical Centers

- East Carolina University
- Neuropsychiatric Research Institute, Fargo ND
- New York Columbia-Presbyterian / Cornell / Valley Hospital
- Oregon Health & Science University / Legacy Good Samaritan Hospital
- University of Pittsburgh Medical Center
- University of Washington / Virginia Mason

Data Coordinating Center

- University of Pittsburgh, Graduate School of Public Health

5.2 Central pathology

- Project Hepatopathologist

5.3 NIDDK

- Project Scientist

5.4 Committees

Executive Committee: Manages day-to-day issues of the study; makes decisions required between the Steering Committee meetings as needed for efficient progress of the study, and reports its actions to the Steering Committee on a regular basis; organizes and sets agendas for Steering Committee meetings. Members consist of the two Steering Committee co-chairpersons, the Data Coordinating Center PI, and the NIDDK Project Scientist.

Steering Committee: Serves as the primary governing body of the study; responsible for policy decisions; votes on and approves all major decisions, provides oversight in planning the overall study design, approves protocols and subsequent amendments, facilitates study conduct and reporting of study results. Members consist of principal investigators of the clinical centers and the Coordinating Center, and the NIDDK project scientist. Two co-chairpersons were appointed by the NIDDK from among the clinical center investigators.

5.5 Subcommittees and Workgroups. Subcommittees work on specific areas of the study and make recommendations to the Steering Committee. Members consist of investigators from the clinical sites, Data Coordinating Center, and NIDDK, including individuals with expertise in the relevant areas.

Adjudication Committee (AC): The AC periodically reviews and classifies deaths and specified post surgical interventions for which the reason for the intervention could not be confirmed at the site (criteria for confirmation are detailed in the Manual of Operations). The AC will use information provided by the clinical sites through the Data Coordinating Center (DCC). Data, masked with respect to patient and medical staff (physician, surgeon, etc.) will be sent to the DCC from the clinical center at which the death or unconfirmed event occurred. The

AC will not interact directly with the LABS clinical investigators concerning the results or the classification of events.

Ancillary Studies Subcommittee (ASC): The ASC evaluates protocols that enhance the ability of LABS: [1] to document the efficacy and complications of bariatric surgery and its role in the overall management of obesity; and [2] to address other important questions related both to clinical aspects of obesity and its co-morbidities and underlying mechanistic and other basic science issues. The LABS Steering Committee has designated the ASC to conduct an initial review of all proposed ancillary studies. The Steering Committee must ultimately approve all ancillary studies recommended for its consideration by the ASC to ensure that they do not impose an unacceptable burden on LABS staff or participating patients or conflict with the aims of LABS. Data collection for funded ancillary studies may not proceed without the approval of the Steering Committee.

Committee to Review Outside Participation (CROP): The CROP supports and develops LABS through industry relationships while maintaining the integrity of LABS research. The CROP works together with the NIDDK to solicit and oversee sponsored research agreements, materials transfer agreements and cooperative research and development agreements. Through these relationships, LABS hopes to further its mission to provide a platform for future bariatric surgery research.

Coordinators Subcommittee: The Coordinators Subcommittee attends to the day-to-day operations of the study including recruitment, protocol adherence, consistent and complete data collection at each clinical center; and makes recommendations to the Steering Committee regarding any study issues that may require modification or resolution.

Protocol Subcommittee: The Protocol Subcommittee prepares the final written protocol and thus prepares summary, background information, study design, inclusion and exclusion criteria, definitions for surgical methods, monitoring schedule, adverse event grading, statistical analysis, patient protection, and references sections of the protocol; develops details of the protocol and study design for Steering Committee and DSMB approval. A subcommittee of the Protocol Committee will prepare the template consent forms for the study.

Publications/Presentations Subcommittee: Develops the policy for publications regarding preparation of abstracts, presentations, and manuscripts; policy as regards to requesting data analysis, authorship policy, and other issues related to publications; prepares a formal publication policy for full manuscripts and abstracts; prepares a list of possible publications that will arise from this study, and prepares paragraphs regarding the scope of each and how they intersect with the designated final major manuscript to arise from this study.

Recruitment and Retention Subcommittee: Attends to all facets of participant recruitment and retention. Committee members prepare strategies that can be implemented study wide to maximize recruitment and to maintain participants in the study.

Safety Committee: The Safety Committee provides on-going review of safety issues related to all of LABS studies. In defining the role of the Safety Committee, it is important to emphasize

that LABS- -2 is observational cohort studies so that the decision to perform bariatric surgery, the type of bariatric surgery and related pre-operative and post-operative management of the individuals who agree to be study participants in LABS is governed by clinical decision making and is not specified by the study protocol *per se*. The Safety Committee will be kept apprised of the summary findings of the Adjudication Committee, but the main charge of the Safety Committee is to focus upon the risk of procedures specific to the various LABS protocols, including LABS-3 mechanistic studies and separately funded ancillary studies.

The procedures specific to LABS pertain to the gathering of research data, and include blood drawing, the 400 meter corridor walk, and a variety of self-report questionnaires, many of which concern potentially sensitive personal information. The Safety Committee will be comprised of a chair, a representative from each clinical site, from the DCC and from the NIH.

The Safety Committee is charged:

- To establish safety parameters and procedures for collecting data pertaining to the safety of participation in the LABS protocols and related Ancillary studies, so that the relevant information can be gathered at clinical sites and collated by the DCC for review by the Safety committee;
- To review at regular intervals data related to the overall safety of study participation in LABS (protocols 1 through 3) and in any Ancillary studies;
- To review at regular intervals summary findings from the Adjudication committee for areas that may relate to the overall safety of LABS or the safety at an individual clinical site;
- To develop reports, with the assistance of the DCC, for presentation to the Steering Committee and to the Data and Safety Monitoring Board related to participant safety; and
- To address IRB issues that arise related to participant safety; and

Website Subcommittee: Recommends design of the website for research use and for public consumption. The latter includes general information about obesity and bariatric surgery, a description of LABS, including the goals of the study, the core information database, clinical projects and ancillary study guidelines; and contact information at the clinical sites for persons interested in enrolling in the LABS.

Working Groups:
Behavioral Assessments
Bio-Specimens
Body Composition
CVD Measures
Diabetes
Executive Committee
Health Services & Economics
Laboratory Measures
Liver Disease
Measures/Operative Risk

Nutrition
Quality of Life
Steering Committee

5.6 Advisory Groups to the NIDDK. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) to monitor conduct of the studies undertaken by the Longitudinal Assessment of Bariatric Surgery consortium (LABS).

DSMB Responsibilities. The initial responsibility of the DSMB will be to approve the initiation of each study. After this approval, and at periodic intervals during the course of the study, the DSMB responsibilities are to:

- review the research protocols, including all proposed revisions, informed consent documents and plans for data and safety monitoring;
- evaluate the progress of the studies, including periodic assessments of data quality and timeliness, participant recruitment and retention, participant risk versus benefit, performance of the clinical sites, and other factors that may affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- evaluate and report the safety of the study participants;
- make recommendations to the NIDDK, the LABS Executive Committee, and, if required, to the Food and Drug Administration (FDA) and the Institution Review Boards (IRB) concerning continuation, termination or other modifications of the studies;
- ensure the confidentiality of the study data and the results of monitoring; and
- assist the NIDDK by commenting on any problems with study conduct, enrollment, sample size, or data collection.

Membership. The DSMB consists of at least eight members (See Appendix 2) Five members will constitute a quorum. The members have been appointed by the NIDDK in consultation with the LABS Executive Committee. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. Collaborators or associates of the investigators in this study are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

Patrick O'Neil, PhD, has been selected by the NIDDK to serve as the DSMB Chairperson. He is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK Project Scientist, Mary Horlick, MD, and the LABS Executive Committee. Ms. Rebecca Torrance will serve as the DSMB Executive Secretary (ES). The Chairperson is the contact person for the DSMB. Other NIDDK official(s) may serve as an *ex-officio* member(s) of the

DSMB. The Data Coordinating Center (DCC), University of Pittsburgh, shall provide the logistical management and financial support for the DSMB.
The Chair of the LABS Safety Committee James Mitchell, MD, will be the LABS contact for reporting any safety issues to the DSMB, including adverse event reporting. Procedures for notifying the Chair of the DSMB and the NIDDK Project Scientist will be discussed and approved by the DSMB. Those procedures will be part of, and included in, the data and safety monitoring plan.

Board Process.The DSMB will meet a minimum of twice a year at the call of the Chair, with advance approval of the NIDDK Project Scientist. An NIDDK representative will be present at every meeting. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by members of the LABS Executive Committee, members of DCC staff, study Principal Investigators, and members of their staff. Meetings may be convened as conference calls as well as in person. An emergency meeting of the DSMB may be called at any time by the Chairperson or by the NIDDK Project Scientist should questions of patient safety arise. The DSMB Chairperson should contact the NIDDK Project Scientist prior to convening the meeting.

Meeting Format. An appropriate format for DSMB meetings consists of an open, closed and executive session. This format may be modified as needed.

Open Session:
The voting members of the DSMB, the NIDDK staff, the LABS Executive Committee, and members of the Data Coordinating Center staff including a study biostatistician will attend the open session. Issues discussed will include the conduct and progress of the studies, including patient recruitment, data quality, compliance with protocol, safety issues, and any other logistical matters that may affect either the conduct or outcome of the studies. Proposed protocol amendments will also be presented in this session.

Closed Session:
The closed session will be attended only by voting DSMB members, the NIDDK Project Scientist, other NIDDK representatives as appropriate, the DSMB executive secretary, and a study biostatistician. **The discussion at the closed session is completely confidential.**
Site-specific data on patient characteristics and outcomes will be presented in closed session. Subgroup data for the mechanistic studies (LABS-3) will be reviewed in closed session. This may include any or all of the following: baseline characteristics, primary and secondary outcomes, adverse events, adherence, and dropouts. Interim analyses (if done) will be reviewed in closed session.

Executive Session:
The executive session will be attended by voting DSMB members, the NIDDK Project Scientist, other NIDDK representatives as appropriate, and the DSMB executive secretary.
The DSMB will discuss information presented during the closed and open sessions and decide whether to recommend continuation or termination, protocol modification or other changes to the conduct of the studies.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. Reasons for early termination include:

- Serious adverse effects resulting from participation in LABS studies
- Logistical or data quality problems so severe that correction is not feasible.

Final Open Session (optional):

The final session may be attended by voting DSMB members, Executive Committee members, the LABS-3 Principal Investigators, a study biostatistician or other DCC members, and the NIDDK staff. Other participants may attend at the discretion of the NIDDK Project Scientist. The Chairperson of the DSMB, the NIDDK Project Scientist, or the Executive Secretary shall report on the recommendations of the DSMB regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Scheduling of the next DSMB meeting may be discussed.

REPORTS

Interim Reports to the DSMB: Interim reports will be prepared by the Data Coordinating Center.. The reports will be distributed to the DSMB and the NIDDK Project Scientist at least 10 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

Part 1 (**Open Session Report**) provides information on study aspects such as accrual, baseline characteristics, safety reports, and other general information on study status. This report is generally shared with all investigators involved with the study. The reports contained in this section will include:

- Comparison of Target Enrollment to Actual Enrollment by Month
- Comparison of Target Enrollment to Actual Enrollment by Site
- Overall Subject Status by Site, including: Subjects Screened, Enrolled, Active, Completed and Terminated
- Aggregated Demographic and Key Baseline Characteristics of Participants
- Adverse Events/Serious Adverse Events by Site and Subject

Part 2 (**Closed Session Report**) may contain data on outcomes and safety data. Mechanistic study data should be reported by subgroup in the closed report. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting.

Reports from the DSMB: A formal report containing the recommendations for continuation or modifications of the study, prepared by the executive secretary with concurrence from the DSMB, will be sent to the Executive Committee. This report will also contain any recommendations or requirements from the NIDDK in reference to the

DSMB recommendations. It is the responsibility of the Executive Committee to distribute this report to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

Each report should conclude with a recommendation to continue or to terminate each of the studies. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The NIDDK is responsible for notifying the Executive Committee of a decision to terminate the study. In the event of a split vote either in favor of, or opposed to, continuation, a minority report should be contained within the regular DSMB report. The report should not include any confidential data.

Mailings to the DSMB: On a quarterly basis, site-specific recruitment, retention, and safety data should be communicated to all DSMB members, the NIDDK Project Scientist, and the DSMB executive secretary. Any concerns noted by the DSMB should be brought to the attention of the NIDDK Project Scientist.

Confidentiality. All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

6 Human Subjects Issues

6.1 Overview. The study protocol, consent forms, and data collection forms will be submitted to each clinical center's Institutional Review Board (IRB) and to the DCC's IRB. Additionally, each clinical center will submit any recruitment materials to be used at their site to their IRB. A site may not initiate any patient contact for LABS-2 until the site has IRB approval. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

6.2 Institutional Review Board Approval. It is the investigator's responsibility to ensure that the LABS-2 protocol and informed consent documents are reviewed and approved by the appropriate IRB. Each clinical site must obtain a letter of approval from the IRB prior to enrolling patients into this study. Sites must provide the DCC with copies of the initial IRB approval notice prior to enrolling the first patient, and subsequent renewals, as well as copies of the IRB approved consent. Additionally, the NIDDK must review the IRB approved informed consent prior to enrollment.

The IRB must also review and approve any other written information provided to the patient prior to any registration of patients.

If, during the study, it is necessary to amend either the protocol or informed consent document, the investigator will be responsible for ensuring the IRB reviews and approves the amended documents. IRB approval of the amended informed consent document must be obtained before new patients consent to participate in the study using the new version of the consent.

The informed consent document will inform patients of their right to refuse any release of their protected health information.

6.3 Informed Consent

6.3.1 Informed Consent Document. A sample informed consent document has been provided at the end of this protocol (see Appendix). Each clinical site, according to local IRB requirements, is allowed to modify this informed consent document and make any necessary editorial changes as long as the meaning or intent of any section is not changed.

6.3.2 Informed Consent Process. The investigator or his/her designee (i.e., research coordinator or study nurse) will inform the patient or the patient's legally authorized representative of all aspects of the study pertaining to the patient's participation in the study.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by the investigator or his/her designee and the patient BEFORE the patient can participate in the study. Once a candidate for LABS 2 has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the two sections of the IRB-approved LABS-2 informed consent document. The first informed consent grants permission to collect information on a participant's health via questionnaires, laboratory values and urine samples while the second section allows for the collection, storage, and use of DNA for genetic research from his/her blood samples. Refusal to sign the genetic informed consent section will not preclude a participant from participating in LABS-2 as long as the primary consent form document is signed. The patient will receive a copy of all signed and dated documents and the originals will be retained in the patient's study file or medical record.

6.3.3 Research Study Costs: Remuneration:. Subjects will not be paid remuneration to participate in this study. Subjects will be reimbursed for some expenses related to the burden of participating in the study.

6.4 Confidentiality of Patient Data. The clinical site is responsible for the confidentiality of the data associated with patients enrolled in this study in the same manner that it is responsible for the confidentiality of any patient information within its sphere of responsibility. All forms used for the study data will be identified by coded identification number, which will be generated at the clinical center, to maintain subject confidentiality. All records will be kept in locked file cabinets at the clinical centers with access limited to LABS-2 study staff, and all study staff will identify patients via their unique identifier. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or Data & Safety Monitoring Board (DSMB). Clinical information may be reviewed during site visits by the DCC and the NIDDK Project Scientist. The patient grants permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data.

Consent procedures and forms, and the communication, transmission and stoppage of patient data will comply with individual site IRB and NIH requirements for compliance with The Health

Insurance Portability and Accountability Act (HIPAA). The Privacy Rule of HIPAA governs the protection of an individual's identifiable health information. The DCC will ensure that clinical centers associated with the project are complying with HIPAA regulations by requiring documentation from the IRBs with the appropriate authorization or consent form. The DCC will maintain copies of all relevant documents from each clinical center. If IRB approvals are not current, data will not be accepted by the DCC. The LABS-2 data management system will ensure the confidentiality of electronic protected health information. The DCC will work with the NIDDK Data and Specimen Repositories to determine their requirements for maintaining participant confidentiality.

6.5 Risk/Benefit Ratio. The risk of physical harm associated with participating in the LABS-2 study is limited. Blood drawing can cause temporary discomfort or bruising at the skin puncture site and in, rare instances (less than 1%), fainting or an infection can occur. The 400 meter corridor walk may cause chest pain, tightness or pressure in the chest, shortness of breath, feeling faint, lightheaded or dizzy, or leg pain. The test will be stopped immediately if any of these symptoms do occur. During the 400 m walk tests, a fully stocked crash cart is available with all necessary emergency equipment (drugs, defibrillator, and airway management).

Of minimal risk to patients is the possible inconvenience of reporting medical status to the research coordinator. Some of the questions may be upsetting. For example, questions will be asked regarding alcohol and drug abuse, sexual practice and emotional problems such as depression. You will be informed that you can decline to answer any questions you wish not to answer. Another possible risk is a breach of confidentiality, although steps have been taken to minimize such an occurrence. All information collected for this research study will be kept confidential. Patients' names will be used only for the informed consent form and medical chart reviews. Patients 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. Patient names will not be recorded in the computerized study database. 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. Blood and urine samples will be labeled with unique patient identifiers and not patients' names before shipment to central facilities. To help us protect patients' privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. Known breaches of confidentiality will be reported to NIDDK.

There will be no direct benefits to patients who participate in LABS-2 only nominal remuneration (see § 6.3.3). Clinically relevant measurements will be made available to the patient and their physician with their permission. Participation may benefit other patients who undergo weight-control surgery.

6.5.1 Data and Safety Monitoring Plan. A data and safety monitoring committee will oversee the study. Their main tasks are to ensure that there are no changes in the risk/benefit ratio during the course of the study, that the study is implemented appropriately, and that the confidentiality of research data is maintained. Investigators and study personnel will meet routinely to discuss

the study (e.g., study goals and modifications of those goals; subject recruitment and retention; progress in data entry; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address any issues or concerns at that time. Minutes will be kept for these meetings. The yearly IRB renewal for this study will include a summary report of the Data and Safety Monitoring Board recommendations from the prior year.

7 Adverse Event Reporting

Any instances of adverse events occurring as a result of procedures performed solely for research purposes, as opposed to standard clinical care, will be reported immediately to the local site IRB using the standard forms and procedures that have been established by the IRB.

7.1 Definitions

Serious Adverse Event
An adverse reaction is considered serious if it is fatal or life-threatening; requires or prolongs hospitalization; produces a disability; or results in a congenital anomaly/birth defect.

Severity of Adverse Event
An adverse reaction is considered to be of moderate or greater severity if it requires medical evaluation (such as additional laboratory testing) or medical treatment; or if it is a serious adverse reaction.

Unexpected Adverse Event
An adverse reaction is considered to be unexpected if it is not identified in nature, severity or frequency in the current IRB-approved research protocol or informed consent process

Adverse Event Associated with Research Intervention
An adverse reaction is considered to be associated with the research intervention if there is a reasonable possibility that the reaction may have been caused by the research intervention (i.e., a causal relationship between the reaction and the research intervention cannot be ruled out by the investigator(s)).

Relatedness
With respect to the research intervention, an adverse event can be considered to be definitely, probably, possibly, or unrelated, or relatedness may be indeterminate.

7.2 Guidelines for Adverse Event Reporting. Investigators involved in LABS-2 will report to their local IRB, the DCC, NIDDK and the DSMB, serious adverse events which are a result of a research-specific procedure or intervention (i.e., venipuncture, corridor walk, StepWatch monitoring). All deaths, regardless of relationship to the study, are deemed serious and must be reported as a serious adverse event. Moreover, investigators involved in LABS-2 will report to their respective IRB, external adverse events which are unexpected, serious and associated with a research-specific procedure or intervention. Any instances of adverse events that necessitate reporting as defined above will be reported immediately to the local IRB using the standard forms and/or procedures that have been established by that IRB.

Adverse reactions which are determined by the investigator to be unrelated to research-specific procedures or interventions need not be reported to the local IRB, unless the local IRB requires otherwise.

8 Other Considerations

8.1 Clinical site eligibility. The clinical site must be formally part of or affiliated with one of the six institutions (East Carolina University, Neuropsychiatric Research Institute [Fargo ND], New York Columbia-Presbyterian / Cornell / Valley Hospital, Oregon Health & Science University, University of Pittsburgh Medical Center, University of Washington / Virginia Mason) participating in the LABS consortium.

8.2 Clinical Site Audits. All clinical sites at which patients are enrolled are subject to an on-site audit by the Data Coordinating Center.

8.3 Performance Monitoring The DCC will perform statistical analyses and prepare materials for monitoring study progress (e.g., recruitment, retention, data processing timeliness and accuracy) and protocol adherence (e.g., proportion of follow-up visits completed on time). For example, reports of observed vs. expected recruitment, and timeliness of data collection and data entry by site will be routinely posted in the private area on the project web site. The pre-established amount of time expected for completing forms will be compared to the actual amount of time required to process the forms.

Problems with adhering to study protocols, data collection, entry, and management will be identified and addressed. Site visits will provide a means for the DCC to become familiar with personnel and basic practices and procedures at each center. With problems identified, solutions can be found and proper procedures implemented to prevent future problems.

Another critical dimension will be the quality of data entry. During data audits at the clinical centers, the DCC will visually check randomly selected source documents, as well as source documents selected because of suspected problems, against the computerized version. The number and nature of errors will be tabulated. These audits will also provide information about the accuracy of data collection.

Inadequate performance in any aspect of the study (e.g., protocol adherence, data collection, data entry, data completeness, data accuracy) will be reported to the site principal investigator and NIDDK project scientist. A subsequent evaluation will be performed to determine whether corrections have been made. Should problems persist, the Steering Committee will be notified and recommendations will be made for resolving persisting inadequacies.

8.4 Inclusion of Women and Minorities. Based on current referral rates of patients undergoing bariatric surgery, LABS expects a ratio of female to male patients at approximately 4 to 1, reflecting surgical populations at the LABS sites. It is anticipated that approximately 18% of the LABS-2 cohort will be African-American and 13% will be Hispanic. The proportions of

other minority groups are expected to be less than 1%, reflecting the surgical populations at the LABS sites.

8.5 Remote Visits to Enhance Retention. To enhance retention, LABS coordinators may utilize Examination Management Services, Inc. to conduct remote study visits. The field representative from Examination Management Services, Inc. will be a trained healthcare professional, subject to confidentiality rules and will be required to become certified on the LABS protocol prior to performing a subject visit. LABS participants who agree to a remote visit will sign an addendum consent form to indicate their permission to provide data to EMSI.

The EMSI representative will be responsible for obtaining data collection forms, weight and physical measurements (waist and neck circumferences) and biospecimens including blood and urine. The EMSI representative will transmit collected data and biospecimens back to the originating clinical center for data entry and biospecimen processing.

In the event of an adverse event or unexpected problem during the visit, the EMSI examiner must report it to EMSI National Service Center (NSC) immediately by phone. EMSI NSC will notify the site coordinator and DCC central study coordinator immediately.

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10 Appendix

Data and Safety Monitoring Board Roster
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