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Surrogate Markers of Success in the Bariatric Surgery Population

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SURROGATE MARKERS OF SUCCESS IN THE BARIATRIC SURGERY POPULATION

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ABSTRACT:

Purpose: The purpose of this study was to examine the associations between pre-operative weight loss, weight loss programs, and clinic attendance relative to the success of gastric bypass in class II and III obese patients.

Background: The increasing number of obese children and adults in the United States poses an extensive social problem in the era of managed care. Notwithstanding the stigmatization associated with obesity, the considerable health implications along with the financial burden it imposes create a formidable adversary. Surgical procedures have proved to be superior to conservative and pharmacotherapeutic interventions in the morbidly obese. Despite the overall success of bariatric surgery, little information exists in the medical literature to predict patient outcome.

Design/Methods: Our study was subdivided into three sections. First, we investigated the effects of patient adherence to pre-operative dietary and exercise recommendations. The change in body mass index (BMI) between initial consultation and pre-operative workup (average 6-8 weeks) was compared to change in BMI at the one year post operative period.

The second study compared the maximum weight loss achieved by popularly used dietary programs to a physician monitored plan. On initial evaluation patients were asked to report information regarding weight loss attempts including program used and weight loss achieved. All individuals who had accurate records of their dieting attempts were included. We performed an ANOVA analysis and then Pearson and Spearman correlations between maximum pre-operative weight loss and one year post-operative weight loss.

The last study conducted analyzed the association between clinic attendance and weight loss at yearly intervals. We also inquired about reasons for non-attendance and patient adherence in regards to vitamin supplementation, exercise regimen, and dietary intake.

Results: From August 26, 2002 to July 31, 2006 a total of 404 laparoscopic Roux-en-y gastric bypass procedures were performed by Dr. Bell at Yale-New Haven Hospital. Of these patients 256 had one year post-operative weight data and were included in the first portion of the study. These subjects had an average pre-operative BMI 51.4 kg/m^2 and ages which ranged from 17 to 64. At the one year post-intervention period, the mean percentage excess weight loss and percentage BMI loss were 62% and 34.5% respectively. Patients were categorized into two groups: those who had lost weight and those who had no change or gained weight after initial consultation. A multiple

regression analysis and ANOVA showed no statistical difference between the two groups at the one year post operative period.

The second portion of the study had 384 participants. A least squares analysis showed that physician monitored weight loss did not confer an advantage over popular commercial programs. In addition, linear regression analysis showed no correlation between maximum weight loss during dieting attempts and success at the one-year post-operative period measured by percentage of excess body weight loss.

Lastly, in our evaluation of clinic attendance as a marker of success 283, 157, and 56 patients at the one, two, and three year interval respectively met inclusion criteria. A t-test at years one and two showed no statistically significant difference between those who attended clinic and those who did not.

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INTRODUCTION

Obesity has become an extensive problem throughout the world due to the incredible financial burden it places on society and multiple physiologic derangements it imposes on the affected. It has recently been touted as one of the most dangerous epidemics due to its wide distribution across all ages and socioeconomic strata even though its recognition has lagged behind malnutrition, smoking, and infectious diseases as a result of uninformed misperception. It has reached sensational recognition with terms such as "globesity" being coined by the World Health Organization (WHO) to describe its ubiquitous nature. Throughout history, corpulence was seen as a sign of good nutrition, well-being, and wealth, but today the pendulum has swung in the direction of appreciating its negative health implications.

The definition of overweight individuals ranges by tools used but is most typically determined by body mass index (BMI), which is calculated by weight in kilograms divided by height in meters squared. The WHO considers overweight individuals as having a BMI >25 kg/m^2 and those that are obese as having a BMI >30 kg/m^2. Many physician scientists have questioned the tool's usefulness and have introduced other measures such as waist hip ratio (WHP), ideal body weight, and excess body weight. Other anthropometric calculations to evaluate obesity continue to arise due to discrepancies in disease burden between different racial backgrounds. Recently, waist stature ratio (WSR) has gained support secondary to greater concordance in the elderly population in regards to morbidity[1], but this tool uses waist circumference as a variable which has been shown to be population dependent [2, 3]. Due to the vast number of tools

available and inherent flaws associated with each, BMI remains the most often used tool as evidenced by its presence in the medical opus.

The WHO estimates approximately 1 billion adults worldwide are overweight with 300 million of those to be clinically obese. It is estimated that an approximate 2.3% of the US population has a body mass index (BMI) of greater than 40 kg/m^2, meaning that about 6 million Americans are considered severely obese [4, 5]. Additional data show that 30,000 deaths in the UK and 300,000 deaths in the United States can be attributed to obesity annually [6, 7]. Furthermore, this epidemic is not limited to the adult population as evidenced by increasing proportions of obesity in the pediatric age group. Approximately 25.6% of children in the US are overweight as reported by NHANES III [8]. In England, this has also become a problem as shown by a national survey in which 14% of 2-11 year olds and 25% of 11-15 year olds were obese (BMI >95^{th} percentile)[9]. Although the cause of this epidemic is multifactorial, including genetic, behavioral, and environmental factors, the rise in obesity is most likely attributable to the globalization of the fast food industry which provides high calorie meals rich in carbohydrates and saturated fats in addition to lifestyles that are increasingly sedentary.

Although the effects of obesity have long been neglected, its conspicuous correlation with public health issues such as dyslipidemia, hypertension, increased risk of various malignancies, and diabetes can no longer be marginalized. It has been postulated that obesity affects every major organ system in the body. INTERHEART, a large international case-control study, showed that obesity was associated with an increased cardiovascular risk throughout the world [10]. A landmark study assessing the mortality associated with obesity showed that a BMI > 40 kg/m^2 increased the risk of death from

all cancers by 52% in men and 62% in women[11]. The incidence of hypertension and diabetes in children has been increasing steadily with the rise in childhood obesity [12] Despite this, the US population continues to live a relative sedentary lifestyle, with approximately 27% of the population self reporting no physical activity and another 28.2% reporting irregular activity [13].

Despite raised concern over the negative health implication of obesity, the formula for weight loss eludes most. The multibillion dollar weight loss industry floods television and radio advertisements with fad diets, books, and supplements which promise miraculous changes in short periods of time but usually fail due to high recidivism rates. Today, being "fit" has been associated with good self-image in addition to better salaries and psychological well-being.

Increased public awareness along with societal perceptions of obese people and risks associated with comorbidities have led many in this subpopulation to seek medical aid. Research has shown that conservative methods of weight loss in the morbidly obese, BMI >40 kg/m^2, such as decreased caloric intake, increased energy expenditure (exercise) and behavior modification fail in providing long term weight loss [14]. Second line treatment for obesity, pharmaceuticals such as anorectic and malabsorptive agents, have also failed to deliver sustained weight loss and have questionable benefit-risk ratio due to lack of long term research [15]. Many remain skeptical of the their use due to historical addictions to amphetamines, misuse of caffeine and ephedrine, and deleterious side effects such as those seen in fenfluramine [16]. Currently, Orlistat and Sibutramine are the only weight loss agents recognized by the FDA. These agents increase the

chances of losing approximately 6-10% of initial body weight while providing the added benefits of improved lipid profile and glycemic control [17].

Today, surgery has become the norm for the morbidly obese as established by the guidelines set forth in the 1991 NIH Consensus Conference on Gastrointestinal Surgery for Severe Obesity [18]. Despite some severe contraindications of surgical interventions such as schizophrenia, personality disorders and uncontrolled depression, this method remains preferred to the less intrusive and more conventional ones. This particularly applies to patients who respond to neither decreased caloric intake and increased activity regimens nor weight loss pharmacotherapy. Surgical weight loss treatment is used in the United States on patients with a BMI > 40kg/m^2 or patients with a BMI > 35kg/m^2 who, in addition, exhibit some of the typical comorbidities of obesity such as diabetes and hypertension.

The most remarkable characteristic of surgical treatment of obesity is the rapid and significant loss of excess body weight, with an average decrease in the range of 50-70%. This results in an observable improvement of patient's condition, and most patients feel "transformed" by the extent of their weight loss and instantaneity of the results. What is more, an extraordinarily low rate of operative mortality of around 1%, especially in experienced surgical centers, makes the levels of both safety and effectiveness of this treatment particularly desirable. Additionally, reversal of comorbid conditions in such high-risk patients is rapid as well, with a swift normalization of glucose handling and blood pressure in patients with diabetes and hypertension. However, sparse long-term studies suggest that there is only slight evidence that surgical treatment of weight loss leads to a decreased long-term mortality in patients. Even though poor dietary habits such

as absence of fruit and vegetables following the surgery do not have a significant effect on development of clinical picture in the post-operational period, continued monitoring is suggested due to the mentioned contraindications.

Surgical intervention in morbidly obese patients has led to great improvements in the overall quality of life of these individuals, but it has also led to some unforeseen complications. Acid reflux has become a common symptom in many of the distinct bariatric procedures. Data to suggest this has been controversial, with multiple studies showing great improvements [19] while others report the contrary, such as an approximate fivefold increase in the total esophageal acid exposure time and up to 75% prevalence of esophagitis in this population [20]. The disparate results are most likely secondary to distinct surgical technique leading to differences in gastric pouch sizes, the specific procedure used, and discrepancies in data collection methods. Although medical literature presents conflicting data regarding the prevalence of GER (gastroesophageal reflux) post surgical intervention, the consequences of unchecked reflux such as achalasia and Barrett's esophagus cannot be overlooked.

Gastrointestinal System:

In order to fully comprehend the pathophysiology and medical / surgical intervention of morbid obesity a comprehensive understanding of the gastrointestinal system must be known. The gastrointestinal system's main role is in the digestion and absorption of nutrients. It is a complex system that spans from the mouth to the anus and is associated with multiple accessory glands and organs. While this hollow tube is continuous, a specialized system of physiologic and mechanical sphincters has evolved to compartmentalize and thus specialize certain regions of the system.

Food enters the body in a form that is not accessible to the intestinal mucosa for absorption. The processing of food begins in the mouth, where mastication (chewing) breaks food into smaller pieces thereby increasing the surface area. In addition, chemical breakdown of food also begins in the mouth via the actions of salivary and lingual lipases and amylases. Although the enzymatic action of oral lipases and amylases play a small role in the breakdown of food, it further facilitates the process. In addition, saliva allows the food bolus to be lubricated to ease its transition down the esophagus.

The esophagus is typically described as a hollow conduit that transports food from the oropharynx to the stomach. The pharynx and the upper portion of the esophagus is separated by the upper esophageal sphincter (UES) which has the highest resting pressure of all the gastrointestinal sphincters. The motor enervation of the UES is mediated by the nucleus ambiguous in the medulla via cranial nerves V (trigeminal), IX (glossopharyngeal), X (Vagus), and XII (hypoglossal); the sensory pathways of the UES terminates in the nucleus tractus solitarius. The closure of the UES prevents atmospheric air insufflation of the stomach during negative intrathoracic events such as breathing; it also prevents the regurgitation of food from the esophagus back into the oropharynx. The sphincter relaxes during swallowing or emesis. The stomach and esophagus are separated by the lower esophageal sphincter (LES) which is composed of specialized smooth muscle cells. The LES is tonically contracted and relaxes during vagally medicated inhibition of the fibers via nitric oxide. It functions in preventing gastric contents from refluxing from the stomach and thus protecting the esophagus from autodigestion secondary to the low pH in the stomach. Dysfunction of the LES is associated with significant morbidity. A LES which does not maintain tonic contracture

leads to regurgitation of stomach contents leading to pyrosis and scaring of the esophagus. In contrast, the LES can fail to relax in the condition known as achalasia.

The stomach serves multiple roles in the digestive process via its humoral, motor, and secretory properties which continue the process of breaking down food into smaller absorbable subunits. Although digestion is typically associated with the stomach, its presence is not necessary for the sustenance of life as evinced by the survival of patients that have undergone total gastrectomies.

The pH of the stomach is typically maintained between 1 to 4. The secretion of hydrogen ions is due to the actions of the parietal cell which is under hormonal (gastrin), paracrine (histamine) and neural signals (vagus nerve). The stomach also secretes pepsinogen from chief cells which aids in the enzymatic digestion of protein. In addition, water, bicarbonate, and intrinsic factor are released by the gastric mucosa. Intrinsic factor binds and is necessary for the absorption of vitamin B12 (cobalamin). The stomach mixes and churns its contents allowing chyme to be broken down further until small enough to enter the small intestine. Lastly, the stomach releases the hormones gastrin and somatostatin which feedback to effect gastric secretions.

The stomach is subdivided into three major regions: cardia, corpus, and antrum. The cardia is located distal to the lower esophageal sphincter and receives the contents of the esophagus. The corpus or body comprises the major portion of the stomach and serves as the primary secretory region. The antrum is the most distal portion of the stomach and facilitates the emptying of gastric contents through the pyloric sphincter into the small intestine.

The small intestine is responsible for most of the digestive and absorptive properties of the gastrointestinal system. In an adult, the small intestine averages 6 meters in length. It is subdivided into the duodenum, jejunum, and ileum. It receives bile and pancreatic juices via the ampulla of Vater in the first portion of the duodenum. Structurally, the small intestine contains plicae circulara that form permanent circumferential folds in the intestinal wall. The mucosal surface is arranged in longitudinal folds, called folds of Kerkring. Villi, fingerlike projections, sprout from these folds which are further subdivided into microvilli, also referred to as brush border due to its appearance under light microscopy. The purpose of these outpouchings is to increase the surface area thereby maximizing brush-border activity and absorptive capacity.

Carbohydrates, lipids, and protein are all handled distinctly by the small intestine. Carbohydrates, which comprise approximately 40-50% of the typical Western diet, are typically ingested in the form of polysaccharides, disaccharides, and monosaccharides. Intestinal epithelial cells are equipped with specialized channels, which can only transport monosaccharides. Therefore, all ingested sugars must be digested into monomers of glucose, galactose or fructose. The breakdown of sugar polymers is accomplished through the actions of salivary amylase, pancreatic amylase and intestinal brush border enzymes.

Protein digestion begins in the stomach with the activity of pepsin and terminates with pancreatic and brush border peptidases in the small intestine. Endo- and exopeptidases of pancreatic secretions, cleave peptide bonds shortening the protein structure. Epithelial cells can absorb amino acids, dipeptides, and tripeptides. Amino

acids enter the cell through a mechanism similar to that seen in monosaccharide absorption, utilizing Na+ as a co-transporter. In contrast, dipeptides and tripeptides are absorbed via an H+ dependent cotransporter. Once inside the cell, these are hydrolyzed into amino acids.

Dietary lipid can be subdivided into triglycerides, phospholipids, and cholesterol. Their decreased solubility in an aqueous environment poses a unique obstacle to absorption. Triglycerides, long chain fatty acyl esters of glycerol, make up the greatest bulk in consumption. They are typically divided into saturated and unsaturated triglycerides depending on double bonds in their fatty acid residues. This subdivision has gained much media attention secondary to research showing the detrimental effects of saturated fatty acids which are found in high ratio in animal fats.

The stomach is responsible for the initiation of lipid digestion by the actions of lingual and gastric lipases which digest approximately 10% of lipids. Most importantly, the stomach increases its emptying time to allow adequate processing of fats by the small intestine. Bile and pancreatic juices join chyme in the duodenum via the relaxation of sphincter of Oddi. Hepatocytes in the liver create the alkaline substance known as bile. It is composed of bile salts, pigments, cholesterol, and water. Bile is released into the small intestine in a pulsatile fashion in response to cholecystokinin (CCK). Bile acts as a detergent, helping to emulsify fats to create smaller droplets of lipids in an effort to increase surface area. This permits the actions of pancreatic enzymes (pancreatic lipase, cholesterol ester hydrolase, and phospholipase A_2) to more effectively hydrolyze lipids into smaller subunits. The products of these reactions are then free to diffuse into epithelial cells. Inside, they are re-esterified in the smooth endoplasmic reticulum and

packed with apoproteins to create chylomicrons. These particles are too large to enter the capillary network in the basolateral side and thus enter the lymphatic system via lacteals.

In addition, the small intestine is also responsible for the absorption of vitamins, inorganic ions, minerals and water. Of clinical importance is the absorption of vitamin B12, which, as previously discussed, needs a cofactor produced by the stomach in order for its absorption to occur in the ileum. In patients that have undergone a gastrectomy or gastric bypass, vitamin B12 is unpredictably absorbed. If not supplemented parentally, a lack of vitamin B12 can lead to pernicious anemia and/ or nerve degeneration. The inorganic ion, calcium, is absorbed throughout the small intestine regulated by the actions of the parathyroid glands and vitamin D. A deficiency in calcium can lead to bone demineralization, osteomalacia. Iron, among other minerals, is also absorbed by epithelial cells in the small intestine; a lack of iron can lead to microcytic anemia.

After chyme traverses the small intestine, it enters the large intestine or colon via the ileocecal valve. The large intestine gains its name due to the thickness in diameter of the viscus and not its length. It is typically 1.5 meters long and consists of the cecum, colon, rectum and anal canal. The colon functions in absorbing remaining water from indigestible food matter and storing this waste until defecation eliminates the remains from the body.

Surgical Intervention:

To understand current operative techniques in the field and possible improvements, one must first look to the past to understand the mechanism of action and rationale for development of gastric bypass procedures. During primary education, students often question why history is an important discipline; the emphasis on memorizing minutia such as innumerable dates and names conceals the main objective of understanding and learning from the past. Although history is not formally taught in medical school, it is omnipresent due to the nature of the medical field—a field that necessarily builds upon previous experiences. This can clearly be seen in the field of bariatric surgery: while early operative techniques could promise dramatic success with weight loss, they were often riddled with complications. These myriad complications forced the abandonment of early procedures, and set physicians and researchers on the path to developing the current gold standard, *Roux-en-y* gastric bypass.

Surgical procedures aimed at reducing weight are subdivided by their mode of action into malabsorptive and restrictive. Malabsorptive procedures attribute their weight loss properties to incomplete uptake of calories and nutrients. This has classically been described by way of two interrelated paths. First, the pancreatic and bile fluids, which are typically released into the first portion of the small intestine, are diverted to a more distal portion of the alimentary tract, typically the ileum. Essentially, this decreases the time that food can be chemically digested and altered into smaller subunits, namely amino acids, oligosaccharides and emulsified fats which can then be absorbed. Secondly, by bypassing a portion of the small intestine, there is less potential area for absorption of

nutrients. Consumption of large amounts of food leads to a greater proportion of unabsorbed hyperosmolar chyme that enters the large intestine causing diarrhea.

Restrictive procedures aim at reducing the volume of the stomach, thereby leading to early satiety and thus contributing to weight loss via decreased food intake. The vertical banded gastroplasty is a prime example of a purely restrictive procedure that does not affect digestive processes. In this procedure, the stomach is stapled 1 cm from the lesser curvature of the stomach starting at the gastroesophageal junction. A circular opening is then created several centimeters down to allow for the creation of a fortified polypropylene stoma with a 1 cm outlet. This procedure does not require rearrangement of the alimentary tract and has low morbidity.

Another restrictive procedure, the adjustable gastric band, has become a popular method of weight reduction in Europe and has recently been approved in the USA by the FDA. This procedure entails the laparoscopic insertion of an inflatable balloon device around the proximal portion of the stomach. A subcutaneous port is attached to the device which allows access to modulate and tailor gastric pouch size. Typically a small pouch of approximately 30 cc is necessitated. While early reports have shown similar weight loss to vertical banded gastroplasty, it has not led to the dramatic and sustainable reduction witnessed in gastric bypass.

Linner is credited with the genesis of bariatric surgery. This operation became the model for malabsorptive procedures and quickly became the most popular surgical weight loss operation for the following two decades. Although the jejunoileal bypass led to appreciable weight loss, it was plagued by copious complications such as hepatic fibrosis and failure, nephrolithiasis, electrolyte derangements, gas-bloat syndrome and

impaired mentation to name a few. Most of the side effects of the jejunoileal bypass were attributed to its blind loop leading to overgrowth of bacteria and toxemia. The popularity of the jejunoileal bypass as a malabsorptive procedure prompted the development of the biliopancreatic diversion in the 1970s and the duodenal switch in the 1990s which avoided the creation of a blind loop.

In 1979, a series of patients who underwent biliopancreatic diversion (BPD) was reported by Nicola Scopinaro[21-23]. Before the first human BPD was performed in 1976, its effects had been studied with canine subjects. The procedure gained popularity due to its combined malabsorptive and restrictive properties. The first portion of the operation entails a partial gastrectomy. Many have claimed that the restrictive properties of the biliopancreatic diversion are minimal given that a large portion of the stomach is retained. Patients are able to eat large quantities of food at a time despite a reduction in the volume of the stomach. This is followed by the division of the small bowel a short distance past the ligament of Treitz. The distal end of the transected bowel is used to create a gastroenteroanastomosis. Then, an anastomosis between the free proximal end and the distal ileum is created. Scopinaro stated that this procedure prevented most of the complications seen with the jejunoileal bypass. In contrast to the jejunoileal bypass, the BPD does not possess a long excluded loop (which leads to hepatic fibrosis). In addition, it maintains an intact enterohepatic bile circulation and decreases malabsorptive complications.

Roux-en-y gastric bypass entails the creation of a small proximal gastric pouch, typically 10-30 cc[24]. A segment of the jejunum is them brought up to make a gastroentero anastomosis, thus creating a Y limb from which it derives its name. The

free jejunal end is anastomosed to the ileum. This procedure thus functions via restrictive and malabsorptive mechanisms. As seen in Bilroth II operations for peptic ulcer disease, this procedure causes dumping syndrome. In addition to the restrictive components which lead to early satiety, dumping syndrome deters patients from eating large quantities of food. Multiple retrospective and prospective studies have shown a reduction of greater than 50% in mean excess weight[25].

Controversy exists in the choice of surgical intervention in the super morbidly obese. A retrospective study comparing Roux-en-y gastric bypass and biliopancreatic diversion with duodenal switch (BPDS) in patients with a BMI >50 kg/m2 showed that BPDS was superior in weight reduction at the three-year post operative period[26]. An abundance of anecdotal evidence supports that BPDS is superior to other malabsorptive procedures, but it is also plagued by increased morbidity and mortality. This has led to several revisions as evidenced by the staged procedure of Gagner, in which a sleeve gastrectomy is performed 6-12 months before undertaking a BPD-DS operation[27]. Due to increased surgical complexity and the risks involved in BPDS, laparoscopic Roux-en-y gastric bypass remains the preferred method. Following the dual-stage procedure in the BPD-DS, a similar protocol was devised for Roux-en-y gastric bypass for the super morbidly obese[28].

Adherence:

Studies that focus on patient adherence to therapy have almost exclusively been associated with chronic diseases. These studies have become indispensable because of the perspectives they offer on the provision of medical care. In the era of managed care,

the relationship between patient behaviors, demographics and outcome has been scrutinized secondary to large discrepancies in care delivery and morbidity/mortality rates between different patient populations. Although many factors contribute to a patient's ability to adhere to post-operative therapy, blame has typically been placed on the patient with little impetus to explore the matter further. An exploration of these factors has the potential to greatly enhance patient outcomes, as well as contribute to the corpus of medical knowledge in the field of bariatric surgery.

STATEMENT OF PURPOSE:

This study will accomplish multifaceted goals in an attempt to elucidate factors that influence the success of gastric bypass. Although surgical intervention is recommended by the NIH for morbidly obese individuals, little is known regarding behaviors that might act as surrogate markers predictive of success. These behaviors such as choice of community based weight reduction programs, pre-operative adherence to physician advice, and attendance to clinic at yearly intervals will aid in understanding possible associations that correlate with greater weight loss.

Gastric bypass procedures have been stigmatized by many, including physicians, throughout its development. Many postulated that obesity should not be seen as a disease and that it should be treated conservatively via behavior modification. Clinical data showing the superiority and sustainability of weight reduction as well as the reversal of comorbidities seen in bariatric surgery has led to a more accepting atmosphere within the medical and social community. Despite this, many insurance companies deny patient claims for surgical intervention. Furthermore, they demand numerous requirements be met before intervention is undertaken in what they believe is an effort to screen patient candidacy for better outcomes. Although their selection criteria might seem beneficial to patients in the long run, studies have not shown this to be the case. In fact, one might postulate the opposite. In the hands of a trained and technically proficient minimally invasive surgeon, excellent weight loss is obtained with minimal mortality. We will examine some of the requirements set by insurance companies such as physician monitored weight loss programs. We hypothesize that a physician monitored plan is not superior to other programs such as Weight Watchers® and that this should not be a

requirement. We also predict that peri-operative weight loss and clinic attendance could present as more efficient predictors of success in this population.

Methods:

This endeavor evaluated possible markers of success in bariatric surgery at Yale-New Haven Hospital. Subjects were recruited from among Dr. Robert Bell's patients who underwent laparoscopic Roux-en-y gastric bypass from August 26, 2002 through July 31, 2006. The study was submitted to the Yale Human Investigations Committee (HI C) for approval.

A master database was constructed from patients' medical charts which included the following:

Subject initials
Medical record number
Age
Sex
Race
Insurance
Maximum weight loss attempt
Program leading to greatest weight loss
Comorbidities
Initial consultation weight
Initial BMI
Pre-operative Weight
Pre-operative BMI
Δ weight initial consult and pre-op
Ideal body weight
Excess body weight
Date of procedure
Weight at 1st year post-op period
BMI at 1st year post-op period
Weight at 2nd year post-op period
BMI at 2nd year post-op period
Weight at 3rd year post-op period
BMI at 3rd year post-op period

Pre-operative weight loss:

On initial consultation, patients who met NIH criteria for surgical intervention were evaluated by an attending physician who obtained a full history and performed a thorough physical examination. Emphasis was placed on dietary intake and exercise regimen. Their responses were evaluated and patients were advised to improve their diet and/or exercise regimen accordingly. Patient weight was recorded at this time. In the weeks before surgery, patients received a psychiatric and dietetic evaluation to determine surgical candidacy. When all requirements were met, patients were asked to return to

clinic for pre-operative workup. Patient weight was again recorded at this interval. The last weight measurement was acquired at the one year post surgical intervention.

We calculated BMI and excess body weight at each interval. We then performed a multiple regression analyses and one-way ANOVA comparing body mass index loss before surgery to percent body mass index loss at one year post surgery.

Weight loss program:

During initial consult, a full history of weight loss attempts including methods used and resultant weight loss/gain was recorded. If patients had accurate documentation of weight loss attempts, the data was entered in a prospective database. A least squares analysis was performed to compare the different programs with each other. We then compared physician weight loss to the rest of the programs combined.

In addition, a linear regression analysis was performed to compare maximum weight loss to weight at the one-year post intervention interval.

Clinic attendance:

To evaluate the association between post-operative clinic attendance and weight loss/maintenance, patient medical charts were reviewed and dates of clinic attendance recorded. Patients are strongly advised to return to clinic at the 2, 6, 12, 24, and 36 month postoperative intervals. During these visits, patients are fully evaluated and weight is recorded.

Patients who missed clinic appointments were contacted by telephone and asked to participate in this study. After verbal informed consent was obtained from all

participants, a scripted questionnaire was used to interview them (Appendix A). This questionnaire inquired about patient compliance to dietary and lifestyle modifications and current weight. In addition, it asked about the primary deterrent to attending clinic and status of calcium and vitamin B12 supplementation. A t-test analysis was performed comparing patient weight loss between those who attended clinic at the 1, 2, and 3 year postoperative period to those who had not.

We invited patients with poor attendance to return to clinic whether or not they had insurance coverage. The importance of a proper diet and exercise regimen was impressed upon those who did not comply with recommendations.

Statistical Considerations:

Dr. Bell performed 404 laparoscopic gastric bypass procedures at Yale-New Haven Hospital in the period in question. All patients were included in this study unless they declined for participation. A series of statistical tests including t-test, chi-squared, least squares, ANOVA, etc. were used to analyze the data. Dr. James Dziura, statistician at the Yale General Clinical Research Center, conducted the statistical analysis using SPSS (SPSS v. 15, Chicago, IL) and SAS software (SAS 9.1, SAS institute, Cary, NC).

Results

Substudy 1: Preoperative Weight Loss:

A total of 404 laparoscopic Roux-en-y gastric bypass procedures were screened for participation in this study. Of these 404, 256 had one-year post operative data and were included in the study. Table 1 shows patient demographics.

Table 1. Preoperative weight loss demographics

Total participants	256
Age	17-64
BMI	36.1-90.5, mean 51.4 kg/m^2
BMI Loss at 1 year	62%
Excess Weight Loss at 1 year	34.5%

Patients were grouped according to pre-operative weight change as a surrogate marker of adherence to physician recommendations regarding their diet and exercise regimen. Table 2 shows the change in body mass index (BMI) between the two groups at different intervals. The category "Pre-op ΔBMI" calculated the change between initial consultation and pre-operative BMI (used to group subjects). "Post-op ΔBMI" calculated the change in BMI between pre-operative BMI and one-year post intervention BMI.

Table 2. BMI change between patients who gained or had no change in weight and those who lost weight.

	Weight Loss	Weight Gain/no change
Subjects	125	131
Pre-op ΔBMI	M -1.7%, sd 2.8	M 1.2%, sd 1.2
Post-op ΔBMI	M -34.6%, sd 8	M -34.4, sd 7.6

An ANOVA analysis, $F(1, 254) = .03$, showed that pre-operative weight loss was not associated with improved outcome at the one year post-operative period. Accordingly, a multiple regression analysis, $F(1, 254) = .09$, showed no correlation between pre-operative weight change and one year results.

Substudy 2: Weight loss program:

384 patients had documentation of dieting history. Most patients made multiple attempts to lose weight with variable methods and mixed results. For the sake of comparing programs to each other, the method which led to the greatest percentage weight loss for each patient was used. Patients had similar BMI within each category.

Table 3. Mean, standard error, range (minimum-maximum) in pounds between different weight loss programs.

Method	Subjects	Mean	SE	Min	Max
Physician	33	49.4	29.3	2	138
Diet pills	48	53.3	32.5	7	150
Jenny Craig®	14	55.4	25.3	20	120
Calorie Diet	53	55.8	29.1	7	150
Nutri-system®	21	50.8	26.5	20	120
Slimfast®	21	62.2	21.2	15	100
Atkins®	34	39.9	17.3	11	80
Weight Watchers®	108	35.9	23.7	5	150
Dietician	33	43.8	25	7	120
Other	19	47.5	23.9	20	100

As can be seen from Table 3, Weight Watchers® was the method that provided most patients (108) with their greatest weight loss. Despite this, mean weight loss and analysis of spread appear to be similar between all programs.

A least squares analysis (Table 4) shows that physician-monitored weight loss does not confer an advantage over popular commercial programs. In addition, there is no statistically significant difference between physician-monitored weight loss versus all other programs combined (p=.49).

Table 4. Least squares analysis. Comparison between physician monitored weight loss and other methods.

	Adjusted P value
Diet pills	0.99
Jenny Craig	0.99
Low calorie diet	0.98
Nutri-system	0.99
Slimfast	0.76
Atkins	0.88
Weight Watchers®	0.21
Dietician	0.99
Other	0.99
All	0.49

A linear regression analysis was then performed to identify if a correlation exists between maximum pre-operative weight loss and post-operative success. Table 5 shows Pearson and Spearman correlation coefficients, which reveal that maximum pre-operative weight loss does not predict outcome at the one, two, and three year post-operative periods. Figures 1, 2, and 3 show scatter plots depicting the random association between maximum weight loss achieved and percentage excess body weight loss.

Table 5. Pearson and Spearman correlation coefficients.

	Pearson	Spearman
Year 1	-0.008	0.009
Year 2	-0.042	-0.017
Year 3	-0.117	-0.122

Figure 1 Scatter plot depicting maximum weight loss versus percent excess body weight loss at the one-year post operative period.

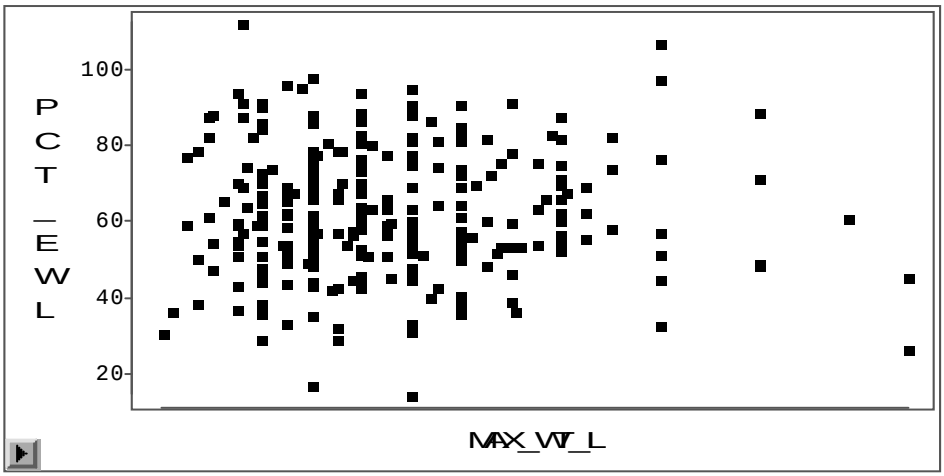


Figure 2 Scatter plot depicting maximum weight loss versus percent excess body weight loss at the two-year post operative period.

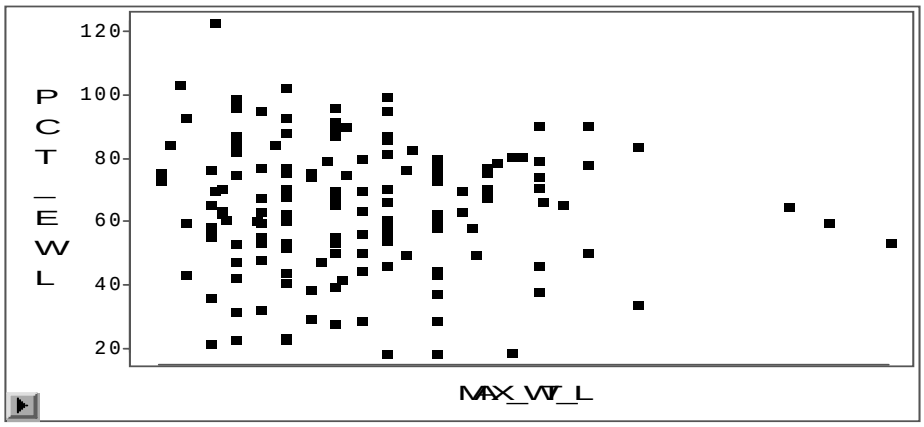
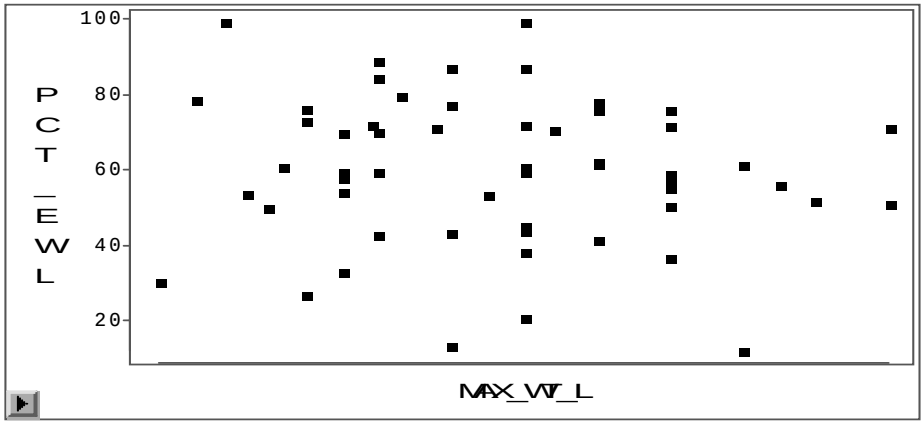


Figure 3 Scatter plot depicting maximum weight loss versus percent excess body weight loss at the three-year post operative period.



Clinic attendance:

There were 283, 157, and 56 eligible subjects at the one, two, and three year follow-up intervals respectively. Patients who attended clinic were placed in the control group while those who did not were placed in the experimental arm. Four patients declined participation: two did not want to state a reason, one was unhappy with staff, and the last subject was unsatisfied with surgical outcome. Table 6 shows patient demographics and Table 7 shows patient comorbidities at the three respective yearly intervals.

Table 6. Patient demographics by percentage for patients who attended and those who were absent to clinic at years one, two and three.

	Year 1		Year 2		Year 3	
	Clinic	No clinic	Clinic	No clinic	Clinic	No clinic
% Male	20	18	23	9	17	19
% Female	80	82	77	81	83	81
% Caucasian	95	88	79	77	83	84
% African A.	3	12	13	16	8	16
% Hispanic	1	0	7	5	8	0
% Other	1	0	1	1	1	0

Table 7. Patient comorbidities by percentages for subjects who attended clinic and those who did not at years one, two, and three.

	Year 1		Year 2		Year 3	
	Clinic	No clinic	Clinic	No clinic	Clinic	No clinic
HTN	52	58	49	55	29	41
DJD	54	35	56	52	71	56
Dyslipidemia	30	29	37	30	29	21
Diabetes Mellitus	31	35	26	27	25	16
Sleep Apnea	28	18	31	34	25	16

As can be seen in Table 6, the distribution of sex and racial backgrounds are indistinguishable between patients who attended clinic and those who did not at yearly intervals. In addition, similar proportions of male/female subjects and racial backgrounds were observed between the three time intervals. To further characterize the groups and avoid bias, patient comorbidities were evaluated. Table 7 shows that patients were evenly distributed between the experimental and control groups at all years with respect

to comorbidities. Tables 6 and 7 are reassuring in that these demographic measures are evenly spread, decreasing potential confounding effects.

A t-test analysis showed no statistically significant difference in weight loss at the one and two year post-operative periods between patients who attended clinic and those who did not (Table 8). The average percent excess weight loss was in the mid 60's which is on par with studies performed at the hands of established and proficient surgeons. Of importance, statistical significance was reached at year three. It can also be noted that there was a significant drop in subjects during this time period which decreases the power of the tool thereby clouding statistical interpretation.

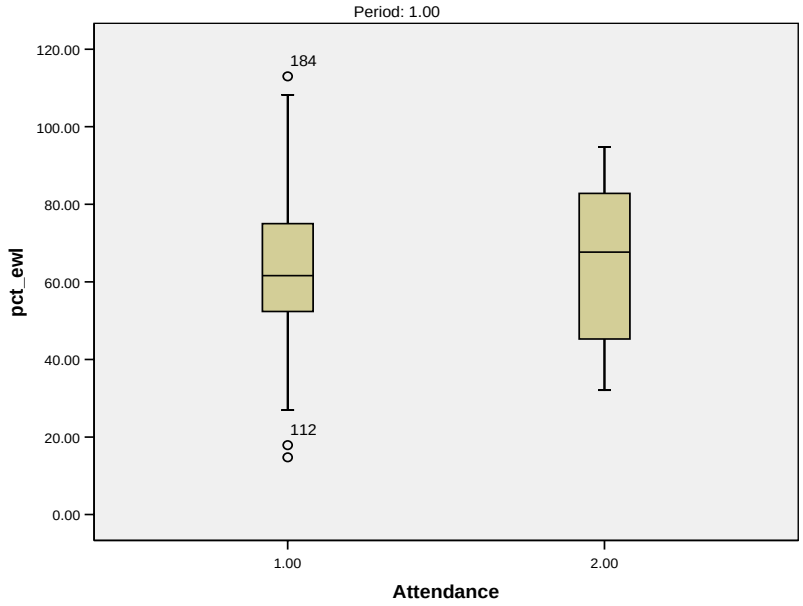
Table 8. Weight loss between patients who attended clinic and those who did not at the one, two, and three year intervals.

	Year 1		Year 2		Year 3	
	Attended	Absent	Attended	Absent	Attended	Absent
Subjects	266	17	113	44	24	32
Mean %EWL	63.18	65.36	65.49	63.29	73.3	51.15
SD	16.32	19.86	20.2	19.24	13.62	18.27
P value	0.6		0.53		<.05	

EWL= excess weight loss, SD= standard deviation

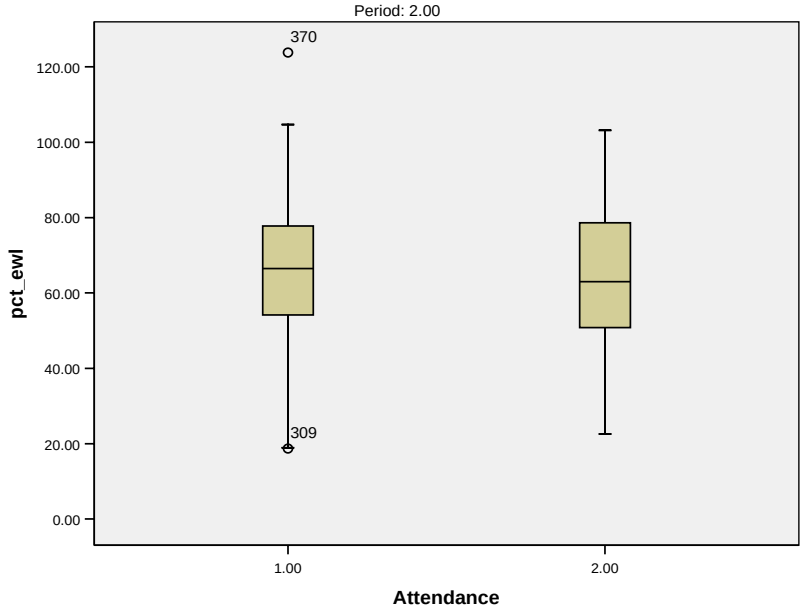
Figures 4, 5, and 6 show boxplots depicting graphically the spread and skewness of the data points at the three yearly intervals. As can be seen, there is notable spread of the data points, but they are centered around similar means except at the third year interval. There are a few outliers which did not seem to affect skewness as evidenced by similar whisker lengths.

Figure 4. Boxplot depicting weight loss at the one-year post-surgical period for patients who attended clinic and those who did not.



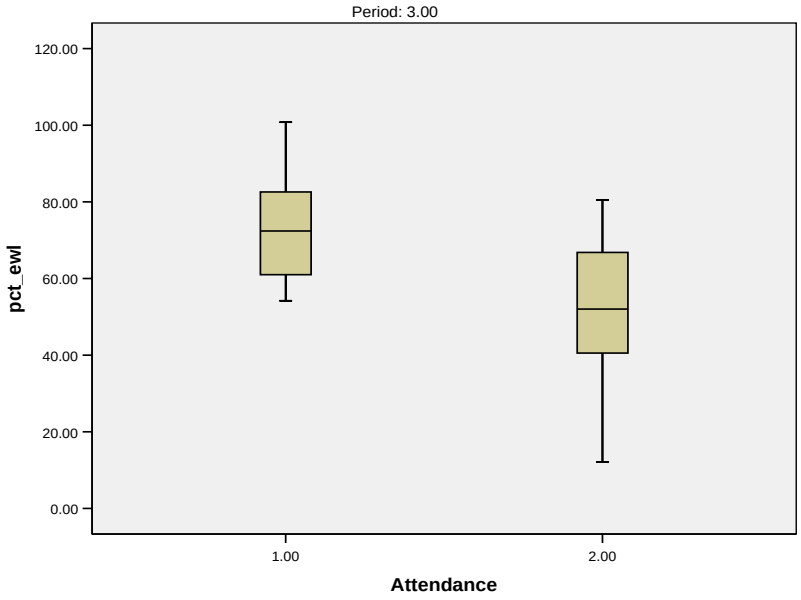
pct_ewl= percent excess weight loss, 1= subjects that attended clinic, 2=patients who did not attend clinic. Open circles represent outliers.

Figure 5. Boxplot depicting weight loss at the two-year post-surgical period for patients who attended clinic and those who did not.



pct_ewl= percent excess weight loss, 1= subjects that attended clinic, 2=patients who did not attend clinic. Open circles represent outliers.

Figure 6. Boxplot depicting weight loss at the three-year post-surgical period for patients who attended clinic and those who did not.



pct_ewl= percent excess weight loss, 1= subjects that attended clinic, 2=patients who did not attend clinic. Open circles represent outliers.

Discussion:

The negative ramifications of the global obesity epidemic are numerous and well-documented. These effects are profound for the provision of health care and portend an emerging public health crisis. At this point, gastric bypass surgery has proven to be the most effective means of combating the epidemic among those who have reached the stage of morbid obesity, as these individuals have been rendered impotent to affect their own aid.

Insurance coverage for weight reduction surgery varies greatly. Despite clear NIH guidelines for patient selection, insurance companies continue to impose countless additional criteria in an effort which, it would seem, deliberately aims to reduce the incidence of surgical intervention. In addition, anecdotal reports claim that pre-authorization processing times and denials have increased substantially. All this is staged before a backdrop of already decreased and denied reimbursements by third party payers.

The additional requirements of insurance companies claim to increase the success of surgical intervention by measuring compliance indirectly, but studies to examine such a correlation have not been performed. Such a requirement is obviated by documentation of failed dietary attempts for a period ranging from six months to several years. Studies have shown incontrovertibly that gastric bypass is by far the most successful method in producing reliable and sustainable weight reduction in the morbidly obese. To make matters worse, some insurance companies do not reimburse patients for attending dietary counseling and/or psychiatric evaluation which are necessary requirements for candidacy.

Morbid obesity causes significant and ongoing suffering in patients. Not only are they affected medically, but socially and economically as well. Although patients have

recently been empowered to seek professional attention, they are hindered by past failures with fad diets, dietary consults, and pharmaceuticals, leading them to be reluctant to ask for bariatric surgery consultation. The extraneous requirements of insurance companies, including prolonged processing times and the likelihood of denial, serve to further reinforce the sense of helplessness experienced by patients in this high-risk group.

The results of this study show that previous weight loss attempts are not associated with an improved outcome post Roux-en-y gastric bypass. In fact, there is a haphazard correlation between maximum weight loss attempts and success post surgical intervention (figures 1-3). Insurance companies deny claims to patients who do not have a verifiable dieting history. Based on the results of this study, it can be postulated that once clinical obesity is reached, these attempts are irrelevant to long-term maintenance of weight reduction.

Many third-party payers require a six-month physician-monitored weight loss plan before eligibility can be met. Although this is necessitated, the parameters of what qualifies as a physician-monitored program are not clearly defined. Although some physicians employ dieticians, this is atypical of offices throughout the United States. A comparison between physician-monitored weight loss programs and commercially available ones reveals that patients tend to fare similarly with regard to weight loss. Additionally, these patients have shown no significant post-operative advantage at the one-year period.

As previously stated, many insurance companies require that patients have a significant period of pre-operative dieting as a way of measuring motivation. Due to the fact that long-term success post Roux-en-y gastric bypass is associated with lifestyle

modifications, it would seem rational, following this logic, to use motivation as a way of predicting outcome. However, this is a shortsighted hypothesis that does not take into account the chronic nature of obesity, fluctuating adherence to diet plans, and the unpredictable motivating effects of the procedure itself. In an attempt to characterize this possible interaction, patient compliance was measured indirectly in the first substudy. At initial consultation, patients were asked to improve dietary intake and exercise regimen. We used weight reduction during this interval as a measure of patient compliance. As can be seen from the results, adherence to physician recommendations regarding lifestyle modifications had no association with long-term weight loss. Therefore, it would appear that preoperative weight loss is not an effective way of predicting outcome and should not be used to stratify patients for candidacy.

Clinic attendance post surgery was not associated with improved outcomes. Despite the fact that clinic serves to reinforce positive lifestyle changes while providing a non-judgmental environment for patients to seek support, patients who did not attend clinic fared as well as those who did attend clinic with regard to weight loss at the one and two-year post operative period. Although patients from both arms of the study are evenly distributed in terms of biographical and anthropomorphic variables, causality cannot be ascertained. For example, patients might not be attending clinic because they are not losing weight. Conversely, patients who are attending clinic, might be doing so because they have deemed the procedure a success. In other words, we cannot predict the directionality of correlation between clinic attendance and weight loss. Although these flaws are inherent in observational studies, a randomized control trial would be necessary to examine the effects of clinic attendance on weight loss post surgical intervention. This

however, would be unethical because patients cannot be randomized not to attend clinic. Thus, despite multiple flaws in methodology and the fact that causality cannot be fully ascertained, this study is the best tool available.

In spite of the aforementioned flaws in the clinic attendance study, much can still be learned. In this study, valuable evidence for the rationale for non-attendance was gleaned. This evidence included factors such as lack of time, disappointment with results, reliance on primary care follow-up, and the absence of insurance coverage. Patients who did not receive care from primary care physicians did not receive proper care necessary post gastric bypass, which includes evaluation for possible ulcers, micro- and macronutrient deficiencies, and electrolyte imbalances. In addition, many patients who deemed the procedure a failure ceased vitamin B12 and calcium supplementation. Their rationale was that because the procedure was not a success, they did not have to comply with medical recommendations. Despite proper pre-operative education, such thinking is understandable considering the complexity of the procedure.

This study has elucidated many factors that influence the success of those who have undergone bariatric surgery. Most importantly, this study has demonstrated that eligibility for this procedure would benefit from significant modification. Further research should be conducted to examine the effects of prolonging surgical intervention while assessing patient motivation and pursuing more conservative treatment options. In addition, a cost analysis should be performed to analyze the effects of prolonging surgical intervention while possibly decreasing patient functionality secondary to worsening comorbidities.

Appendix A

Hello,

May I speak to _____.

My name is Alain Ramirez and I am calling from Dr. Bell's office. The purpose of this phone call is two-fold. One is to make sure that you are doing well overall. Secondly, we are conducting a research study at Yale looking at the outcome of your gastric bypass operation with Dr. Bell.

All the information to be obtained will be held confidential and will not affect your future treatment. You may choose not to answer any of the questions and can stop the interview any time if you feel uncomfortable. Do I have your permission to ask a few questions?

Questions:

1. Do you believe you have attended all of your follow-up appointments?
   If not, then Why?

   If patient gives a vague reason then he/she will be prompted to select from the following reasons:
   a. unsatisfied with outcome
   b. travel inconvenience
   c. conflict with work
   d. satisfied with outcome and do not want to continue attending clinic
   e. was not aware of appointment
   f. unsatisfied with surgeon/staff.

   If patients answers:
   A. Then, why?
   B. How far is clinic from home?
   C. Ask patient whether their primary care physician is providing care….Aware of dietary restrictions and possible complications?
   D. Same as C
   F. Why?

2. What is your current weight? (is weight current)
3. What is your dietary regimen? Ask patient to describe.
4. Are you exercising? Ask patient to describe.
5. Are you taking supplements: calcium, multivitamin, vitamin B12?
6. Are you being followed by your primary care physician?

Thank you for answering my questions.

Do you have any questions?

If you would like to return to clinic we would be glad to make an appointment. Please call our office at your earliest convenience.

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