

TABLE OF CONTENTS

Page

<u>List of Attachments</u>	2
<u>Introduction and Background</u>	3
<i>Garren Gastric Bubble (P840025)</i>	4
<i>Lap-Band® Adjustable Gastric Banding System (P000008)</i>	5
<i>Revised Indication for the Lap-Band® Adjustable Gastric Banding System (P000008/S017)</i>	6
<i>Realize® Adjustable Gastric Band (P070009)</i>	7
<i>Survey on Patient Risk Tolerance for Devices to Treat Obesity</i>	8
<u>Overview of Obesity</u>	9
<i>Body mass index and other measures of obesity</i>	9
<i>Measures of weight loss</i>	10
<i>Predictors for co-morbidities due to obesity</i>	10
I. <u>Overview of obesity associated morbidity and mortality</u>	11
<i>Effect of weight loss on morbidity and mortality</i>	12
<i>Effect of exercise on morbidity and mortality</i>	14
II. <u>Obese population without metabolic abnormalities</u>	14
III. <u>Role of obesity in diabetes</u>	15
<i>Effect of weight loss on diabetes</i>	15
IV. <u>Role of obesity in dyslipidemia</u>	16
<i>Effect of weight loss on dyslipidemia</i>	17
V. <u>Role of obesity in hypertension</u>	17
<i>Effect of weight loss on hypertension</i>	17
VI. <u>Role of obesity in coronary heart disease</u>	18
<i>Effect of weight loss on coronary heart disease</i>	19
VII. <u>Role of obesity on quality of life</u>	20
<i>Effect of weight loss on quality of life</i>	20
VIII. <u>Durability of weight loss and behavioral predictors</u>	21
IX. <u>Effect of surgical intervention on obesity and comorbidities</u>	22
X. <u>Impact of adjustable gastric banding on diabetes, hypertension, and dyslipidemia</u>	23
XI. <u>Effect of weight cycling</u>	24
<u>Choice of Control Group Treatment</u>	25
XII. <u>Sham as control treatment</u>	25
XIII. <u>Use of an approved obesity device or established procedure as control treatment</u>	26
XIV. <u>Diet and exercise as control treatment</u>	26
XV. <u>Performance goal in a single arm study</u>	28
<u>Benefit Risk Assessment of Devices</u>	29
XVI. <u>Proposal for systematically assessing expected and unexpected events</u>	29
XVII. <u>Proposal for systematically assessing device risk levels</u>	30
XVIII. <u>Proposed risk-based effectiveness targets</u>	33
XIX. <u>Items for consideration</u>	34
XX. <u>Implementation of the framework</u>	35
<u>Bibliography</u>	36

ATTACHMENTS

Summary of Safety and Effectiveness (SSED) for Garren Gastric Bubble	Attachment 1
Summary of Safety and Effectiveness (SSED) for Lap-Band®	Attachment 2
FDA Executive Summary for Lap-Band® Lower BMI Indication ($\geq 30 \text{ kg/m}^2$)	Attachment 3
Summary of Safety and Effectiveness (SSED) for Realize® Band	Attachment 4
Post-Approval Update for Lap-Band® and Realize® devices	Attachment 5
Survey on Patient Risk Tolerance for Devices to Treat Obesity	Attachment 6
Literature Review on the Impact of Adjustable Gastric Banding on Comorbidities	Attachment 7

Introduction and Background

Over the past few years the growing body of medical literature has identified obesity and its associated metabolic and cardiovascular comorbidities as one of the major public health problems facing our nation. The primary treatments for obesity have ranged from diet and exercise, with and without counseling and behavior modification, to prescription drugs and surgical procedures. The use of medical devices has also played a role in the treatment of obesity since the early 1980s.

The Center for Device and Radiological Health (CDRH) in the Food and Drug Administration (FDA) has responsibility for the review and approval of medical devices, including those for the treatment of obesity. CDRH is also responsible for the inspection of device manufacturing facilities and the overseeing of post-marketing issues associated with medical devices. Since 1985, FDA has only approved three medical devices for the treatment of obesity despite a variety of innovative initiatives in this field by the medical device community. Of the three medical devices approved, all through the Class III premarket approval (PMA) process, only two remain on the market today: Allergan Lap-Band® Gastric Banding System and Realize® Gastric Band. The PMA for the Garren-Edwards Gastric Bubble was voluntarily withdrawn from the market in 1992.

The regulatory process for medical devices requires that various levels of information be available at the major milestones associated with device development, clinical study (feasibility and pivotal), and marketing. Limited safety and effectiveness information may be available from a feasibility study as a manufacturer moves towards a pivotal study. While this information can be used to make an initial assessment on the risks associated with the device, additional data are gained during the pivotal study that may alter or further confirm the risk profile. The pivotal study information is then considered during the assessment of the device for marketing. Often, follow-up of the study cohort continues past the point of marketing, and safety and effectiveness data continue to be collected on these individuals as part of a post-market evaluation. For some devices, there may also be additional post-market data generated from a formal post-approval study, from collection of data from use of the device in the general population (such as a registry), or from additional clinical studies. Experience has shown that risks and benefits of a device may differ in a clinical study in comparison to when the device is being used by a wider range of physicians in a non-study setting.

As data are generated and collected through the life cycle of a device, the benefit-risk profile may change. Likewise, as FDA evaluates medical devices from both the pre-market and post-market sides, safety and effectiveness information is gathered and knowledge obtained that may impact the decision making on future device applications for a given device type in a specific patient population.

Garren Gastric Bubble (P840025)

The first obesity device approved by the FDA, on September 17, 1985, was an intragastric balloon called the Garren Gastric Bubble. The device, which later became known as the Garren-Edwards Gastric Bubble, was a cylinder-shaped elastomeric polyurethane balloon with a hollow central channel and a self-sealing valve located at one end through which a removable air insufflation tube could be attached. The balloon was inserted into the stomach via an orogastric tube and then inflated with 200 to 220 cubic centimeters of air resulting in a balloon of 3 inches long and 1.75 inches in diameter with the hollow central core of 0.75 inches in diameter through which fluid and gas could pass. The device moved freely in the stomach. The device was to be removed after 4 months.

Clinical studies were conducted on 78 implanted patients who had previously failed diet and behavior modification therapy. After 4 months of uninterrupted use, 50 patients had a mean accumulated weight loss of 33.8 pounds per patient. Adverse events included mild gastric erosions and/or ulcers and a 6-10 % balloon deflation rate which resulted in one case of bowel obstruction and one case of partial gastric outlet obstruction. For more details on this study, the Summary of Safety and Effectiveness Data for this device can be found in Attachment 1.

The PMA for the Garren Gastric Bubble was presented to the Gastroenterology-Urology (GU) advisory panel on December 11, 1984. The panel recommended approval of the device with the condition that the 1 year follow-up data demonstrate the continued safety and effectiveness of the device. They also recommended that the indications for use be changed from a “treatment of morbid obesity” to “the reduction of weight in combination with diet and behavior modification therapy”. The final indication for use which was approved by the FDA was as a “temporary adjunct to diet and behavior modification therapy to reduce the weight of those individuals who have failed to reduce their weight with those measures alone and who are at least 20 percent above ideal weight (defined in the 1983 Metropolitan Life Tables) and where the expected benefits are greater than the risks of the procedure.”

Within the first year of marketing of the Garren Gastric Bubble, significant problems with spontaneous deflations of the device were being reported. FDA received numerous Medical Device Reports and letters regarding this problem which raised concerns about the safety and effectiveness of the device. The firm (American Edwards Laboratories) worked to resolve the problems by making device and labeling changes, as well as enhanced physician training. They also chose to restrict the implantation duration of the device to 3 months and to limit the use of the device to only morbidly obese patients. FDA also requested in 1987, that post-marketing safety and effectiveness data be provided to FDA on a minimum of 400 patients who had been implanted with the device for at least 3 months. FDA was particularly concerned about the rate and severity of complications with the device.

After publication of a number of randomized, double blind sham controlled clinical trials which concluded that the Garren Gastric Bubble was of no added benefit compared to sham insertion when combined with standard weight loss programs, the sales of the device decreased. By 1988 the device was no longer being sold by American Edwards Laboratories. In 1992 the PMA for the Garren Gastric Bubble was voluntarily withdrawn by the owner.

Lap-Band® Adjustable Gastric Banding System (P000008)

The Lap-Band® (Adjustable Gastric Banding System) was the next obesity device to be approved by the FDA. It was approved on June 5, 2001. Based on the concerns raised with the Garren Gastric Bubble, the FDA focused initially on the use of this surgically implanted restrictive device in the higher Body Mass Index (BMI) morbidly obese patients.

The device is an inflatable silicone elastomer band which is surgically placed (either laparoscopically or with an open procedure) around the stomach to create a small gastric pouch with a smaller stoma into the remainder of the stomach. The inflatable Lap-Band® is attached to kink-resistant silicone tubing which is then connected to an access port that is usually placed in or on the right rectus muscle. Postoperatively, the surgeon is able to adjust the inner diameter of the Lap-Band®, and thus, the size of the stoma below the small gastric pouch, by percutaneously injecting or removing sterile saline through the access port. This restrictive device is intended to induce weight loss by limiting the food consumption of the patient and inducing early satiety.

The Lap-Band® was initially approved with the indication for the “use in weight reduction for severely obese patients with a Body Mass Index (BMI) of at least 40 kg/m² or a BMI of at least 35 kg/m² with one or more severe comorbid conditions, or those who are 100 lbs. or more over their estimated ideal weight according to the 1983 Metropolitan Life Insurance Tables (use the midpoint for medium frame).” It was further indicated for “use only in severely obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs. Patients who elect to have this surgery must make the commitment to accept significant changes in their eating habits for the rest of their lives.”

Two hundred and ninety-nine subjects were enrolled into the US study, with 178 of the patients evaluated after three years of device implantation. Patients reaching the 3 year time frame lost on average 36% of their excess weight with 62% of these patients achieving at least 25% EWL. Regarding Adverse events (AE), 89% of patients enrolled reported at least one adverse event with 34% reported as being severe. Nausea and vomiting were the most common AEs, with gastroesophageal reflux followed by band slippage/pouch dilatation as the next most frequently seen. During the GU Advisory panel meeting held on June 19, 2000 (when only 2 year implantation data was available), the occurrence of esophageal dilatation raised concerns and the panel voted to disapprove the device until 3 year data could be provided. Additional information about this study can be found in the Summary of Safety and Effectiveness Data for this device, which is Attachment 2.

When the PMA was approved in June of 2001, a post-approval study (PAS) requirement was one of the approval conditions. The PAS consisted of collection of long-term safety and effectiveness data by the continued follow-up of subjects enrolled in the premarket studies. Based on the 752 patients enrolled in the original study, including 152 who enrolled in the PAS, FDA estimated an explant rate of 6.5 per 100 person-years. In response, the FDA requested that the sponsor: (1) develop a new PAS, with emphasis on the explant rate, and (2) change their product label to reflect the above noted estimated explant rate. The Sponsor is now conducting HERO, a prospective, international, multi-center study testing the hypothesis that the explant rate over a 5-year period will be no greater than 39.3%. Subjects are currently being enrolled and starting follow-up. A detailed postmarket update summary of this post-approval study can be found in Attachment 5.

Revised Indication for the Lap-Band® Adjustable Gastric Banding System (P000008/S017)

On February 16, 2011, FDA approved a revised indication for use for the Lap-Band® to include a lower BMI indication: BMI of at least 40 kg/m² “or a BMI of at least 30 kg/m² with one or more obesity related comorbid conditions.”

The expanded indication was supported by a prospective, multicenter non-randomized study where one hundred forty-nine patients were implanted with the device with 145 patients completing 12 months of follow-up. Eighty percent (80.5%) of patients achieved an excess weight loss of 30% or greater at one year of implantation. Sixty-six percent (65.8%) of all implanted patients lost at least 50% of their excess weight. The determination of excess weight for this study was based on an “ideal” weight of a BMI of 25 kg/m². This correlated to 75.2% of patients (compared to 80.5%) losing 30% EWL when the Met Life tables were used. The mean excess weight decreased 64.5% from baseline to 12 months. At two years, 85.9% of the 128 evaluable patients achieved at least 30% EWL. The mean excess weight decreased 70.4% from baseline to 24 months for the 128 evaluable patients. Regarding adverse events, 87.9 % of patients experience an adverse event; 70.5% experience a device-related AE. The most common AEs were nausea and vomiting; dysphagia and gastroesophageal reflux. The majority were mild in severity with only 2.3% being severe events. One band erosion was reported; two reports of esophageal dilatation; 7 re-operations in year one (4 device removals) and 4 re-operations in year two. An FDA Executive summary, part of 12/3/2010 GU panel package, containing the safety and effectiveness data supporting this PMA supplement, can be found in Attachment 3.

The GU Advisory panel reviewed this PMA supplement on 12/3/2010 and recommended in a vote of 8 to 2 that the benefits of the device for its stated use outweighed the risks. The sponsor agreed to conduct two post approval studies to evaluate the long-term effectiveness and the incidence of adverse events. The first study (Premarket Cohort) continues to follow patients enrolled in the investigational device exemption (IDE) pivotal study. The second study plans to enroll patients from the Bariatric Outcomes Longitudinal Database (BOLD) registry database. A detailed postmarket update summary of this post-approval study can be found in Attachment 5.

Realize® Adjustable Gastric Band (P070009)

A second gastric band device called the Realize® Gastric Band (also known as the Swedish Adjustable Gastric Band) was approved on September 28, 2007. The Realize® Band is a laparoscopically implanted device which is similar to the Allergan Lap-Band® in that it consists of three components: the reinforcing band with balloon, kink-resistant tubing, and the injection port. It is also implanted around the upper stomach to form an artificial stoma. This placement creates a small pouch in the proximal stomach and a larger pouch in the distal stomach. After the band is in place, the patient cannot consume large quantities of food and weight reduction ensues. It is customized by increasing or decreasing the amount of fluid in the balloon component by way of the injection port. The reinforcing band provides structural support for the balloon, which provides 360 degree coverage around the stomach. One end of the tubing is pre-attached to the balloon and the other end must be connected to the Injection Port during surgery.

The Realize® Adjustable Gastric Band is “intended for use in weight reduction for morbidly obese patients and is indicated for individuals with a Body Mass Index (BMI) of at least 40 kg/m², or a BMI of at least 35 kg/m² with one or more co-morbid conditions. The Band is indicated for use only in morbidly obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs.”

The clinical study to support this PMA device was a prospective, multi-center, single-arm trial in which each subject served as his or her own control. Subjects were followed for 3 years post-implantation. Two-hundred and seventy-six patients were implanted with device, with 3-year follow-up data available for 228 patients. At 36 months, the mean %EWL was 42.8% for the 228 patients. Seventy-seven percent (77.2%) of patients lost at least 25% of their excess weight. Regarding Adverse events (AE), 94.6% of patients enrolled reported at least one adverse event with 24% reported as being severe. The most commonly experienced adverse events were nausea and vomiting, constipation, gastroesophageal reflux and abdominal pain. Dysphagia was also reported in 9.4% of patients. Band slippage, pouch dilation, band erosion and port displacement were reported as “migration of the implant” in a total of 17 patients (6.2%). Esophageal dilatation was reported in 3.3% of the patients. In general, the safety and effectiveness of the Realize® band was very similar to that seen with the Lap-Band®. For more details on these studies see the Summary of Safety and Effectiveness Data in Attachment 4.

Due to the similarities between the Allergan Lap-Band® and this device (i.e., a second of a kind device), the Realize® Band PMA was not presented to the GU Advisory Panel. The recommendations from the original Lap-Band® panel meeting were applied to the Realize® Band.

The Realize® Band was approved on the condition that the sponsor conduct a post-approval study (PAS) that follows the premarket cohort and newly enrolled patients out to five years, to assess safety (nature, onset date, severity and relationship to device of adverse event) and effectiveness (changes in weight, quality of life, hemoglobin A1c and serum lipid levels) of

the device. Preliminary safety data show the device is performing at an acceptable postmarket safety level. The follow-up rate for the premarket cohort at 60 months and the newly enrolled patients at 24 months are above 90%. The 12- and 24-month %ELW were 36.6% and 40.2%, respectively. A detailed postmarket update summary of this post-approval study can be found in Attachment 5.

Survey on Patient Risk Tolerance for Devices to Treat Obesity

CDRH is also evaluating processes to incorporate patient preferences regarding treatment benefits and risks in its decision making process. In order to obtain such preferences in a systematic and scientifically valid way, CDRH has commissioned a nationally representative web-based survey to collect data on patient preferences when assessing benefits and risks of different weight reduction devices. 450 subjects with BMI greater than 30 kg/m² will be surveyed from a panel which closely represents the general US population. Approximately 100 subjects who underwent gastric bypass or banding procedures will be included among the 450 subjects to assess preferences of patients before and after having a procedure. Benefit-risk tradeoff curves will be estimated with data provided by these subjects. In addition, the preferences of those subjects who underwent gastric bypass or banding procedures will be compared with those who did not. The results of this survey will provide significant information on patient preferences, and we will ask this panel to discuss how to incorporate these preferences into the Center's decision making process. A more detailed summary of their ongoing process can be found in Attachment 6.

Overview of Obesity

Obesity and its associated conditions have reached epidemic proportions.¹ This development is particularly evident in the developed world, where the consequences include substantially increased morbidity, mortality and cost to the health care system. According to national population surveys between 1960 and 1994, the prevalence of obesity, defined by body mass index ($BMI \geq 30 \text{ kg/m}^2$) has more than doubled, from 13% to 32%.^{2,3} In the United States in 2009-2010, the prevalence of obesity was 35.5% among adult men and 35.8% among adult women, with no significant change compared with 2003-2008.⁴

Body mass index and other measures of obesity

According to the Centers for Disease Control, overweight and obesity are both labels for ranges of weight that are greater than what is generally considered healthy for a given height. For adults, overweight and obesity ranges are commonly determined by using weight and height to calculate the BMI. BMI is used because, for most people, it correlates with their amount of body fat. BMI is calculated from measurement of height and weight and is reported as kg/m^2 .

- An adult who has a BMI between 25 and 29.9 kg/m^2 is considered overweight.
- An adult who has a BMI of 30 kg/m^2 or higher is considered obese.

BMI values are also used to categorize patients into three classes of obesity:

- Class I (mild): BMI of 30.0 to 34.9 kg/m^2
- Class II (moderate): BMI of 35.0 to 39.9 kg/m^2
- Class III (severe): BMI of $\geq 40 \text{ kg/m}^2$

Although BMI correlates with the amount of body fat, BMI does not directly measure body fat. As a result, some people, such as athletes, may have a BMI that identifies them as overweight even though they do not have excess body fat. Other methods of estimating body fat and body fat distribution include measurements of skinfold thickness and waist circumference, calculation of waist-to-hip circumference ratios, and techniques such as ultrasound, computed tomography, and magnetic resonance imaging.

While different methods of measuring obesity exist, the literature most often uses BMI. Although, as noted above, BMI may not be the ideal way to define obesity in all individuals, for the population that often presents for clinical trials, it is an easy, reproducible, assessment tool to be used in general practice clinics.

Measures of weight loss

For studies relating to weight loss and obesity, the Division currently assesses and compares weight loss for devices using percent excess weight loss (%EWL). The benefit of using %EWL is that it provides a clear indicator of how much assistance a device provides a subject in achieving their ideal body weight; however, there are several issues related to using %EWL for assessing weight loss. First, in order to calculate %EWL, one must determine the ideal weight of an individual. There is no recognized standard definition of ideal weight. Common definitions for ideal weight include use of the 1983 Metropolitan life tables or a BMI of 25 kg/m². Second, for patients with relatively lower initial BMIs, losing a modest amount of weight may result in a high %EWL. This effect may be more important if a device is being tested in lower BMI patients using %EWL as an endpoint. Third, it is not clear that patients need to reach their ideal body weight to experience clinically meaningful benefits of weight loss. On the basis of these issues, it has been proposed that the Division consider an alternative assessment measure, such as percent total body weight loss (%TBL), in future obesity studies.

As panel members consider the literature regarding the assessment of weight loss, we ask them to think about which measurement provides the best indication of clinical significance, or if there are other reasons to select one measure over another for endpoints in clinical trials.

Predictors for co-morbidities due to obesity

Women with a waist circumference of more than 35 inches and men with a waist circumference of more than 40 inches may have more health risks than people with lower waist circumference because of their body fat distribution. Rexrode and colleagues⁵ studied 44,702 women aged 40 to 65 years of age who were free of prior coronary heart disease, stroke, or cancer in 1986 and found that waist circumference of 38 inches or more was associated with a relative risk of 3.06 for the development of heart disease compared to those with waist circumference less than 28 inches. The mechanism of increased metabolic risk is hypothesized to be related to the metabolically active adipose tissue found in the visceral region. Furthermore, in a study of 25 obese (130-190% of ideal body weight), and 9 non-obese women,⁶ those with predominant upper body obesity were more likely to have abnormal glucose tolerance tests and dyslipidemia compared to those with lower body obesity.

Among 27,270 men in the Health Professionals Follow-Up Study followed for 13 years, Wang and colleagues⁷ found that both overall obesity (reflected by higher BMI) and central adiposity (reflected by higher waist circumference and waist to hip ratio) predict the risk of type 2 diabetes independently. Waist circumference appeared to be a better predictor than BMI and waist to hip ratio for predicting type 2 diabetes.

Stefan and colleagues⁸ evaluated 314 subjects using total body, visceral, and subcutaneous fat based on magnetic resonance (MR) tomography and fat in the liver and skeletal muscle based on proton MR spectroscopy. An estimate of atherosclerosis was made based on the common carotid artery intima-media thickness. Insulin sensitivity

was estimated from oral glucose tolerance test results. Subjects were divided into 4 groups: normal weight (BMI < 25.0 kg/m²), overweight (BMI of 25.0-29.9 kg/m²), obese-insulin sensitive (IS) (BMI ≥ 30.0 kg/m²), and obese-insulin resistant (IR) (BMI ≥ 30.0 kg/m²).

Total body and visceral fat were higher in the overweight and obese groups compared with the normal weight group, however, no differences were observed between the obese groups. In contrast, ectopic fat in skeletal muscle and particularly the liver and the carotid artery intima-media thickness were lower and insulin sensitivity was higher in the obese-IS vs. the obese-IR group. Unexpectedly, the obese-IS group had almost identical insulin sensitivity and the intima-media thickness was not statistically different compared with the normal-weight group. The authors concluded that a metabolically benign obesity that is not accompanied by insulin resistance and early atherosclerosis exists in humans. Furthermore, ectopic fat in the liver may be more important than visceral fat in the determination of such a beneficial phenotype in obesity.

I. Overview of obesity associated morbidity and mortality

Obesity has been shown to be associated with many diseases. A substantial literature has emerged which has found that being overweight or obese are major health issues which can lead to further morbidity and mortality. As the number of associated co-morbidities continues to increase, systematic reviews and meta-analysis are important tools to summarize the findings and produce more precise estimates of risk associated with overweight and obesity. Several of the findings have demonstrated improvements in biomarkers relating to diabetes, cardiovascular disease, and cancer risk.⁹

In a systematic review and meta-analysis of 89 studies for 20 co-morbidities, Guh and colleagues¹⁰ found statistically significant associations for being overweight (BMI of 25-30 kg/m²) with the incidence of type 2 diabetes, all cancers except esophageal (female), pancreatic and prostate cancer, all cardiovascular diseases (except congestive heart failure), asthma, gallbladder disease, osteoarthritis and chronic back pain. The strongest association was noted between being overweight and the incidence of type 2 diabetes in females (relative risk = 3.92 (95% CI: 3.10–4.97)). Statistically significant associations with being obese (BMI ≥ 30 kg/m²) were found with the incidence of type 2 diabetes, all cancers except esophageal and prostate cancer, all cardiovascular diseases, asthma, gallbladder disease, osteoarthritis and chronic back pain. Obesity defined by BMI measurement was most strongly associated with the incidence of type 2 diabetes in females (relative risk = 12.41 (95% CI: 9.03–17.06))

A large collaborative analysis of almost 900,000 adults by Whitlock and colleagues¹¹ pooled data from 57 prospective observational studies was performed to evaluate the associations of BMI with overall and cause-specific mortality. The mean BMI was 25 kg/m². To limit reverse causality, the first 5 years of follow-up were excluded, leaving 66,552 deaths of known cause during a mean of 8 years of subsequent follow-up per person. In both sexes, mortality was lowest at about a BMI of 22.5–25 kg/m². Each additional 5 kg/m² higher BMI was on average associated with about 30% higher overall

mortality: 40% for vascular mortality, 60–120% for diabetic, renal, and hepatic mortality, 10% for neoplastic mortality and 20% for respiratory and for all other mortality. At a BMI of 30–35 kg/m², the median survival was reduced by 2–4 years and at 40–45 kg/m² it was reduced by 8–10 years.

The National Health and Nutrition Examination Survey (NHANES) is a survey conducted to examine a nationally representative sample of about 5,000 each year to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. Data from a sample of 13,745 US men and women who participated in NHANES between 1999 and 2004 was reviewed by Nguyen and colleagues.¹² A BMI between 18.5 and 24.9 kg/m² was categorized as normal. With increasing degrees of obesity, there was an increase in the prevalence of hypertension (18.1% for normal weight to 52.3% for BMI \geq 40 kg/m²), diabetes (2.4% for normal weight to 14.2% for BMI \geq 40 kg/m²), dyslipidemia (8.9% for normal weight to 19.0% for BMI \geq 40 kg/m²), and metabolic syndrome (13.6% for normal weight to 39.2% for BMI \geq 40 kg/m²). These trends were statistically significant with p-values < 0.01. With normal weight individuals as a reference, individuals with a BMI \geq 40 kg/m² had an adjusted odds ratio of 4.8 for hypertension, 5.1 for diabetes, 2.2 for dyslipidemia, and 2.0 for metabolic syndrome.

Thompson and colleagues¹³ developed a dynamic model of the relationship between BMI and 5 diseases: hypertension, hypercholesterolemia, type 2 diabetes mellitus, coronary heart disease, and stroke. To estimate the life time risks, the authors combined data from NHANES III for hypertension, hypercholesterolemia, and type 2 diabetes mellitus, and the Framingham Heart Study for coronary heart disease and stroke. The Framingham Heart Study which consisted of over 5,000 adult subjects studied since 1948, and other secondary sources. This model estimated (1) risks of hypertension, hypercholesterolemia, and type 2 diabetes at future ages; and (2) lifetime risks of coronary heart disease and stroke for men and women aged 35 to 64 years with a BMI of 22.5, 27.5, 32.5, and 37.5 kg/m², (non-obese, mildly, moderately, and severely obese, respectively). In this study, the risk of hypertension for moderately obese 45- to 54-year-old men was roughly 2-fold higher than for their nonobese peers (38.1% vs. 17.7%), whereas the risk of type 2 diabetes mellitus was almost 3-fold higher (8.1% vs 3.0%). Lifetime risks of coronary heart disease and stroke were similarly elevated (41.8% vs. 34.9% and 16.2% vs. 13.9%, respectively).

Effect of weight loss on morbidity and mortality

Intentional weight loss improves many of the medical complications associated with obesity. Many of these beneficial effects have a dose-dependent relationship with the amount of weight lost, and they begin after a modest weight loss of only 5% of initial body weight. In addition, weight loss can decrease the risk of developing new obesity-related diseases such as diabetes.¹ Studies from over 20 years ago showed that for obese patients with type 2 diabetes, hypertension or hyperlipidemia, modest weight reduction (approximately 10% or less) appeared to improve glycemic control, reduce blood pressure, and reduce cholesterol levels.¹⁴

The Look AHEAD¹⁵ (Action for Health in Diabetes) trial is a multicenter randomized clinical trial that included 5,145 individuals with type 2 diabetes and obesity. Participant eligibility included having a BMI ≥ 25 kg/m², (≥ 27 kg/m² if treated with insulin), systolic and diastolic blood pressure (systolic and diastolic blood pressure) $< 160/100$ mmHg (with or without antihypertensive drugs), and triglycerides < 600 mg/dL. The average BMI was 36.0 kg/m² and the average duration of type 2 diabetes was 6.8 years. Participants were randomly assigned to intensive lifestyle intervention (ILI) or to usual care, referred to diabetes support and education (DSE).

ILI participants had a weight loss of 8.7 kg compared with 0.8 kg in the DSE group from baseline to 1 year. The magnitude of weight loss at 1 year was highly related to the improvements in blood pressure, glycemic control, and lipids, with the notable exception of low-density lipoprotein. The strongest associations between changes in weight and risk factors were seen for measures of glycemic control, and clinically significant improvements were observed with just a 2 to $< 5\%$ reduction in initial weight. Compared with weight-stable participants, those who lost 5 to $< 10\%$ of their body weight had increased odds of achieving a 0.5% point reduction in HbA1c, a 5 mmHg decrease in diastolic blood pressure, a 5 mmHg decrease in systolic blood pressure, a 5 mg/dL increase in high-density lipoprotein and a 40 mg/dL decrease in triglycerides. The odds of clinically significant improvements in most risk factors were even greater in those who lost 10-15% of their body weight.

The Look AHEAD Research Group¹⁶ also examined the effects of continued lifestyle intervention on changes in weight, fitness, and cardiovascular disease risk factors over 4 years. More than 93% of participants completed the outcome assessments at each of the 4 years. The mean maximal weight loss of 8.6% body weight for the ILI group occurred at year one, but participants in the ILI group maintained a mean weight loss of 4.7% at year 4 compared with 1.1% in the DSE group. Weight losses in the ILI group were significantly greater than in the DSE group at each year. Averaged across the 4 years, participants in the ILI group experienced greater improvements in weight, fitness, glycemic control, blood pressure, and levels of high-density lipoprotein and triglycerides than those in the DSE group.

For several risk factors, the differences between the ILI and DSE groups were most apparent at year one. Initial differences between groups for diastolic blood pressure and triglycerides levels were not maintained at year 4. The ILI and the DSE groups had reductions in low-density lipoprotein levels at years 1 and 2 with no differences between the 2 groups. However, by years 3 and 4, DSE participants experienced greater decreases in low-density lipoprotein levels than ILI participants, resulting from their greater use of lipid-lowering medications.

In contrast, another systematic review¹⁷ of 16 studies that involved 5,698 subjects, found that dietary and lifestyle therapy provided 1.7–4.9 kg weight loss after 2–4 years from baseline weight. The meta-analysis showed no consistent association between weight loss of $\geq 5\%$ baseline weight and improvements in cardiovascular risk except in those with cardiovascular risk factors such as impaired glucose tolerance, type 2 diabetes, or

hypertension. The obesity paradox in which overweight and obese people with established cardiovascular disease, including hypertension, heart failure, coronary heart disease, and peripheral arterial disease have a better prognosis compared with non-overweight and non-obese patients was also described by Lavie and colleagues.¹⁸

Effect of exercise on morbidity and mortality

There have also been reports of reduced rates of coronary heart disease, hypertension, and non-insulin dependent diabetes mellitus in obese people who perform regular physical activity, even if no weight is lost.¹⁹ Exercise, with or without weight loss, has been shown to improve plasma lipoprotein status. Similarly, large cross-sectional studies demonstrate reduction in blood pressure in those who regularly exercise, compared with sedentary persons, irrespective of weight.²⁰ It has been confirmed that overweight individuals decrease their risk of premature death by being physically active, even if their weight does not change.²¹

II. Obese population without metabolic abnormalities

Despite the well established association of obesity and comorbidities, a segment of the overweight and obese population appears to be metabolically normal (0 or 1 metabolic abnormalities). In an analysis of 5440 NHANES participants between 1999 and 2004, Wildman and colleagues provided an estimate of the prevalence of cardiometabolic abnormalities that included: elevated blood pressure, elevated levels of triglycerides, fasting plasma glucose, and C-reactive protein; elevated homeostasis model assessment of insulin resistance value, and low high-density lipoprotein levels. Among the overall US population 20 years and older, 17.9% are overweight yet metabolically healthy and 9.7% are obese yet metabolically healthy, whereas 8.1% were normal weight but metabolically abnormal (≥ 2 metabolic abnormalities).²²

In a study of the Pima Indians of Arizona,²³ even lean individuals, with a BMI of less than 24 kg/m², have a higher risk for developing type 2 diabetes than the general US population. Individuals without a familial history of type 2 diabetes, when compared with other Pima Indians, have a marked reduction in the incidence of type 2 diabetes, even in those individuals with a BMI of over 40 kg/m².

In an Italian study,²⁴ a population of obese subjects from Rome and surrounding areas were evaluated for comorbidities between 2000 and 2003. There were 681 obese subjects (514 women and 167 men), with a mean BMI of 40.2 kg/m² and a history of obesity for 20.5 years. The prevalence of subjects that were metabolically normal was 27.5%. No statistical difference for the prevalence of impaired fasting glucose, glucose intolerance, high triglycerides, high total cholesterol, low-density lipoprotein, and high-density lipoprotein among BMI categories (from mild to extremely severe) was found. Obese subjects with a BMI > 50 kg/m² showed a higher prevalence of high blood pressure only when they were compared with the group with a BMI of 30 to 35 kg/m².

III. Role of obesity in diabetes

The marked increase in the prevalence of obesity in the past 20 years has played an important role in the 25% increase in the prevalence of diabetes. The risk of diabetes is associated with increasing BMI. In NHANES III (2005-2006), the prevalence of diabetes increased from 2% in those with a BMI of 25.0 to 29.9 kg/m², to 8% with a BMI of 30 to 34.9 kg/m² and to 13% with a BMI greater than 35 kg/m².²⁵

In the Nurses' Health Study²⁶ of 114,281 registered nurses ages 30 to 55 years who did not have diagnosed diabetes mellitus, the risk of diabetes began to increase with a BMI over 22 kg/m². Weight gain since age 18 years was strongly related to risk. Compared with women with a stable weight and after adjustment for age and body mass index at age 18 years, the relative risk for type 2 diabetes among women who had a weight gain of 5.0 to 7.9 kg was 1.9. The corresponding relative risk for women who gained 8.0 to 10.9 kg was 2.7. In contrast, women who lost more than 5.0 kg reduced their risk for diabetes mellitus by 50% or more.

In another study²⁷ of 51,529 U.S. male health professionals without diabetes, 272 cases of type 2 diabetes were diagnosed over a 5 year period. Relative risks associated with different anthropometric measures were calculated controlling for age, and relative risks were calculated controlling for smoking, family history of diabetes, and age. The analysis found a strong positive association between BMI and the risk of diabetes. Men with a BMI \geq 35 kg/m² had a relative risk of 42.1 when compared with men with a BMI < 23.0 kg/m². The BMI at age 21 and absolute weight gain throughout adulthood were also significant independent risk factors for diabetes.

Effect of weight loss on diabetes

In obese patients with type 2 diabetes, weight loss significantly correlated with improvements in insulin sensitivity and glycemic control.²⁸ Type 2 diabetic patients (N = 114) were treated in a behavioral weight control program and followed up for one year. Patients (N=20+6) who lost more than 6.9 kg or had more than 5% reduction in body weight had significant improvements in HbA1c values at one year (HbA1c improvement of 0.6%) and those with a > 10% weight loss had an improvement of HbA1c of 1.6%. Patients losing less weight had no significant changes and those gaining weight had significant worsening of HbA1c (+ 0.6%).

The Diabetes Prevention Program also showed a reduction in the risk of developing diabetes with weight loss.²⁹ There were 3,234 subjects with impaired glucose tolerance who were followed for an average of 2.8 years. The mean BMI was 34.0 kg/m². Subjects were randomized to the intensive lifestyle treatment, metformin or placebo. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle intervention groups, respectively. The lifestyle intervention group reduced the incidence of diabetes by 58 percent (95% CI, 48 to 66 percent) compared with the placebo group.

Using data from the Framingham Study, Moore and colleagues³⁰ examined the effects of sustained and non-sustained weight loss on risk of developing diabetes among 618 overweight (BMI ≥ 27 kg/m²) participants over two consecutive 8 year periods. The diagnosis of incident diabetes was made on the basis of one of the following: a history of diabetes mellitus diagnosed by a physician during follow-up, treatment with insulin or oral hypoglycemic agents, or a blood glucose level of 200 mg/100 ml or more. Those who lost 8.1-15 lb during the first 8 years had a 33% reduction in diabetes risk, whereas those losing more had a 51% reduction in risk. Weight loss that was not sustained, regardless of the amount of weight lost, had little effect on diabetes risk.

In the Finnish Diabetes Prevention Study,³¹ 522 overweight subjects with a mean BMI of 31 kg/m² and impaired glucose tolerance were randomized to an intervention or a control group. Each subject in the intervention group received individualized counseling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fiber and physical activity. The mean duration of follow-up was 3.2 years.

The mean amount of weight lost between base line and the end of year one was 4.2 kg in the intervention group and 0.8 kg in the control group. Waist circumference, fasting plasma glucose concentration, plasma glucose concentration two hours after oral glucose challenge, and serum insulin concentration two hours after glucose challenge decreased significantly more among subjects in the intervention group than among those in the control group. By the end of year 2 the net weight loss was 3.5 kg in the intervention group and 0.8 kg in the control group. The cumulative incidence of diabetes after four years was 11% in the intervention group and 23% in the control group. During the trial, the risk of diabetes was reduced by 58% in the intervention group.

IV. Role of obesity in dyslipidemia

Being obese (BMI ≥ 30 kg/m²) is associated with several serum lipid abnormalities including reduced high-density lipoprotein levels, and an increased low-density lipoprotein level. This association is especially strong in persons with abdominal obesity. Data from NHANES III³² of 7933 men and 8748 women between 1988 and 1994 showed that in men there was a progressive increase in the prevalence of hypercholesterolemia (total blood cholesterol ≥ 240 mg dL) with increasing BMI. Among men, the prevalence of high blood cholesterol ranged from 13% at the lowest BMI level (<25 kg/m²) to 22% at the highest BMI level (≥ 30 kg/m²). The prevalence of high blood cholesterol increased from 13% among women at the lowest BMI level (< 25 kg/m²) to 27% to 30% among women with higher BMI levels (≥ 30 kg/m²); however, there was no consistent rise with increasing BMI above 25 kg/m².

The study also found a negative relationship of BMI and high-density lipoprotein levels. The mean high-density lipoprotein level for men with BMI < 25 kg/m² was 50 mg/dL and declined to 40 mg/dL at a BMI ≥ 30 kg/m². Among women, the age-adjusted mean high-density lipoprotein level decreased from 59 mg/dL for women with a BMI of < 25 kg/m² to 49 mg/dL for women with a BMI of ≥ 30 kg/m².

Effect of weight loss on dyslipidemia

In a meta-analysis by Dattilo and colleagues,³³ the results of 70 studies (1,295 subjects) were analyzed. On average, the mean initial weight for all subjects was 98.5 kg and the average weight loss was 16.6 kg. When the results from the studies were treated independently and pooled together, weight reduction was associated with only moderate decreases for total cholesterol (0.79 mg/dl), low-density lipoprotein (0.39 mg/dl) and triglycerides (0.66 mg/dl).

Stefanick and colleagues³⁴ studied the effects of diet and exercise on plasma lipoprotein levels in 180 postmenopausal women and 197 men over 1 year. The mean baseline BMI was 26.3 kg/m² for women and 27.0 kg/m² for men. Subjects all had low high-density lipoprotein levels (≤ 59 mg/dl in women and ≤ 44 mg/dl in men) and moderately elevated levels of low-density lipoprotein (> 125 mg/dl but < 210 mg/dl in women and > 125 mg/dl but < 190 mg/dl in men). The subjects were randomly assigned to aerobic exercise, the National Cholesterol Education Program (NCEP) Step 2 diet, diet plus exercise, or to a control group which received no intervention.

For women and men, significant weight loss occurred in both diet groups (2.8–4.2 kg) as compared with the control and exercise groups (0.5–0.6 kg), and changes in weight did not differ significantly between the diet and diet plus-exercise groups or between patients assigned to exercise only and controls. The results of the study showed that the NCEP Step 2 diet failed to reduce low-density lipoprotein levels significantly in either men or women as compared with controls (7.3 mg/dl for diet vs. 2.5 mg/dl for controls). When the diet was combined with aerobic exercise, however, the resulting reductions in low-density lipoprotein levels (14.5 mg/dl for women and 20.0 mg/dl for men) were significant.

V. Role of obesity in hypertension

Being overweight has been shown to be a major determinant of hypertension in the general population. Studies have shown that there is a linear relationship between hypertension and BMI.^{32,35} Brown and colleagues³² found from the NHANES III survey that among men, the prevalence of hypertension (defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication) increased progressively with increasing BMI from 15% at a BMI of < 25 kg/m² to 42% at a BMI of ≥ 30 kg/m². Among women, the prevalence of hypertension increased from 15% at a BMI of < 25 kg/m² to 38% at a BMI of ≥ 30 kg/m².

Effect of weight loss on hypertension

The Framingham study data was used to evaluate the incidence of hypertension among 623 overweight (BMI ≥ 25 kg/m²) middle-aged (aged 30–49 years) subjects and 605 overweight older (aged 50–65 years) subjects over a period of 4 years. The results showed that a weight loss of at least 6.8 kg or more led to a 28% reduction in the risk of hypertension in middle-aged adults (adjusted relative risk of 0.72) and a 37% reduction in older adults (adjusted relative risk of 0.63).³⁶

In the Trials of Hypertension Prevention Phase II (TOHP II),³⁷ 2,382 overweight and obese men and women not taking antihypertensive drugs were evaluated. Criteria included a diastolic blood pressure of 83 to 89 mm Hg, a systolic blood pressure lower than 140 mm Hg and a BMI representing 110% to 165% of desirable body weight. Subjects were randomly assigned to a weight loss intervention program, sodium restriction or usual care. From baseline, participants in the intervention groups had their weight decreased by 4.3 to 4.5 kg at 6 months and by approximately 2 kg at 36 months compared with the usual care group. Compared with the usual care group, blood pressure decreased by 3.7/2.7 mm Hg in the weight loss intervention group at 6 months. At 36 months, blood pressure decreases remained greater in the weight loss intervention group (1.3/0.9 mm Hg) than in the usual care group. Through 48 months, the incidence of hypertension (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 or the use of antihypertensive drugs) was significantly less in both intervention groups (average relative risks, 0.78-0.82) than the usual care group. The study demonstrated that in adults with hypertension, weight loss was effective in lowering blood pressure, especially in the short term (6 months), although the effects on blood pressure declined over time.

The Nurses' Health Study³⁸ of 82,473 US nurses between 30 and 55 years of age followed for 12 to 15 years, also observed a significant correlation between the risk of developing hypertension and changes in body weight among normotensive women. There were 16,395 incident cases of hypertension diagnosed during 923,544 person-years of follow-up. Compared with women who had a BMI less than 20 kg/m², women with a BMI of 31 kg/m² or more had a relative risk of 6.31. A higher BMI at 18 years of age was associated with an increased risk for hypertension later in life. The study also found that with weight losses of 5.0 to 9.9 kg, the risk of developing hypertension decreased by 15% and with a loss of 10 kg or more it decreased by 26%.

VI. Role of obesity in coronary heart disease

The association of obesity in cardiovascular diseases including coronary heart disease, heart failure and sudden death was reviewed by Poirier and colleagues.³⁹ A variety of changes in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of systemic hypertension or underlying organic heart disease. To meet increased metabolic needs, circulating blood volume, plasma volume, and cardiac output all increase. Systemic hypertension, pulmonary hypertension, left ventricular failure, and coronary heart disease all occur with disproportionately high frequency in obese individuals and may cause or contribute to alterations in cardiac structure and function. There is also an increased risk of sudden cardiac death in obesity.

In a meta-analysis involving 21 cohort studies and 300,000 patients, Bogers and colleagues⁴⁰ found 18,000 coronary heart disease events. There was a coronary heart disease relative risk of 1.32 for patients with a BMI between 25 and 30 kg/m², and 1.81 in obese patients (BMI >30 kg/m²) when compared with non-obese patients. In this large meta-analysis, a 5-unit increment in BMI was associated with a 29% increase in risk of coronary heart disease. The study found that the adverse effects of being overweight on

blood pressure and cholesterol levels could account for about 45% of the increased risk of coronary heart disease, and that there is still a significantly increased risk of coronary heart disease that is independent of these effects.

The Nurses' Health Study was reviewed by Manson and colleagues.⁴¹ There were 881 cardiovascular deaths reported over a period of 16 years among 115,195 women who were free of cardiovascular disease at entry. In this report, mortality among the obese women (BMI ≥ 29.0 kg/m²) was more than twice that among the leanest women (BMI < 19.0 kg/m²). Although mortality did not increase substantially until the BMI reached 27.0 kg/m², a trend toward higher mortality due to coronary heart disease and other cardiovascular diseases was apparent even among women at normal weights and those who were mild to moderately overweight (BMI of 19.0 to 21.9 kg/m², relative risk = 1.2; BMI of 22.0 to 24.9 kg/m², relative risk = 1.2; BMI of 25.0 to 26.9 kg/m², relative risk = 1.3; 27.0 to 28.9 kg/m², relative risk = 1.6; BMI 29.0 to 31.9 kg/m², relative risk = 2.1). Furthermore, a BMI of 22.0 kg/m² or higher at 18 years of age was associated with a significant elevation in subsequent mortality from cardiovascular disease. A weight gain of 10 kg or more since the age of 18 predicted increased mortality from cardiovascular disease, cancer, and all causes.

An additional analysis of the data from the Nurses' Health Study between 1986 and 1994 documented 320 coronary heart disease events (251 myocardial infarctions and 69 coronary heart disease deaths) in a study by Rexrode and colleagues.⁵ Higher waist to hip ratio and greater waist circumference were independently associated with a significantly increased age adjusted risk of coronary heart disease. After adjusting for BMI and other cardiac risk factors, women with a waist to hip ratio of 0.88 or higher had a relative risk of 3.25 for coronary heart disease compared with women with a waist to hip ratio of less than 0.72. A waist circumference of 96.5 cm (38 in) or more was associated with a relative risk of 3.06 compared to women with waist measurements of less than 71.1 cm (28 in). The waist to hip ratio and waist circumference were independently strongly associated with increased risk of coronary heart disease also among women with a BMI of 25 kg/m² or less. After adjustment for reported hypertension, diabetes, and high cholesterol level, a waist to hip ratio of 0.76 or higher or waist circumference of 76.2 cm (30 in) or more was associated with more than a 2-fold higher risk of coronary heart disease compared to women with waist measurements of less than 71.1 cm (28 in).

Effect of weight loss on coronary heart disease

Modest weight loss can simultaneously affect the entire cluster of cardiovascular risk factors associated with obesity.⁴² In a prospective community sample of 2,406 men and 2,569 women aged 18 to 74 years at baseline, a weight loss of 5 lb (2.25 kg) or more over 16 years was associated with reductions of 48% (in men) and 40% (in women) in the sum of these risk factors (defined as the highest quintile of systolic blood pressure, serum triglyceride, serum total cholesterol, fasting blood glucose, BMI and the lowest quintile of high-density lipoprotein).

Improvements in cardiovascular structure and function associated with weight loss includes reductions in blood volume and hemodynamic demands on the heart, left ventricular mass and chamber size, and septal wall thickness, according to a study of 41 overweight subjects with hypertension in 1986.⁴³ Weight loss may also delay the progression of atherosclerosis. In a study of 20 patients who underwent weight-reducing gastroplasty,⁴⁴ the progression of common carotid artery intimal wall thickening over 4 years was three times higher in untreated obese subjects who did not lose weight than in obese subjects who lost weight after gastric surgery.

As a result, the American Heart Association has obesity as a major preventable risk factor for coronary heart disease.^{45,46}

Moderate weight loss has also been shown to improve left ventricular diastolic and systolic function. In a single-site randomized study of 60 subjects comparing reduced-calorie diets, partial weight regain diminished the maximal observed beneficial effects of weight loss; however, cardiovascular parameters of cardiac and vascular ultrasound measured at 2 years still showed a net benefit compared with baseline.⁴⁷

VII. Role of obesity on quality of life

It is clear that obesity can have a profound impact on quality of life. In one study the relationship between obesity and health-related quality-of-life (HRQL) was examined using data from the 2000 Medical Expenditure Panel Survey.⁴⁸ The HRQL was determined using multiple validated scores. HRQL decreased with increasing levels of obesity. HRQL values start low when BMI values are approximately 15 kg/m². The scores increase as BMI increases and peak at a BMI of approximately 20–24.9 kg/m², then the HRQL scores decline with further increases of BMI and the decrements continue to their lowest point when the BMI approaches 50 kg/m². Compared to normal weight respondents, persons with severe obesity had significantly lower scores that were similar to the decrements seen with diabetes or hypertension.

Effect of weight loss on quality of life

Blissmer and colleagues⁴⁹ conducted a randomized clinical trial in which all participants completed a 6 month clinical weight loss program and were randomized into two 6-month extended care groups. Participants then returned at 12 and 24 months for follow-up assessments. A total of 144 individuals (mean BMI of 32.5 kg/m²) completed the 6 month intervention and 104 returned at 24 months. The mean weight loss at 6 months was 5.6 kg (6.1% body weight), following the 6 month intervention, and 3.4 kg (3.7% body weight) and 2.7 kg (3% body weight) at the 12 month and 24 month follow-ups. Thirty percent of the sample that returned for testing had maintained a weight loss of at least 5% at 24 months.

At baseline, the participants scored lower than U.S. age-specific population norms (combined scores for men and women ages 45-54) for bodily pain, vitality, and mental health. At the completion of the 6 month clinical intervention there were increases in the

physical and mental composite measures as well as physical functioning, general health, vitality, and mental health subscales of the Medical Outcome Study Short Form-36 (SF-36). The SF-36 is a survey of patient health that consists of eight scaled scores used in health economics and for determination of cost-effectiveness of a health care treatment. Despite some weight regain, the improvements in the mental composite scale as well as the physical functioning, vitality, and mental health subscales were maintained at 24 months. Of interest, maintaining a significant weight loss (> 5%) was not necessary to have and maintain improvements in HRQL.

VIII. Durability of weight loss and behavioral predictors

A meta-analysis of 46 randomized, controlled trials was performed by Dansinger and colleagues⁵⁰ including 6,386 people receiving dietary counseling and 5,467 receiving usual care. People receiving dietary counseling had a maximum net treatment effect of -1.9 BMI units (approximately 6% of initial body weight [5 kg]) at 12 months. Changes in weight over time showed a change of approximately -0.1 BMI units per month from 3 to 12 months of active programs and a regain of approximately 0.02 to 0.03 BMI units per month during subsequent maintenance phases. However, the statistical significance of these changes could not be assessed due to the limitation of the available data. Compared with usual care, dietary counseling interventions produced a modest weight loss that diminished over time.

Other studies have shown that many obese persons are capable of achieving long-term weight loss. The National Weight Control Registry (NWCR)⁵¹ consisted of 629 women and 155 men with enrollment criteria of aged 18 year or older, lost 13.6 kg (30 lb.) or more, and maintained the weight loss for 1 year or longer. These subjects had extensive histories of being overweight, and most had childhood-onset obesity. On average, they lost 30 kg and maintained a weight loss of 13.6 kg for 5 years. The average maximum lifetime BMI was 35 kg/m². After their weight loss, registry members were within the normal to mildly overweight ranges. Approximately 55% of the sample group reported using a formal program or professional assistance to lose weight. The vast majority of the group reported modifying both their dietary intake and physical activity level to achieve their weight loss. Over 90% of the group reported previous attempts to lose weight. Registry members reported that they had greater social reasons, health reasons, or both, for losing more weight than in previous attempts.

More recently, Appel and colleagues⁵² conducted a randomized, controlled trial to examine the effects of two behavioral weight-loss interventions in 415 obese patients with at least one cardiovascular risk factor. Participants were recruited from six primary care practices. At baseline, the mean BMI for all participants was 36.6 kg/m². Participants received three possible interventions including remote weight loss support, in-person support during group and individual sessions or self-directed management. Participants in the intervention groups achieved significant weight loss compared to those in the control group over a period of 24 months. At 24 months, the mean weight loss from baseline was 0.8 kg in the control group, 4.6 kg in the group receiving remote support and 5.1 kg in the group receiving in-person support. The percentage of participants who lost 5% or more of their initial weight was 18.8% in the control group,

38.2% in the group receiving remote support only, and 41.4% in the group receiving in-person support. The change in weight from baseline did not differ significantly between the two intervention groups.

Several studies have been undertaken to determine the profile for those who are successful at weight loss. In a survey of 108 obese women,⁵³ most of the 30 women who were able to maintain their weight loss exercised regularly, were conscious of their behaviors, used available social support, confronted problems directly, and used personally developed strategies to help themselves. In contrast, among the 44 women who relapsed after weight loss, few exercised, most ate unconsciously in response to emotions, few used available social support, and few confronted problems directly.

Data was also collected from a large community-based survey on dieting and weight loss commissioned by Consumer Union.⁵⁴ A total of 1,165 men and women were grouped into successful weight loss maintainers (Maintainers) who reported having lost at least 10% of their highest adult weight and having maintained that weight loss for at least three years, or unsuccessful weight-loss maintainers (Regainers) who reported not ever having been able to maintain a significant weight loss and having lost and regained a minimum of 10 to 19 pounds at least once. In response to a dietary lapse, Maintainers, as compared with Regainers, reported being more likely to use direct coping and less likely to seek help.

In addition, Teixeira and colleagues⁵⁵ analyzed the association of several baseline personal factors associated with weight management outcomes among 158 healthy overweight and obese women, ages 40 to 55 years, after 16 months. The inclusion criteria for BMI was between 25 and 38 kg/m², and the mean baseline BMI was 31.0 kg/m². Participants who maintained a weight loss of 5% or more at 16 months (or 10% or more of initial fat mass) were classified as successful. Participants who dropped out and completers who had not lost weight at follow-up were included and considered non-successful. Independent baseline predictors of success at 16 months were more moderate weight outcome evaluations, lower level of previous dieting, higher exercise self-efficacy, and smaller waist-to-hip ratio. Non-completion was independently associated with more previous weight loss attempts, poorer quality of life, more stringent weight outcome evaluations, and lower reported carbohydrate intake at baseline.

IX. Effect of surgical intervention on obesity and comorbidities

An analysis by Cremieux and colleagues⁵⁶ found that among 5,502 patients, a significant decrease in the prevalence of reported comorbidities was observed during the short-term postsurgery period, and sustained for up to 3 years of follow-up. The Roux-en-Y procedure was the most common surgical procedure in this group. The authors performed an analysis based on the participants' health care claims records.

Compared to the presurgery period, significant decreases were observed after 3 years for total cardiovascular disorders (43.6% vs. 14.2%), type 2 diabetes (19.9% vs. 7.7%), chronic obstructive pulmonary disease and other respiratory conditions (57.7% vs. 16.2%), diseases of the musculoskeletal system and connective tissue (32.6% vs. 27.7%)

and mental disorders (30.7% vs. 14.8%). Over the same period, the frequency of medication use decreased significantly for a number of conditions including infections, pain, respiratory, cardiovascular, gastroenterologic, lipidemic, and diabetic conditions.

In addition, in a retrospective study of medical records in Sao Paulo, Brazil, Donadelli and colleagues⁵⁷ obtained weight, body mass index, systolic blood pressure, diastolic blood pressure, lipid profile, diabetes, and history of cardiovascular disease for obese patients before and 2 years after Roux-en-Y gastric bypass surgery. Forty-two patients were included in the study. All indicators of cardiac risk improved significantly after gastric bypass, except for systolic blood pressure and diastolic blood pressure, although 43% of the patients were taking antihypertensive medication before surgery and 17% continued with antihypertensive treatment 2 years after surgery. Diabetes was reduced by 23.2%, total cholesterol by 11.8%, low-density lipoprotein by 19.3%, and triglycerides by 51.3%. High-density lipoprotein was increased by 45.7%. The ten-year cardiovascular risk was calculated using the Framingham score. There was a significant reduction of 10-year cardiovascular risk mainly associated with weight reduction and improvement of comorbidities associated with obesity. The benefits were greater among patients who already presented with known risk factors such as diabetes and hypertension.

X. Impact of adjustable gastric banding on diabetes, hypertension, and dyslipidemia

CDRH's Division of Epidemiology, in the Office of Surveillance and Biometrics, conducted a systematic literature review to evaluate the impact of weight loss from laparoscopic adjustable gastric banding (LAGB) with Lap-Band® and Realize® devices on diabetes, hypertension, and dyslipidemia (Attachment 7). On March 2, 2012, we searched PubMed, EMBASE, and CINAHL electronic databases for studies with each of the following three domains: 1) Use of LAGB device; 2) Weight loss; and 3) At least one of the following conditions of interest: diabetes, hypertension, and dyslipidemia. Results were limited to human studies published in English from January 1, 2001 to present. Randomized controlled trials, observational studies, systematic literature reviews and meta-analyses were considered for inclusion. Seventeen articles were identified in the literature that met our inclusion criteria (1 randomized controlled trial and 16 observational studies). In these studies, the impact of weight change from LAGB on either the clinical classification and/or biomarkers related to one or more of the conditions of interest was evaluated using correlation estimates or statistical modeling. Sample size ranged from 26 to 650 patients, with 8 of 17 studies enrolling less than 100 patients. The average follow-up period ranged from 6 months to 5 years, with 14 studies reporting 1 year or more of follow-up.

Among the 17 studies, 16 evaluated the impact of LAGB-induced weight loss on *diabetes*. Of these studies, statistically significant relationships between at least one measure of weight loss and the following variables were found: diabetes remission or reduced severity, decreases in hemoglobin A1C percent (HbA1c), decreases in plasma glucose levels, decreases in plasma insulin levels, increases in insulin sensitivity (HOMA %S), and decreases in insulin resistance (HOMA IR). However, none of the 4 studies

that evaluated the impact of weight loss from LAGB on *hypertension* found statistically significant changes in blood pressure (systolic or diastolic) post-procedure. There were nine studies that assessed the effect of weight loss from LAGB on *dyslipidemia*, and the results were mixed. Among the studies identified, statistically significant relationships were found between at least one measure of weight loss and the following biomarkers: triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol.

Thus, studies reported significant correlations between weight loss and diabetes showing improvement/remission, mixed results with regard to the relationship between weight loss and dyslipidemia, and no association between weight loss and hypertension. However, information in the published literature regarding the long-term effectiveness of LAGB and whether sustained weight loss leads to sustained reductions in cardiometabolic risk is limited. Future studies with longer follow-up periods and larger sample sizes are necessary to further clarify these issues.

XI. Effect of weight cycling

Many obese persons can achieve short-term weight loss by dieting alone, but successful long-term weight maintenance is much more difficult to achieve. “Weight cycling” and “yo-yo dieting” are popular terms used to describe repetitive cycles of weight loss and subsequent regain.⁵⁸

Using data from 5,127 participants in the Framingham population, Lissner and colleagues⁵⁹ reported that subjects with highly variable body weights had increased total mortality, mortality from coronary heart disease and morbidity due to coronary heart disease. Another review of 13 observational studies which included 62,633 patients performed by Andres and colleagues⁶⁰ in 1993 showed that weight loss or weight fluctuation increases mortality. Weight cycling may also have negative psychological and behavioral consequences. Studies have reported an increased risk for psychopathology, life dissatisfaction, and binge eating.⁶¹

In contrast, Stevens and colleagues⁶² recently reviewed the association of weight cycling with death among 55,983 men and 66,655 women in the Cancer Prevention Study II Nutrition Cohort from 1992 to 2008. A weight cycle was defined as an intentional loss of 10 or more pounds (≥ 4.5 kg) followed by regain of that weight, and the lifetime number of weight cycles was reported on a questionnaire administered at enrollment. After adjustment for BMI and other risk factors, low numbers of weight cycles (1–4 cycles) were associated with slightly lower mortality rates (hazard ratio = 0.93). In addition, higher numbers of weight cycles (≥ 20 cycles) were not associated with increased mortality.

Despite some controversy, the recommendation from the National Task Force on the Prevention and Treatment of Obesity is that the possible detrimental health effects of weight cycling are inconclusive, and should not deter obese persons from attempting to lose weight.⁵⁸

Choice of Control Group Treatment

A critical element in the design of a randomized, controlled study is choosing an appropriate control group. A control group should be ethically and scientifically valid. Standard of care for a condition that does not cause serious harm would generally be considered as an ethically sound comparator. However, standard of care for treating obesity has not been established yet: Although most consider diet and exercise as the first line of treatment for obesity, there is no uniform and/or standardized regimen. Moreover, from a scientific perspective, investigators should also evaluate whether the selected control group will provide the most meaningful data to address the study objective. Furthermore, other device specific factors may need to be considered when choosing a comparator. Therefore, the Division does not use a one-size-fits-all strategy for weight reduction devices. We have considered four main categories of treatment as possible comparator: (1) sham, (2) obesity device or procedure, (3) diet and exercise, and (4) performance goal.

XII. Sham as control treatment

Placebo-controlled randomized design has long been held as the gold standard in demonstrating effectiveness of an intervention. In the absence of a well-established standard of care for an obesity indication, using sham as control is ideal if the sham device and the procedure that place it do not cause any serious harm and the patient cannot easily unmask their own treatment assignment. Use of a sham can potentially address the placebo effect of a device. Depending on the design of the sham arm, it may also provide a method for separating the effects of the device procedure or a specific component of a system versus the fully functional device.

The benefits of a sham control must be balanced with the risk to patients of having a sham surgery.⁶³ If the obesity device is placed using endoscopy a sham endoscopy procedure could be used as a control arm. This would involve the patient undergoing a procedure with as many similar aspects as possible to the actual procedure without the device being placed; sedation, endoscope insertion (to mimic throat irritation after procedure), and similar pre- and post-operative steps. For a device that is placed using laparoscopy, the sham control arm could undergo a procedure in which the abdomen would still be insufflated, the same number of incisions as the device would require (i.e., for ports) would be performed, and similar preoperative and postoperative steps would be taken.

There may be cases where treatment assignments can easily be unmasked, because the patient can detect the presence or absence of the device, e.g., device may be felt on the skin surface or changes have to be made to the device. In these cases, the control arm patients would not only have the sham procedure, but have the inactivated device placed as well, such as the “delayed activation” control used in neurological device studies. This would help discern the effect of knowledge of having the device placed against the device actually working.

Moreover, if the investigative device is intended to be used with a diet and exercise program, patients in the control group should also take part in the same standardized program as those in the treatment group.

Because of the advantages mentioned above, the Division encourages investigators to use a sham control in the randomized, masked clinical trial design used to support the safety and effectiveness of their device when technically feasible. However, if there is evidence that a sham treatment may cause serious harm or masking of treatment assignment is impossible, it may be unethical to conduct a sham control arm and other types of control treatment should be considered.

XIII. Use of an approved obesity device or established procedure as control treatment

When there is an intervention with established evidence of safety and effectiveness, such an intervention may be a good choice of control arm. With a well-understood record, such a device and procedure can provide a meaningful yardstick to measure the performance of the test device. Moreover, the public's familiarity with these inventions may help with the recruitment and retention of patients, and both can contribute positively to the quality of study data.

In some cases, an existing intervention is not the best choice of control arm. For an investigative device that is minimally invasive in nature and with a less ambitious claim for weight reduction (both in magnitude and duration), a comparison to a more invasive intervention may not be applicable. An existing intervention is also not an ideal control if the indicated population of the existing intervention and the intended population for the investigative device are different.

XIV. Diet and exercise as control treatment

The current cornerstone of therapeutic interventions to treat or prevent these diseases is weight loss through lifestyle modifications.⁹ These include reducing energy intake through dietary change and increasing energy expenditure by increasing physical activity along with behavioral techniques.²⁰ Typical weight loss resulting from lifestyle change is reported to be between 5 and 10% of baseline weight. Although this amount may not bring an obese individual to a normal body weight, losing even a modest amount of weight brings health benefits, as discussed in Section I. Behavioral interventions, such as enhanced weight-loss counseling, have also been reported to help obese patients achieve clinically meaningful weight loss.⁶⁴ Behavioral support, whether in-person or delivered remotely, without face-to-face contact, has been shown to cause clinically significant weight loss.⁵²

Recommendations as to what exactly constitutes a proper diet and/or exercise regimen are available and based on expert opinion supported by the available data, but vary.⁹

- The NIH Obesity Education Initiative Expert Panel suggests a caloric deficit of 500–1,000 kcal/day using an individualized dietary strategy, along with 45 min of moderate-intensity physical activity 5 days/week.
- The Institute of Medicine recommended at least 1 hour per day of moderately intense physical activity coupled with a caloric deficit.
- The US Department of Agriculture similarly suggests individuals engage in close to 1 hour of moderate-to-vigorous intensity exercise on most days of the week, without exceeding caloric intake requirements
- The US Center for Disease Control instead suggests at least 30 minutes per day of moderate-intensity exercise most days of the week while maintaining sensible portion sizes.

It can be difficult to draw conclusions regarding standardized programs for several reasons. Differences exist across the institutions performing the studies themselves. This is evident in the literature, where differences exist in the population being studied (i.e. postmenopausal women, diabetics), the interventions being compared (i.e. diet, exercise, and/or counseling alone and/or in combination), the measure of weight loss (i.e. % weight loss, actual kg, BMI units as compared to baseline), and the duration of the intervention. Regarding the intervention itself, the diet (amount of caloric deficit) as well as type, duration, intensity, and frequency of exercise varies greatly.

Despite the absence of a uniform and/or standardized regimen, diet and exercise is still a natural choice of the control group for some medical device trials as it has been regarded as safe and the first line treatment of obesity in public health messages. As mentioned above, differences across investigative sites that actually implement the program and an asymmetric lost-to-follow-up rate between the treatment and control groups due to different level of adherence could raise significant issues when comparing a new obesity device with a diet and exercise control. For most studies, failure of using diet and exercise to control weight is one of the inclusion criteria for patient enrollment. Patients may not want to be randomized to a group in which they feel an intervention has already failed, however, significant differences most likely exist between the diet and exercise regimen they used prior to enrollment and the regimen in the study. Finally, the diet and exercise program may be specially designed for the investigative device and thus, the program can be qualitatively different from the standard program practiced by the patients in the control arm. In this case it is not clear if the control arm should have a standard diet and exercise program, or if it should have the same program as the treatment arm.

Since lifestyle modification is the current first line standard of care and poses very low risk to the patient as compared with more invasive alternatives, such as having a endoscopic or surgical procedure to have a device placed, and/or risk from device use itself, having it as a control arm in an obesity device trial should be considered.

XV. Performance goal in a single arm study

Randomized comparator-controlled studies of medical devices, such as the three comparator options mentioned above, are usually preferred; however, there may be cases when they are deemed to be inapplicable or unethical, and a non-randomized design such as a single-arm study with performance goal may be considered. In general, when designing a single-arm study, investigators should attempt to minimize the bias due to placebo effect, improvement in the disease's natural history, regression to the mean effect, concurrent therapies such as diet and exercise, as well as operational bias such as patient selection bias.

In the context of a weight reduction medical device, a single arm study with a performance goal may be an appropriate choice. Since body weight is an objective measurement, the placebo effect in a weight loss device trial may not be as pronounced compared to other double-blinded trials using subjective patient self-reported outcomes, such as visual analog scale for pain or quality of life scales. Furthermore, unlike other diseases that have a natural history with short life cycle, such as common cold, obesity is a chronic condition that would rarely resolve itself without any intervention and thus regression to the mean may be less of an issue. The bias due to regression to the mean effect might be further controlled in some proposed single-arm trial designs by using multiple baseline measurements over a sufficient time period to establish the stability of patient's baseline weight and thus patients potentially could be used as their own control.

Benefit Risk Assessment of Devices

As outlined in FDA's "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications," issued on March 28, 2012, the Agency believes that when evaluating medical devices, a benefit-risk determination should be made during the premarket review process. The goal of this meeting is to provide an updated paradigm for the assessment of obesity devices that more formally takes into consideration this benefit-risk determination when reviewing applications for the study and marketing of these devices.

By creating a system to objectively assess the benefit-risk relationship using the best available information prior to the initiation of a pivotal study, the Division hopes to provide a transparent and consistent pathway for the review of obesity devices. As stated previously in this package, we believe that the proposed approach takes into consideration many of the important concepts of benefit-risk assessment, such as the following:

- Type of benefit
- Magnitude and duration of benefit
- Probability of a patient experiencing benefit
- Number, severity, and types of harmful events associated with the use of the device
- Probability of a harmful event
- Duration of harmful events

The intent of this meeting is to seek your feedback on some of the details surrounding these concepts.

The Division is proposing a benefit-risk assessment system that would allow sponsors to determine the expected success criteria for their pivotal study based on available safety data. The Division anticipates that should a device, during the pivotal study, demonstrate higher risk than anticipated, it would be expected that the study show correspondingly greater benefit. Conversely, if a device is shown to be less risky than anticipated, a lower success margin may be considered acceptable.

XVI. Proposal for systematically assessing expected and unexpected events

The first step of the Division's approach was to identify categories of expected and unexpected events, including adverse events and expected follow-up procedures. It was intended that the categories would be mutually exclusive, and together cover all events. All events that fit into a single category are intended to be of approximately equal severity/risk. Table 1 provides suggested categories and examples of events included in each category.

The Division's proposal categorizes adverse events differently from the traditional way of reporting events in a study. For the purposes of this benefit-risk assessment, the Division is categorizing events by their relative risk based on outcome. For example, whereas vomiting would traditionally be reported as mild, moderate, or severe, we are proposing a method to categorize the severity of the vomiting, and to group the vomiting with other events of similar severity. With the categories proposed in Table 1, vomiting could fall into several categories ranging from "A" if it can be controlled with over the counter medication to "I" if it led to severe dehydration requiring the administration of IV fluids in a hospital setting. Note that it does not matter if the event was anticipated or unanticipated: it adds risk either way.

The second step was to determine a paradigm for using these categories to assess the expected and unexpected events. We are proposing to consider the number of different types of harmful events that can potentially result from using the device and the severity of each event. We also intend to capture the risk of their aggregated effect or of simultaneous effects. When multiple harmful events occur at once, we consider their aggregated effect to be the sum of all the individual effects. Therefore we consider a cascading event to be cumulative for risk assessment purposes, and we consider simultaneous events to be counted individually so that both are captured.

For example, if a patient had pain that was not adequately managed with prescription medication and led to an exploratory endoscopy, which revealed esophageal mucosal bleeding, the series of events would be counted under several event categories: "G" for the pain, "D" for an unscheduled visit to a physician, "E" for the endoscopy, and "H" for the mucosal bleeding. Similarly, if two events occurred simultaneously, such as nausea resulting in a band adjustment, both events would be counted.

While these examples focus on the assessment of a single patient event, it should be noted that in order to make a final risk level assessment for the device, all events from all patients are accounted for from a data set, the events are totalled, and a final risk categorization is determined based on the highest risk level from any event category.

XVII. Proposal for systematically assessing device risk levels

The Division proposes defining risk levels of devices based on the percent of patients who experience each category of events over the time period of one (1) year. With the numbers suggested in Table 1, the least risky devices, Level 1 devices, may have high rates of the most mild events (up to 100%), low rates of events of intermediate severity (2-5%), and very low rates of the more severe events (<0.1%). Level 2 devices may have high rates of mild events and some intermediate events and lower rates of other intermediate and severe events. Occurrence of more severe events results in a Level 3 risk level categorization.

The overall risk level for a device will be based on the highest risk level for *any* category. For example, if a device has 25% of patients experiencing tissue damage that does not

require an operation to resolve, the device would be considered a Level 3 risk level, even if all other rates of events place the device in the Level 2 risk level.

As discussed above, a sequence of related events may result in events being counted in more than one category. For example, if a patient were admitted to the hospital for an operation, there would likely be pain medication prescribed. When assessing the device risk as a whole for the entire study population, if the device were to end up being categorized as a Level 3 risk, it would likely be because of the operation, not because of the use of pain medication following that surgery. (As proposed in Table 1, up to 100% of patients can be treated with prescription medication for pain to be categorized as a Level 2 risk device). Therefore while all events are counted in a cumulative fashion, it is unlikely that an event such as pain associated with a surgery would result in a higher risk level; the hospitalization with surgery would cause the higher risk level.

Table 1: Definition of risk levels based on percent of expected and unexpected events in 1 year, defined by category

Category	Level 1	Level 2	Level 3	Examples
A. Discomfort that does not require prescription drugs or other medical intervention, but may need over the counter medications	up to 100%	up to 100%	Any percentage higher than those listed for Level 2 place the device into this risk level.	<i>nausea; vomiting; pain; constipation; burping; bloating; gas; cramps; dyspepsia; diarrhea; dehydration</i>
B. Scheduled visit to doctor	up to 100%	up to 100%		<i>band adjustment</i>
C. Problems that can be managed with prescription drugs or diet, or topical care or mild interventions such as administering of IV fluids	<5%	up to 100%		<i>nausea; vomiting; pain; infection; dehydration; cutaneous bleeding; GERD; esophagitis; gastritis; non-hemorrhagic anemia; dysphagia; inflammation</i>
D. Unscheduled visit to doctor	<5%	up to 100%		<i>band adjustments due to dysphagia</i>
E. Follow-up or repeat endoscopic procedure	<2%	up to 100%		<i>device removal; device adjustments; diagnostic evaluation or therapeutic intervention, e.g. due to dysphagia or bleeding</i>
F. Short/long term health consequences of malabsorption	<5%	<20%		<i>Nutritional deficiencies, e.g. anemia, iron deficiency, electrolyte imbalances; or effect on medication levels</i>
G. Substantial discomfort, not managed even with drugs	<0.1%	up to 100%		<i>severe nausea, vomiting, bloating; GERD</i>
H. Tissue damage not requiring an operation	<0.1%	<20%		<i>erosion; ulcer; GI or esophageal mucosal bleeding</i>
I. Hospitalization, no operation	<0.1%	<5%		<i>IV antibiotics for infection; IV medication for severe pain; severe anemia - with or without need for blood transfusion; pneumonia; need for anticoagulation for pulmonary embolism</i>
J. Hospitalization, with operation	<0.1%	<1%		<i>GI or esophageal perforation, gall bladder removal; obstruction (all etiologies); unscheduled device removal due to severe pain or other symptoms</i>
K. Death	<0.1%	<0.1%		

XVIII. Proposed risk-based effectiveness targets

Based on these risk levels, the Division has also proposed corresponding effectiveness targets for discussion. The targets for Level 1 devices are loosely based on the endpoints utilized by CDER for weight loss drugs, while the targets for Level 3 risk devices are roughly based on the only approved obesity devices, the banding devices Lap-Band® and Realize®, which are considered to be Level 3 risk devices.

Tables 2 and 3 show proposed effectiveness targets. For Level 2 and Level 3 devices, targets are presented both as an objective performance criteria for single arm studies, and as a comparison to sham for sham-controlled studies. Level 1 risk devices are not anticipated to utilize a sham control, and therefore instead have a comparison to diet and exercise as a control.

Tables 2 and 3 use different methods of assessment for the success criteria. As discussed earlier, the Division currently uses percent excess weight loss (%EWL) for effectiveness assessments; however, it is being proposed that we shift to %TBL.

For ease of discussion the effectiveness targets in Tables 2 and 3 are not written as statistically based endpoints, although statistically based endpoints will be expected for a clinical study. The observed mean values over sham are larger values than when written as a true statistical endpoint where the value would reflect the lower bound of the confidence interval. The Level 3 target in Tables 2 and 3, incorporating a sham control, reflects the Division’s current recommendations for all studies, where we expect to see the lower bound of the mean %EWL in the treatment group to be 25% over sham. This performance target was originally designed to reflect similar success to the 35% observed EWL as listed as a performance criterion, assuming a sham success of about 5-10% EWL.

Table 2: Proposed effectiveness targets based on risk level using %EWL

Level 1	Level 2	Level 3
<p>12% observed mean EWL and statistical superiority to diet and exercise control</p>	<p>With sham control arm: 20% observed mean EWL over sham AND 50% patients with 15% EWL in treatment group</p> <p>No control arm: 25% observed mean EWL as performance criterion</p>	<p>With sham control arm: 30% observed mean EWL over sham AND 50% patients with 25% EWL in treatment group</p> <p>No control arm: 35% observed mean EWL as performance criterion</p>

Table 3: Proposed effectiveness endpoints based on risk level using %TBL

Level 1	Level 2	Level 3
5% observed mean TBL and statistical superiority to diet and exercise control	With sham control arm: 8% observed mean TBL over sham AND 50% patients with 5% TBL in treatment group No control arm: 10% observed mean TBL as performance criterion	With sham control arm: 13% observed mean TBL* over sham AND 50% patients with 10% TBL in treatment group No control arm: 15% observed mean TBL as performance criterion

*The current endpoints assessing weight change using %EWL were “converted” to %TBL values, using a BMI of 39 kg/m² for the conversion

At the panel meeting, the Division will be asking your input on many facets of this proposed benefit-risk classification system. Considering the elements of risk and benefit listed previously, you will be asked to comment on several elements of this benefit-risk paradigm, as detailed in the Division’s discussion questions.

XIX. Items for consideration

As the Division is exploring the option of having less demanding effectiveness endpoints for obesity devices that have been demonstrated to have less risk associated with them, a systematic approach for assessing and characterizing the expected and unexpected events that may be associated with these devices became necessary. Based on the proposed categorization scheme shown in Tables 1, 2, and 3, you will be asked to discuss several items as follows:

- Do the event categories cover the range of expected and unexpected events that may occur in association with the use of obesity devices? If not, what alternative categories should be used?
- Are the events that fit into each category of approximately equal severity/risk? If not, what alternative categories should be used?
- Do you agree with the proposal that device risk levels be based on the percentages of patients who experience events in each category over one year following device placement? If not, what do you propose?
- Are the proposed acceptable event rates for Level 1 and Level 2 devices appropriate for each event category? If not, what rates would you propose?
- Are the proposed minimum effectiveness targets (Table 2 and 3) appropriate when compared to the proposed event rates and associated device risk levels (Table 1)? If not, what effectiveness targets do you recommend given the device risk levels and event rates that you have proposed?

XX. Implementation of the framework

The Division understands that there may be challenges to implementing the proposed assessment paradigm. The proposed paradigm is admittedly complex; however, the processes of assessing risk *a priori* in an objective and systematic way is fairly difficult. Our experience has been that, especially given the diversity of weight loss devices, any robust system will likely have a high degree of complexity. As you formulate your thoughts for the discussion, there are several points that the Division would like you to consider. When designing a pivotal study, the device manufacturer will usually have limited safety data, perhaps only from a small, short-term, feasibility study. Therefore there is likely to be a large degree of uncertainty in the event rates, making the device risk profile difficult to characterize. Such a study will be unable to statistically demonstrate event rates for rare events, like those listed above where rates of less than 0.1% or 1% are listed as acceptable. Also, while some of the expected and unexpected events described above may occur during or soon after a medical device procedure, others may occur weeks, months, or years later. This timing may depend on the procedure and on the duration of a temporary device.

As an example of the limitations of small sample sizes, if a feasibility study had a sample size of 20 patients, an observed event rate of zero could indicate a true event rate of up to 14%. Even for a sample size of 49 patients, with an observed event rate of zero, the true rate could be as high as 6%. Similar issues exist with detecting rare events, even in a pivotal study, where with a sample size of 299, an observed event rate of zero could have a true rate of up to 1%. With these issues in mind, please consider the following questions:

- Should the time period for assessing expected and unexpected events in each category be different for permanently implanted devices versus removable devices?
- Given the lack of certainty of device risk level when a pivotal study is being designed, to what extent should the Division approve a pivotal study with a Level 1 or Level 2 effectiveness target? For example, the Division could approve a pivotal clinical study having a Level 2 effectiveness target, contingent on the pivotal study demonstrating the Level 2 risk of the obesity device. If the risks proved to be higher than Level 2, then the study would have to demonstrate Level 3 effectiveness to be approved. Keep in mind that if a study was sized to demonstrate Level 2 effectiveness, it may be difficult to demonstrate Level 3 effectiveness.

The Division would like you to consider, when discussing the above questions, the regulatory paradigm, the levels of evidence available at various points in time, and how changes in the available risk information may drive decision making.

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