Pivotal Aspiration Therapy with Adjusted Lifestyle (PATHWAY) Study

Protocol #: P012-001V

October 13, 2014

Aspire Bariatrics, Inc.
3200 Horizon Drive, Suite 100
King of Prussia, PA 19406 USA
www.aspirebariatrics.com
610-590-1577
610-279-1546 (FAX)

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CLINICAL PROTOCOL NUMBER P012-001V
13 **October 2014**

PROTOCOL SIGNATURE PAGE (SPONSOR)

Approved By: _____ _____
Samuel Klein, MD Date
Clinical Trial Medical Consultant

Approved By: _____ _____
Katherine Crothall, PhD Date
President/ CEO Aspire Bariatrics

Pivotal Aspiration Therapy with Adjusted Lifestyle (PATHWAY) Study

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PROTOCOL SIGNATURE PAGE (INVESTIGATOR)

I have read and understood this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

SYNOPSIS of PATHWAY STUDY

Objective:

The objective of this study is to demonstrate the safety and efficacy of the AspireAssist™ Aspiration Therapy System as a weight loss therapy for obese adults.

Study Population:

The study population is 175 obese men and women who (i) have a Body Mass Index (BMI) between 35.0 and 55.0 kg/m^2, (ii) are 21-65 years old, and (iii) have failed to achieve and maintain weight loss with non-surgical weight loss therapy.

Overview of Study Design:

This is a multi-center, randomized, controlled, open-label, 52-week trial to support FDA premarket approval with additional long-term safety and efficacy monitoring of the treatment group for post market reporting and publication purposes. Eligible subjects will be randomized in a 2:1 (treatment: control) ratio to treatment with the Aspiration Therapy (n=117) or lifestyle therapy (behavior education, diet and exercise) program (n=58). The AspireAssist™ Aspiration Therapy System involves percutaneous endoscopic placement of a gastric device that permits aspiration of a portion of stomach contents after meals, in conjunction with lifestyle therapy.

Aspiration Therapy subjects who lose and maintain at least 10% weight loss from baseline will be given the option to continue in the study for an additional four years after the 52-weeks of therapy.

Primary Outcomes:

The first effectiveness primary endpoint is the mean percent excess weight loss (%EWL) at 52-weeks. The hypothesis for the first primary effectiveness endpoint is that the difference in the mean percent excess weight loss (%EWL) at 52-weeks for the Aspiration Therapy (AT) group and Control group is at least 10%. %EWL is defined as absolute weight loss divided by baseline excess weight and multiplied by 100. Excess weight will be determined from ideal body weights based on a BMI=25 kg/m^2.

The second effectiveness primary endpoint is that at least 50% of the AT group at 52-weeks realizes a %EWL $\geq$ 25%.

Both primary endpoints must be met for the study to be considered a success.

Secondary Outcomes (at 52-weeks)

i) Mean percent absolute weight loss in AT compared to Control group, ii) proportion of subjects who achieve ≥10% absolute weight loss in AT compared to Control group, iii) mean percent change serum lipids (triglyceride, HDL-cholesterol and LDL-cholesterol concentration) in the AT group compared to the control group; iv) mean percent change in systolic and diastolic blood pressures in the AT group compared to the control group; v) "Impact of Weight on Quality of Life" (IWQOL) questionnaire; vi) change in mean hemoglobin A1C (only subjects with T2 diabetes at baseline) , vii) percent procedural success (defined as successful endoscopic placement of the A-Tube) in all subjects undergoing endoscopy; viii) mean percent change in medications

Safety Outcomes:

The incidence of procedure-related, device-related, and therapy-related adverse events will be measured, as well as the incidence of device related, or unrelated, serious adverse events, including unanticipated adverse device effects. Also, the development of adverse eating behaviors will be assessed.

Schedule of Assessments:

The Schedule of Assessments for the Control Group and the AT group are shown in **Tables 1-3.**

Table 1: Schedule of Assessments, Year 1-AT Group

YEAR 1	Screen	Random	Day				Week of Therapy															
Visit	Screen		0	1	7	14	0	0.5**	2	6	10	14	20	24	28	32	36	40	44	48	52	*Total*
Visit window (±days)			0	0	1	4	2	1	2	7	7	7	7	7	7	7	7	7	7	7	7	
Informed consent	x																					**1**
Screening interview	x																					**1**
Medical History & Physical Exam	x																				x	**2**
EKG	x																				x	**2**
IWQOL	x																				x	**2**
Questionnaire on Eating and Weight Patterns (QEWP)	x											x			x						x	**4**
Eating Disorders Examination (EDE)	x											x			x						x	**4**
Randomization phone call		x																				**1**
A-Tube placement			x																			**1**
Skin-Port placement, Aspiration training, Initiate treatment						x																**1**
Phone check (RC or RN)				x			x															**2**
MD visit					x							x			x						x	**4**
Medical & Study Visit (weight, vital signs, concom meds, med adherence, AE's)					x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	**16**
Initial body weights	x		x*																			**2**
Dietary Evaluation					x																	**1**
Lifestyle Therapy						x			x	x	x	x	x		x		x		x		x	**10**
Height	x																					**1**
Urine pregnancy	x																					**1**
Urine protein (dipstick)						x		x	x	x	x	x	x		x		x		x		x	**11**
Electrolyte panel+ magnesium + calcium								x	x	x	x	x	x				x		x			**8**
CMP + Magnesium	x														x						x	**3**
CBC	x																				x	**2**
Hemoglobin & hematocrit												x			x							**2**
PT/PTT	x																					**1**
TSH	x																					**1**
Lipid Panel	x														x						x	**3**
Iron	x											x			x						x	**4**
Vitamin D 25-OH	x																				x	**2**
Hemoglobin A1C	x											x			x						x	**4**
DEXA	x																				x	**2**
Subject photograph			x																		x	**2**
Town Hall meetings***							Every other month after 3 AT group subjects are enrolled															
A-Tube shortening							As needed															

*A body weight measurement does not need to be done on Day 0, unless the screening occurred more than 7 days prior

Table 2: Schedule of Assessments, Years 2-5-AT

YEARS 2-5	Week of Therapy																	
Visit	60	68	76	90	104	117	130	143	156	169	182	195	208	221	234	247	260	Total
Visit Window (± days)	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Physical Examination					x				x				x				x	4
EKG					x				x				x				x	4
IWQOL					x				x				x				x	4
Questionnaire on Eating and Weight Patterns					x				x				x				x	4
MD visit			x		x		x		x		x		x		x		x	8
Medical & Study Visit (weight, vital signs, concom meds, med adherence, AE's)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	17
Urine, Pregnancy																		0
Electrolyte panel + magnesium + calcium	x	x	x	x		x	x	x		x	x	x		x	x	x		13
CMP+ magnesium					x				x				x				x	4
CBC					x				x				x				x	4
Hemoglobin & hematocrit			x				x				x				x			4
Lipid Panel					x				x				x				x	4
Hemoglobin A1C			x		x		x		x		x		x		x		x	8
Iron					x				x				x				x	4
Vitamin D 25-OH					x				x				x				x	4
DEXA					x				x				x				x	4
Town Hall meetings***	**Every other month**																	
A-Tube shortening	**As needed**																	
A-Tube replacement	**As needed**																	
A-Tube removal	**As needed**																	

CMP: glucose, calcium, sodium, potassium, chloride, CO2, BUN, creatinine, albumin, total protein, alkaline phosphatase, ALT, AST, bilirubin +magnesium
Electrolyte panel: sodium, potassium, chloride, and CO_2 + magnesium + calcium
Lipid panel: Total cholesterol, LDL-C, HDL-C, Triglycerides
CBC: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, **MCV**: mean corpuscular volume; **MCH**: mean corpuscular hemoglobin **MCHC**: mean corpuscular hemoglobin concentration, platelet count

*Day 0 weight should be obtained on same scale used during the study
** Week 0.5 denotes 48-72 hours after AT initiation
***Town Hall meetings shall begin after 3 subjects are enrolled

Table 3: Schedule of Assessments, Control Group

YEAR 1	Screen	Random	Week of Therapy														
Visit	screen		0	2	6	10	14	20	24	28	32	36	40	44	48	52	Total
Visit window (± days)			0	2	7	7	7	7	7	7	7	7	7	7	7	7	
Informed consent	x																1
Screening interview	x																1
Medical History & Physical Exam	x															x	2
EKG	x															x	2
IWQOL	x															x	2
Questionnaire on Eating and Weight Patterns (QEWP)	x									x						x	3
Eating Disorders Examination (EDE)	x									x						x	3
Randomization call		x															1
MD visit			x				x			x						x	4
Medical & Study Visit (weight, vital signs, concom meds, med adherence, AE's)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	14
Phone check (RC or RN)																	0
Dietary Evaluation			x														1
Lifestyle Therapy			x	x	x	x	x	x		x		x		x		x	10
Height	x																1
Urine pregnancy	x																1
Urine protein (dipstick)	x			x	x	x	x	x		x		x		x		x	10
Electrolyte panel+ magnesium + calcium				x	x	x	x	x				x		x			7
CMP +Magnesium	x									x						x	3
CBC	x															x	2
Hemoglobin & hematocrit							x			x							2
PT/PTT	x																1
TSH	x																1
Lipid Panel	x									x						x	3
Iron	x																1
Hemoglobin A1C	x						x			x						x	4
Vitamin D 25-OH	x																1
DEXA	x																1
Town Hall Meetings							**Every other month**										

Town Hall meetings shall begin after 3 subjects are enrolled

Table of Acronyms/ Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
b.i.d.	twice per day
BMP	Basic Metabolic Panel
CRF	Case Report Form
CV	Curriculum Vitae
GCP	Good Clinical Practices
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Investigational Review Board
SAE	Serious Adverse Event
q.d.	once per day
AT	Aspiration Therapy
ASPIRE	Aspire Bariatrics, Inc.
PEG	Percutaneous Endoscopic Gastrostomy
DEXA	Dual Energy X-Ray Absorptiometry

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Table of Appendices

[1] Appendix G has been incorporated in Appendix I

1.0 Introduction

Obesity is a chronic and stigmatizing disease that has become a major health problem in the United States and many other countries throughout the world because of its high prevalence, causal relationship with serious medical illnesses, adverse effect on quality of life, and economic impact.

In the United States, approximately 68% of adults (age 20 to 74 years) are overweight or obese[1,5]. Data from US national population surveys obtained since 1960 [1960-62 National Health Examination Survey I (NHES I), 1971-74 National Health and Nutrition Examination Survey I (NHANES I), 1976-80 NHANES II, 1988-94 NHANES III, and 2007-2008 NHANES data] have demonstrated that the prevalence of obesity (BMI $\geq$ 30 kg/m^2) has nearly tripled, from 12.8% to 34%[2].

Obesity can be defined as an excessive amount of body fat, which increases the risk of medical illness and premature death. However, accurate assessment of body fat mass requires the use of sophisticated and expensive technologies that are not readily available to most physicians. Therefore, the World Health Organization and the National Institutes of Health (NIH) proposed guidelines for classifying weight status by body mass index (BMI), which is calculated as weight (in kg) divided by height (in m^2)[3,4]. Both men and women who have a BMI $\geq$ 30 kg/m^2 are considered obese and are generally at higher risk for adverse health events than are those who are considered overweight (BMI between 25.0 and 29.9 kg/m^2) or normal weight (BMI between 18.5 and 24.9 kg/m^2). For example, women who have a BMI of 33 kg/m^2 have a 50-fold increased relative risk of type 2 diabetes than women who have a BMI <22 kg/m^2 [5]. In general, the risk of medical complications associated with obesity increase with increasing BMI.

Weight loss improves most of the medical complications associated with obesity. Moreover, many of these beneficial effects are apparent after only moderate weight losses of 5% to 10% of initial body weight[6]. In addition, moderate weight loss can delay or decrease the risk of developing new obesity-related diseases, such as diabetes[7,8]. Bariatric surgery-induced weight loss in extremely obese subjects (BMI $\geq$40 kg/m^2) has considerable medical benefits, including normalizing glucose homeostasis in subjects with type 2 diabetes or impaired glucose tolerance[9], preventing the future development of diabetes[10], improving or normalizing blood pressure in subjects with

hypertension[11,12], improving or completely eliminating obstructive sleep apnea syndrome[13,14,15], decreasing joint pain[16], and improving health-related quality of life[17].

Despite the medical benefits of bariatric surgery, less than 2% of the extremely obese population avail themselves of bariatric surgery in any one year. The reasons cited by patients for not choosing bariatric surgery include (i) concerns of the risks and complications associated with bariatric surgery, (ii) a disinclination to adopt the special diets required of bariatric patients, (iii) economic concerns (being out of work force during recovery, lack of insurance coverage), and (iv) the lack of reversibility.

1.1 Non-Surgical Treatments (Medical Therapy)

Non-surgical treatments of obesity include: 1) diet, exercise, and behavior modification programs, and 2) weight loss medications.

Many different diets have been proposed for treating obesity. These dietary approaches vary in their total energy prescription, macronutrient (fat, carbohydrate, and protein) content, energy density, glycemic index, and whether or not pre-packaged meal replacements are used to enhance portion control. A meta-analysis of randomized controlled trials (RCTs) that compared diet therapy that focused on fat restriction with those that focused on energy restriction found that both dietary approaches result in about a 3% weight loss at 12 months after starting therapy[18]. An expert panel convened by the National Heart, Lung and Blood Institute (NHLBI) recommended the use of a low-calorie diet that decreases energy intake by 500 to 1000 kcal/day4. This type of diet is most effective when used in conjunction with behavioral therapy to enhance dietary compliance and increase physical activity, and results in a weight loss of about 4%-8% at 1 year[19,20]. For a 5'6" person, this is approximately 10% - 20% excess weight loss (EWL). Unfortunately, it is difficult to maintain long-term weight loss by lifestyle modification, and most patients who lose weight by dieting regain their lost weight over time[21].

Drugs have been developed to enhance weight loss in obese patients. Of the drugs that are approved by the United States Food and Drug Administration (FDA) to treat obesity, only orlistat, is approved for long-term use. This medication was approved by the FDA in 1999; a low-dose form of orlistat has

received over-the-counter approval. A meta-analysis of RCTs that evaluated the clinical efficacy of orlistat therapy found that compared with placebo therapy, orlistat-treated subjects had a 2.9% greater weight loss at 1 year of therapy[22]. Moreover, weight recidivism still occurs despite continued drug treatment. Data from the longest clinical trial of drug therapy for obesity (a 4-year randomized controlled trial comparing orlistat therapy plus lifestyle intervention with placebo therapy plus lifestyle intervention) found that study subjects achieved their lowest body weight during the first year, with gradual weight regain thereafter[23]. Therefore, even pharmacotherapy provided in conjunction with lifestyle intervention achieves only moderate short-term weight loss (about 8%-10% body weight loss at 1 year), with weight regain thereafter, despite continued therapy.

Orlistat treatment has side effects[24]. The most common side effects associated with orlistat therapy are related to orlistat's action on gastrointestinal lipases. Approximately 70% to 80% of subjects treated with orlistat experienced one or more gastrointestinal events, such as loose and frequent stools, urgency and incontinence. In addition, long-term orlistat treatment can affect the homeostasis of certain fat-soluble vitamins, particularly vitamins D and E. Orlistat can also affect the absorption of lipophilic medications and sub-therapeutic plasma cyclosporine levels have been reported in organ transplant recipients after they began orlistat therapy for obesity[25,26].

1.2 Bariatric Surgery

Bariatric surgery is the most effective available weight loss therapy for obese patients. However, surgical therapy is also more expensive and associated with a greater risk of complications than other treatment approaches. Therefore, bariatric surgery is limited to those patients who are considered "morbidly obese" and have been unable to lose weight by non-surgical treatment approaches. An NIH Consensus Conference on Gastrointestinal Surgery for Severe Obesity, held in 1991, established guidelines for bariatric surgery[27]. The panel concluded that patients with morbid obesity, defined as a BMI $\geq$ 40 kg/m^2 or a BMI $\geq$ 35 kg/m^2 plus high-risk co-morbid conditions, are eligible for surgery. The use of bariatric surgery to treat obesity has increased worldwide and the number of patients that are eligible for bariatric surgery far exceeds the current capacity for providing this therapy.

The two most commonly performed bariatric surgery procedures are Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding. More recently, the use of sleeve gastrectomy to treat obesity has been increasing.

1.2.1 Roux-en-Y Gastric Bypass (GBP)

The gastric bypass procedure, also known as *Roux-en-Y gastric bypass* accounts for more than 70% of bariatric surgery procedures in the United States. Gastric bypass involves constructing a small proximal gastric pouch by stapling across or completely transecting the stomach. The pouch has a small outlet that is anastomosed to a segment of jejunum, brought up to the pouch as a Roux-en-Y limb. This results in a bypass of most of the stomach and duodenum. On average, patients who have had gastric bypass surgery lose about 60% of their excess body weight or about 30% of their initial body weight. Serious complications after gastric bypass (e.g., pulmonary emboli, anastomotic leak, bleeding, and wound infection) occur in about 5% of patients[28]. Perioperative mortality within 30 days of surgery is approximately 0.5% at experienced centers, but higher in community practice[14].

1.2.2 Laparoscopic adjustable gastric banding (LAGB)

Laparoscopic adjustable gastric banding (LAGB) is the least invasive bariatric operation, and involves placing a band around the upper stomach without stapling or resecting the stomach. The size of the band can be changed by inflating or deflating a balloon in the band that is connected to a subcutaneous port. Band circumference size is routinely adjusted after surgery, depending on weight loss response and gastrointestinal symptoms. Weight loss after LAGB is not as great as after gastric bypass surgery. However, these two procedures have not been compared in a randomized controlled trial. On average, patients who have had LAGB lose about 40%-50% of their excess body weight or about 20%-25% of their initial body weight. Laparoscopic adjustable gastric banding is associated with fewer and less severe complications compared with other bariatric surgery procedures. These complications include band prolapse, gastric erosions, esophageal dilatation, band and port infections, and balloon or system leaks that can impair weight loss[29,30,31]. Perioperative mortality within 30 days of surgery is approximately 0.1%[23].

1.2.3 Sleeve gastrectomy

Laparoscopic sleeve gastrectomy (LSG) was originally intended as a first-stage procedure in high-risk patients but has now become a stand-alone operation and is increasing in popularity. This procedure involves dividing the stomach along its vertical length in order to create a slender pouch or sleeve, and the excess stomach is removed. Data from several series suggest that early weight loss (1-2 yrs after surgery) is similar to Roux-en-Y gastric bypass, but long-term (≥5yrs after surgery) weight loss is worse because of greater weight regain[32]. The most serious relatively common complication after sleeve gastrectomy is gastric leaks, which occur in about 2.5% of patients[33]. Perioperative mortality within 30 days of surgery is approximately 0.2%[34].

1.3 AspireAssist™ and Aspiration Therapy

Aspiration Therapy is a novel treatment for obesity that provides the patient with a method for achieving effective "portion control" of food intake at the level of the stomach, lowering the threshold for successful weight loss and facilitates lifestyle behavior change for long-term weight management. Aspiration Therapy involves placing a specially designed gastrostomy tube, known as the A-Tube™ in the stomach and allowing the subject to aspirate a portion of gastric contents after meal ingestion. The aspiration procedure is performed about 20 minutes after the entire meal is consumed and takes about 5-10 minutes to complete. The apparatus that enables the subject to aspirate is known as the AspireAssist, developed by Aspire Bariatrics, Inc., the sponsor of the proposed trial. To date, 24 obese subjects (BMI 35.5-48.6 kg/m^2) have used this therapy for weight loss: 3 in a proof-of-principle trial in the US; 10 in pilot trial in Mexico; and 11 in the most-recent (and still-ongoing) randomized controlled feasibility trial in the US.

1.3.1 Percutaneous Endoscopic Gastrostomy

The AspireAssist A-Tube is a modified PEG (Percutaneous Endoscopic Gastrostomy) tube; and the endoscopic procedure used to implant the A-Tube is the same as used to implant PEG tubes (Ponsky Pull Method).

Endoscopically placed gastrostomy (Percutaneous Endoscopic Gastrostomy [PEG]) tubes are commonly used to provide enteral nutrition support to subjects who are expected to require long-term tube feedings. Several case

series have documented technically successful and safe placement of PEG tubes in obese patients, even those with BMI >60 kg/m^2, without evidence of greater rates of placement failure or complications than PEG tubes inserted in lean patients[35] [36].

Large diameter gastrostomy tubes are also used for gastrointestinal decompression in subjects with severe motility abnormalities or mechanical obstruction of the gastrointestinal tract. PEG tubes can be placed safely, in the outpatient setting with a success rate of 95 to 98%[37,38,39]. The endoscopic technique has been widely reported since its initial clinical use in 1980[40,41,42].

The number of PEG tubes placed in the U.S. has been steadily increasing. Approximately 81,000 PEG tubes were placed in 1991, 123,000 in 1995 and 240,000 in 2003[43,44]. The overall complication rate reported for PEG placement is in the range of 4.9 to 10.8% and are mostly minor complications[45,46,47,48]. The most common complication is PEG site infection which occurs in about 6% of patients [27,49] and responds to oral or tube administration of antibiotics. Data from a meta-analysis of seven published studies found that a single intravenous dose of a broad-spectrum antibiotic was effective in reducing the incidence of peristomal infection[50]. Other rare complications include peritonitis, necrotizing fascititis, gastrocolocutaneous fistula and gastrointestinal bleed. Procedure related mortality is rare, but when it does occur it is almost always in severely-ill patients [30].

PEG tubes can remain functional for long periods of time. Data from one study found the average durability of PEG tubes was 690 days and that of low profile gastrostomy tubes was 1701 days. Degraded tubes can be easily replaced[51]. Data from a recent large patient series found that obesity does not reduce the success rate of PEG tube placement or increase the risk of PEG tube complications.[52]

1.3.2 Principles of the Aspiration Therapy

Diet education and behavior modification has had limited success in managing obesity. Even patients who are able to achieve short-term weight loss are often unable to maintain the changes in eating behavior necessary to maintain successful long-term weight management. One of the key principles of dietary weight loss is to decrease calorie intake by decreasing meal portion size. The AspireAssist provides obese persons with the ability

to achieve successful portion control at the level of the proximal gastrointestinal tract, so that a portion of ingested food is removed from the stomach, preventing its delivery into the small intestine for absorption. In addition, Aspiration Therapy is a comprehensive system for weight loss, which involves careful medical monitoring to ensure clinical safety, in conjunction with behavioral therapy to change unhealthy eating and physical activity behaviors.

The AspireAssist will be used within a structured and regulated medical and behavioral education program. Subjects will aspirate a portion of gastric contents after consuming each of the three major meals daily. The rate of weight loss will be controlled by careful monitoring and by regulating the frequency of postprandial aspirations. The goal is for subjects to lose ~1.0% body weight per week until energy balance is achieved at a healthier BMI. Medical risk caused by overuse or "abuse" of the AspireAssist™ by study subjects is highly unlikely for the following reasons:

1. Most obese persons are trying to reach a healthier body weight and do not desire to be underweight; they do not suffer from anorexia nervosa.
2. Subjects who have evidence of psychological abnormalities that could increase the risk of non-adherence with the study protocol will be excluded from participation.
3. The study protocol requires frequent, careful and comprehensive medical monitoring to reduce the risk of complications.
4. The number of aspirations is monitored by a cycle counter within the Connector. When the cycle counter reaches a preset limit (i.e. approximately 6 weeks of aspiration sessions) aspiration through the A-Tube™ will not be mechanically possible. A new Connector, which can only be provided by the study site, will be required to allow continued aspiration. Therefore, subjects must return regularly to the study site for continued access to the A-Tube.
5. If a subject experiences rapid or excessive weight loss, the frequency of postprandial gastric aspirations will be decreased or Aspiration Therapy stopped completely until the subject responds to retraining.
6. The study protocol involves a behavioral and diet education program to change unhealthy lifestyle behaviors, which takes advantage of the reduced threshold for achieving weight management success provided by the AspireAssist.
7. The anticipated daily absorption of calories and rate of weight loss is safe. The weight loss goals of subjects in this study are equivalent to adherence

with a low-calorie diet (~1200 kcal to 1800 kcal/day) by combining a balanced deficit diet with aspiration therapy that decreases the absorption of calories from major meals by ~30%.

1.3.3 Preliminary Data

a) Proof-of-Principle Study. A "first-in-man" study was conducted at a U.S medical center prior to development of the AspireAssist™ A-Tube™ and Companion™. Gastrostomy devices were endoscopically placed in three obese women (BMI $\geq$ 40 kg/m^2), who had been unable to lose weight by self-dieting or diet programs. In one subject, the gastrostomy device was removed within several weeks of placement because of leakage of gastric contents around the ostomy site. Two subjects completed at least 6 months of Aspiration Therapy; both lost approximately 20% of their body weight at 6 months. One of these two subjects has continued therapy with this system for 5 years. At 5 years (260 weeks) of aspiration therapy, she lost 36.2 kg (36.5% of her initial body weight or 99.3% of her excess body weight) to a BMI of 25.1 kg/m^2. This subject requires treatment with a proton pump inhibitor (omeprazole 20 mg po bid) and potassium (K) supplementation (KCl 20 mEq po bid) to maintain normal serum potassium concentrations.

b) Pilot Study. A single center, prospective, open-label, 12-month, pilot study was conducted at Hospital Universitario de Nuevo Leon in Monterrey, Mexico. The purpose of the study was to evaluate the safety and weight loss effects of the A-Tube™ and Companion™, which were specifically designed for the AspireAssist™. The pilot study enrolled 12 obese subjects (mean BMI = 40.5 ± 2.82 kg/m^2, range 36.4 to 44.9 kg/m^2).

Successful A-Tube™ endoscopic implantation was performed in all subjects, with a typical procedure time of 15 minutes. Except for one case of overnight observation, all subjects were discharged from the hospital within 3 hours after the procedure was performed. Aspiration Therapy was initiated in 10 of 12 enrolled subjects (two subjects voluntarily withdrew prior to initiating therapy; there were no complications.)

Seven serious adverse events occurred: five which were incomplete fistula closures after A-Tube removal, requiring surgical repair. This hospital did not have the appropriate size endo-clips to attempt endoscopic closure, so it's unknown as to whether these fistulas could have been repaired with a clip. The sixth SAE's was a migration of the internal A-Tube bumper into the

fistula tract at 18 weeks after the initiation of therapy, requiring an incision at the fistula tract to remove the A-Tube. It was believed this complication was caused by the research team who applied excessive tension on the outer portion of the A-Tube during the shortening procedures. The seventh SAE was an overnight hospital stay for observation of a subject who complained of abdominal pain after endoscopic A-Tube implantation.

Several minor adverse events occurred, including pain at the A-Tube site during the first week after implantation (normal recovery); skin complications (irritation, dermatitis, and erythema resolved with Neutrocort™ and Stomahesive™); and abdominal discomfort (successfully treated with Ultram™). One subject experienced a decline in plasma potassium concentration below the normal range at 20 weeks of therapy; the subject's plasma potassium returned to normal after a reminder by the study physician to take the prescribed K supplements. No other electrolyte abnormalities were detected.

Although this pilot study had no primary efficacy endpoints, body weight data was collected. At 6 months of therapy, mean percent excess weight loss, based on a normal weight defined as the midpoint of the medium frame of the Metropolitan Life tables (%EWL^{ML}), in 9 subjects still enrolled in the study was 22.7% ± 13.7% (9.7% ± 5.7% absolute weight loss). Six subjects requested to continue therapy for a full one-year. The 1-year mean %EWL^{ML} in these subjects was 37.2% ± 20.3% (16.0% ± 8.4% absolute weight loss); five of these six subjects achieved greater than 30% EWL and two subjects achieved greater than 55% EWL at 1 year.

c) Feasibility Trial This trial is an ongoing US single-center, randomized, controlled, open-label, 12-month trial. Subjects were randomized to treatment with either the AspireAssist™, which includes Aspiration Therapy plus lifestyle therapy (AT group), or to lifestyle therapy alone (behavior education, diet and exercise) (Control group), in a 2:1 ratio, respectively.

Eighteen obese subjects, 11 in the AT group (BMI: 42.6 ± 4.7 kg/m^2) and 7 in the control group (BMI: 43.4 ± 5.3 kg/m^2), were enrolled in the study. A-Tube placement was successful in all AT subjects, but 1 subject dropped out after 4 weeks of Aspiration Therapy because of abdominal discomfort. The remaining 10 AT subjects completed 52 weeks of therapy and 7 subjects completed 104 weeks (2 years). Three control subjects dropped out (one after

2 weeks, one after 8 weeks, and one after 32 weeks of therapy) and the remaining 4 control subjects completed 52 weeks of the study.

Results:

Safety: No serious adverse events occurred. However, a variety of minimal adverse events were reported, including discomfort at the A-Tube site during the first week after implantation (normal recovery) and abdominal discomfort after the first week (successfully treated with medication). No adverse psychological effects or adverse effects on eating behavior associated with AT were detected; there were no adverse attitudes towards eating, no evidence that subjects engaged in any binge eating behaviors or that they consumed more food during any meals because of the ability to remove food from the stomach, and no evidence of adverse effects on mood. In fact, there was evidence of improvement in eating behavioral traits (improved restraint, less disinhibition, more control over food intake, and decreased hunger) in the AT group.

Efficacy: At 52 weeks of therapy, mean %EWL, based on a normal weight defined as a BMI of 25.0 kg/m^2, was 49.0%±24.4% in the AT group (n=10) and 14.9%±24.4% in the control group (n=3). Successful weight loss (≥ 25% EWL) was achieved in 100% of the AT group. Percent EWL^{ML} was 42.2%±19.9% in the AT group (n=10) and 13.1%±21.5% in the control group (n=3). Successful weight loss (≥ 25% EWL^{ML}) was achieved in 90% of the AT group; the one AT subject who did not achieve "successful weight-loss" had 23.4% EWL^{ML} at 52 weeks.

Subjects in the AT Group, on average, continued to lose weight after the 52-week period. At 64, 96, and 104 weeks respectively, mean %EWL was 56.6% ± 10.9% (N=8) group, 56.9%±12.2% (N=7), and 54.7%±12.0% (N=7). At 52, 64, 96, and 104 weeks respectively, mean %weight loss was 18.6% ± 2.3%, 21.2 ± 3.1%, 21.0 ± 3.5%, and 20.1± 3.5% respectively, and mean absolute weight loss was 20.6 ± 2.5 kg , 23.0 ± 3.2 kg, 22.3 ± 3.5 kg, and 21.3±3.4 kg respectively.

Average total Impact of Weight on Quality of Life score (IWQOL) improved by 34.4 % and 20.0 % after 52 weeks of therapy in the AT and control groups, respectively. Technical success of A-Tube™ implantation was 100% in the 11 AT subjects.

1.3.4 AspireAssist Components and Use

Please refer to the Investigator's Brochure for a complete overview of the device.

Briefly, the AspireAssist consists of five components: one (1) implantable component (the A-Tube), three (3) external components, and one (1) component used for installation and adjustment purposes, each of which is described below.

- The **A-Tube**™ is similar in design and implantation techniques (via endoscopic pull-through method) to a standard PEG tube. The external portion of the A-Tube is cut to a length (using the Skin-Port Installation Tool Kit) so that it is almost flush with the abdominal skin, and its length is adjusted, by a healthcare professional, as the subject loses weight.

- The **Skin-Port**™ connects to the proximal end of the A-Tube and prevents the tube from migrating into the stomach. The Skin-Port contains a valve that is normally closed to prevent gastric leakage, and is opened, by engaging the Connector (see below), when the subject aspirates after a meal. The Skin-Port is installed by a healthcare professional (using the Skin-Port Installation Tool Kit) but operated by the subject (solely through engaging and disengaging the Connector).

- The **Connector**™ mates with the Skin-Port and allows coupling between the A-Tube and the Companion (see below). The Skin-Port valve opens when the subject connects the Connector to the Skin-Port and closes when the subject disconnects the Connector. The Connector contains a "counter" that tracks the number of times the Connector is attached to the Skin-Port. When the count reaches 115 aspiration cycles (about 5 - 6 weeks of therapy), the Connector locks up and the Skin-Port can no longer be accessed for aspiration. This provides an additional safety measure against long-term unsupervised use or overuse. The subject must return to the clinic to obtain a new Connector in order to continue aspiration therapy.

- The **Companion**™ allows the subject to aspirate his/ her gastric contents by alternately draining stomach contents and infusing (potable) water into

the stomach when the apparatus is fully connected (see **Figure 1.2.1**). The Companion is an entirely passive device and is reusable.

- The **Skin-Port™ Installation Tool Kit** facilitates (i) cutting of the A-Tube to length and (ii) removal and installation of the Skin-Port, both procedures done by the healthcare professional.

1.3.4.1 Principles of Operation

The AspireAssist is intended to assist in weight reduction of obese subjects. The therapy begins after the stoma track is healed 10 days after A-Tube placement. **Figure 1.2.1** illustrates typical use of AspireAssist.

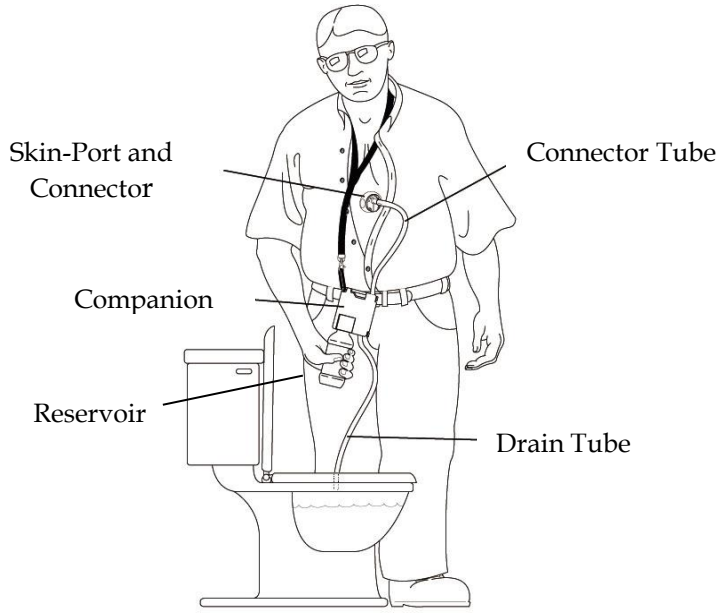

Figure 1.2.1. Patient using the AspireAssist

Per the instructions for use, subjects are instructed to aspirate 20-30 minutes after a meal. In the Proof of Principle Trial, 20-30 minutes was found to be the optimal time period for aspiration: the particle size of ingested food in the stomach was sufficiently small to allow aspiration without clogging the tube and yet minimal amounts of food had passed to the intestines.

Prior to beginning aspiration, the subject must connect the apparatus as follows:

- Fill the reservoir with potable water

- Attach the Connector tube and Drain Tube to the T-Fitting, then insert into the Companion with the arrow pointing down. Place the Lanyard of the Companion around his/ her neck
- Attach the Connector to the Connector Tube
- Attach the Reservoir to the Companion

To begin aspiration, the subject, while standing in the upright position, attaches the Connector to the Skin-Port, and the Drain Clamp on the Companion is opened to drain. The Connector when attached to the Skin-Port opens the valve and initiates the aspiration process. After the initial stomach contents are evacuated, water is infused into the stomach by closing the Drain Clamp and squeezing the Reservoir. Infusion aides to further mobilize food trapped in gastric folds and aspiration is repeated to remove the water and food from the stomach. The infusion and aspiration of water is repeated until there are no food particles observed in the evacuated fluid. Based upon energy balance studies conducted in two subjects, this process will remove approximately 30% of the ingested calories from that meal. The final step in the process is to disconnect the Connector from the Skin-Port and rinse the system out for later use.

The entire aspiration process typically takes between 5 and 10 minutes.

1.3.4.2 Training

Prior to study initiation, each endoscopist placing the A-Tube will undergo training with an experienced endoscopist and qualified Aspire personnel. In addition, investigators and designees will be fully trained on the AspireAssist Aspiration Therapy System Instructions for Use, as well as procedures for training research subjects on AspireAssist use and Aspiration Therapy. Documentation of training will be kept at each study site.

Training of study subjects will be performed by the research team at each study site.

All principal investigators, co-investigators, and designees will be trained on this clinical investigation plan prior to involvement in this clinical trial. Documentation of training will be kept current at each study site.

2.0 Study Objective

The objective of this study is to demonstrate the safety and efficacy of the AspireAssist™ Aspiration Therapy System as a weight loss therapy for obese adults.

2.1 Primary Efficacy Endpoints (52-week)

The first effectiveness primary endpoint is the mean percent excess weight loss (%EWL) at 52-weeks. The hypothesis for the first primary effectiveness endpoint is that the difference in the mean percent excess weight loss (%EWL) at 52-weeks for the Aspiration Therapy (AT) group and Control group is at least 10%. %EWL is defined as absolute weight loss divided by baseline excess weight and multiplied by 100. Excess weight will be determined from ideal body weights based on a BMI=25 kg/m^2.

The second effectiveness primary endpoint is that at least 50% of the AT group at 52-weeks realizes a %EWL $\geq$ 25%.

Both primary endpoints must be met for the study to be considered a success.

2.2 Secondary Efficacy Endpoints (52-week)

i) Mean percent absolute weight loss in the AT group compared to the Control group
ii) Proportion of subjects who achieve ≥10% absolute weight loss in the AT group compared to the Control group

The percent change in the AT Group compared with the percent change in the Control Group will be assessed for the following variables:
iii) Serum triglyceride, HDL-cholesterol and LDL-cholesterol concentration
iv) Systolic and diastolic blood pressures
v) "Impact of Weight on Quality of Life" (IWQOL) questionnaire
vi) Hemoglobin A1C (for subjects with T2 diabetes at screening only)
vii) mean percent change in medications

In the AT group only:
viii) Procedural success defined as successful endoscopic placement of the A-Tube™ in all subjects undergoing endoscopy

2.3 Safety Outcomes

Safety will be evaluated by:

1. Incidence of device-related, procedure-related and therapy- related adverse events
2. Incidence of device-related or unrelated serious adverse events, including unanticipated adverse device effects
3. Development of adverse eating behaviors as measured by EDE and QEWP-R

3.0 Study Design

This is a prospective randomized, active treatment controlled, parallel group, multi-center superiority trial of an endoscopically-placed device for weight loss. After the informed consent process, consent forms will be signed and dated, and all subjects who pass the screening process will be randomized in a 2:1 fashion to one of two groups for 52 weeks: AspireAssist plus Lifestyle Therapy ("AT Group") or Control Group (Lifestyle Therapy only). Lifestyle therapy involves treatment with a behavioral education weight loss program delivered as 10 individual or group sessions, in person or by webinar, over 52 weeks. It is, at the site's discretion, whether to provide (i) individual or group sessions or (ii) in-person or by webinar, but a site must provide the same therapy for all subjects. However, in the event, a site that has chosen group sessions are unable to schedule a patient for a group session, the site may provide an individual session for that patient. Aspiration Therapy involves percutaneous endoscopic placement of a gastrostomy device, which permits aspiration of a portion of gastric contents after meals, in addition to lifestyle therapy.

After 52 weeks, Control Group participation will end. The duration of therapy in the Control Group will end at 12 months because the number of drop-outs and rate of weight regain typically increases after 52 weeks of diet and behavioral therapy.

Subjects assigned to the AT Group will have the option to remain in the study for up to 4 more years for follow-up, provided they maintain a minimum of

10% weight loss (from baseline). Since AT requires subjects to perform active therapy and non-responder subjects (e.g., those unable to maintain 10% WL) are not able or do not desire to fulfill this activity, continuing these subjects long-term does not add meaningful data to the study or provide adequate benefit to the subjects. AT subjects who are either non-responders or wish to withdraw from the study will have their A-Tubes removed as soon as can be scheduled and will be followed for 6-months post-tube removal to assess safety and weight maintenance. For those non-responder subjects who have maintained between 5% and 9.9% WL during the study, the option to continue Aspiration Therapy may be considered if the subjects are willing to enroll in the Enhanced Coaching sub-study (provided the study site is participating in this optional sub-study and has received local IRB approval). Since these subjects have already received the A-Tube but have not derived the full benefit of the therapy, it is possible that the additional support and interaction provided in the Enhanced Coaching study may help them become more compliant with AT and improve their weight loss to greater than 10%. Additional information regarding this sub-study is provided in Section 5.5.12.

Safety and efficacy data post-52 weeks will only be summarized for post-market reporting and publications and no statistical hypothesis tested.

4.0 Study Population & Recruitment

The study population is 175 obese men and women who (i) have a Body Mass Index (BMI) between 35.0 and 55.0 kg/m^2, (ii) are 21-65 years old, and (iii) have failed to achieve and maintain weight loss with non-surgical weight loss therapy.

Subjects will be enrolled at 8-12 sites within the United States. Each site is encouraged to enroll, on average 15 subjects (i.e. 10 treatment group and 5 control group) and no fewer than 10 subjects. No site may enroll more than (30) subjects.

Randomization will be stratified for both initial BMI and sex to help ensure equal number of males in both the therapy and control group and to guarantee that extremely obese subjects (BMI >40 kg/m^2) are equally distributed between the study groups. Initial BMI, sex, and race will be compared between study groups and adjusted in the analysis as covariates if an imbalance is found between groups.

4.1 Inclusion Criteria

1. Measured BMI of 35.0-55.0 kg/m^2 at time of screening.
2. 21- 65 years of age (inclusive) at time of screening.
3. Failed attempt for a duration equal to 3-months at weight loss by alternative approaches (e.g. supervised or unsupervised diets, exercise, behavioral modification programs).
4. Stable weight (<3% change in self-reported weight) over the previous 3 months at time of screening).
5. Women of childbearing potential must agree to use at least one form of birth control (prescription hormonal contraceptives, diaphragm, IUD, condoms with or without spermicide, or voluntary abstinence) from time of study enrollment through study exit.
6. Willing and able to provide informed consent in English and comply with the protocol.

4.2 Exclusion Criteria

1. Previous abdominal surgery that significantly increases the medical risks of gastrostomy tube placement
2. Esophageal stricture, pseudo-obstruction, severe gastroparesis or gastric outlet obstruction, inflammatory bowel disease
3. History of refractory gastric ulcers
4. Ulcers, bleeding lesions, or tumors discovered during endoscopic examination.
5. History of radiation therapy to the chest or abdomen
6. Uncontrolled hypertension (blood pressure >160/100).
7. Diabetes treated with insulin or sulfonylurea medications
8. Any change in diabetes medication in previous 3 months
9. Hemoglobin A1C >9.5%
10. History or evidence of serious pulmonary or cardiovascular disease, including acute coronary syndrome, heart failure requiring medications, or NYHA (New York Heart Association) class III or IV heart failure (defined below):

    Class III: patients with marked limitation of activity and who are comfortable only at rest

    Class IV: patients who should be at complete rest, confined to bed or chair and who have discomfort with any physical activity

11. Coagulation disorders (platelets < 100,000, PT > 2 seconds above control or INR > 1.5)
12. Anemia (Hemoglobin <11.0 g/dL in women and <12.5 g/dL in men)
13. Liver enzymes (ALT and AST) ≥3.0 times the upper limit of normal
14. Thyroid Stimulating Hormone (TSH) >1.5 x upper limit of normal at screening.
15. Osteoporosis (DEXA T-Score ≤ -2.5 standard deviations below normal peak values).
16. History of fragility fractures (fractures resulting from a fall from a standing height or less, or presenting in the absence of obvious trauma)
17. Pregnant or lactating
18. Diagnosed Bulimia or diagnosed Binge Eating Disorder (using DSM IV criteria)
19. Night Eating Syndrome (diagnosed by EDE)
20. Serum potassium < 3.8 mEq/L
21. Chronic abdominal pain that would potentially complicate the management of the device
22. Taking a GLP-1 agonist < 6 months.
23. Taking prescription or over-the-counter medications for weight loss in the last 3 months before screening, or planning to participate in a commercial weight loss program in the next 24 months. This includes taking medications for an unrelated medical condition which have been shown to result in weight loss such as Topiramate or Bupropion.
24. Taking medication once or more per week that causes weight gain (e.g. atypical antipsychotics, monoamine oxidase inhibitors, lithium, selected anticonvulsants, tamoxifen, glucocorticoids)
25. Self- reported history of substance abuse in last 3 years.
26. Malignancy in the last 5 years (except for non-melanoma skin cancer).
27. Physical or mental disability or psychological illness that could interfere with compliance with the therapy.
28. At high risk of having a medical complication from the endoscopic procedure or Aspiration Therapy weight loss program for any reason, including poor general health or severe organ dysfunction, such as cirrhosis or renal dysfunction (GFR <60 mL/min/1.73 m^2 at screening, calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation).

5.0 Study Procedures

5.1 Screening

After signing the Informed Consent Form, all potential subjects will complete the following screening procedure:

Subjects should fast for 12 hours overnight before this visit.

- Verification of subject eligibility according to all Inclusion and Exclusion Criteria.
- "Impact of Weight on Quality of Life" (IWQOL-Lite). This self-administered questionnaire is used to address specific areas of quality of life, including Physical Function, Self-Esteem, Sexual Life, Public Distress, and Work; takes approximately 10-15 minutes to complete. (See **Appendix A**)
- Questionnaire on Eating and Weight Patterns – Revised (QEWP-R). This self-reported measure assesses binge eating, purging and other eating behaviors and takes approximately 10 minutes to complete. (See **Appendix A**)
- Eating Disorder Examination (EDE) version 12.0D[53] . EDE is an interview-based assessment of disordered attitudes and behaviors related to eating, body-shape, and weight that also has items designed to diagnose eating disorders based on DSM-IV criteria. The psychometric properties of the measure are sound[54], and it is currently considered to be the best eating disorder assessment interview (Garner, 2002). The EDE will be administered by interviewers trained on interview administration and scoring. The EDE takes approximately 1 hour to complete.
- Screening interview to determine subject's ability to comply with Aspiration Therapy or Lifestyle Therapy and ensure subject fully understands all aspects of study involvement. (See **Appendix A**)
- Medical history
- Physical examination (including height, weight, and blood pressure outlined in **Appendix B**)
- Resting 12-lead electrocardiogram read locally by site physician
- Blood tests; a central lab will analyze samples for the following analytes:
    - Complete Blood Count (CBC): hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH),

and mean corpuscular hemoglobin concentration (MCHC), platelet count
    - PT, PTT (prothrombin time, partial thromboplastin time)
    - TSH
    - Complete Metabolic Panel (CMP):glucose, calcium, sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, ALT, AST, bilirubin), plus magnesium
    - Lipid panel (Total cholesterol, LDL-C, HDL-C, triglycerides)
    - Serum iron
    - Vitamin D 25-OH
    - Hemoglobin A1C
- Urine pregnancy test in women of childbearing potential
- Urine protein dipstick
- Dual Energy X-Ray Absorptiometry (DEXA); Total body, hip and spine bone mineral density will be assessed by using DEXA to screen for osteoporosis. Osteoporosis is defined as a DEXA T-Score ≤ -2.5 standard deviations below normal peak values. Whole body, hip and spine scans will be performed annually throughout the study in subjects assigned to the Aspiration Therapy Group. Changes in bone mineral density in the AT Group will be compared to baseline values and with changes in bone mineral density reported in previous weight loss studies (historical controls).

5.2 Randomization

Eligible subjects who fulfill all enrollment criteria obtained during Screening will be randomized to the Treatment or Control Group in a 2:1 ratio, stratified by sex and BMI (< or ≥ 40.0 kg/m2) at each study site. A web-based randomization scheme will be established to ensure there is no possibility that group assignment can be known in advance. To avoid temporal bias, randomized blocks of varying sizes will be used to prevent investigators from having advanced knowledge of the assignment of the last subject in a given block. Randomization will occur within 14 days of the screening visit. Subjects will be notified by telephone of their group assignment.

5.3 Control Group

Subjects randomized to the Control Group will participate in 14 Medical & Study visits and a 10-session diet and behavioral education weight loss

program called "Lifestyle Therapy" (see **Appendix C**), which will be delivered to subjects over 52 weeks. These Lifestyle Therapy sessions may be given individually during the same visit as the Medical & Study visits or in a group with other subjects who are assigned to the Control Group.

Each individual Lifestyle Therapy session will last 20-30 minutes and group sessions, about 60 minutes; the sessions will be given at week 0, 2, 6, 10, 14, 20, 28, 36, 44, and 52.

Topics include includes nutritional, physical activity, and behavioral education topics. Subjects are instructed to follow a structured eating plan, which involves eating three meals a day, eating slowly and chewing food well, drinking plenty of fluids with each meal, and limiting snacking between meals. Physical activity topics include the health benefits of physical activity and strategies for increasing lifestyle activity. The behavioral program emphasizes strategies of self-monitoring and goal-setting, and includes problem-solving, dealing with high-risk situations / cues for unhealthy eating, and stress management.

All subjects will be asked to take a multivitamin and mineral supplement daily during the lifestyle intervention program.

The Medical & Study visits occur at weeks 0, 2, 6, 10, 14, 20, 24, 28, 32, 36, 40, 44, 48, and 52, as outlined in the study assessment schedule in **Table 3**.

All Medical & Study visits will include the following assessment and procedures:

- Body weight
- Blood pressure and temperature
- Presence of normal menses in women
- Adverse Events
- Concomitant medications
- Adherence with taking study-related medications (i.e. multivitamin supplement)
- Lifestyle Therapy (only at weeks 0, 2, 6, 10, 14, 20, 28, 36 ,44, and 52)

Additional procedures and assessments are performed at visits as shown in **Table 3**:

- Blood tests
- Urine (dipstick) protein test

- Physical Examination
- EKG
- Eating Disorder Examination (EDE)
- DEXA
- Questionnaires (IWQOL, QEWP-R)

If a subject develops 2+proteinuria (100mg/dL) as measured by two successive dipstick analyses, random urine shall be collected to measure protein and creatinine to calculate protein to creatinine ratio.

For subjects who have diabetes, subjects will obtain a check (by fingerstick) of their fasting blood glucose every morning and a postprandial (2-3 hours after the evening meal) every evening for the first 6 weeks after starting AT, and report this blood glucose data to the study site every week by phone call, electronically, or during the study visit. Subjects will also be instructed to contact the research site immediately if their fasting blood glucose is <70 mg/dL or >200 mg/dL, or if their postprandial blood glucose is >400 mg/dL.

After the first 6 weeks, the protocol for home blood glucose monitoring will be determined by the study site physician. All changes in diabetes medications, based on changes in glycemic control, will be made in conjunction with the subject's private physician to ensure medical care is coordinated.

5.3.1 Retention Plan

Several strategies will be used to enhance adherence with lifestyle intervention and reduce the rate of drop-outs in the Control Group: 1) a philosophy of partnership and collaborative relationships will be encouraged between research site personnel and study participants; 2) reimbursement for time required for study visits will be provided; 3) self-monitoring of dietary intake and physical activity, which will be incorporated into the lifestyle therapy program; 4) Town Hall Meetings will be held for subjects to share experiences and encourage each other, 5) participants will be specifically encouraged to return for key visits that involve outcome measures, so that this data will be captured even in participants who have not regularly attended the other visits, and 6) for participants who, in the opinion of the study team, are losing motivation, one or more meetings with a behavioral

consultant or a successful study participant may be arranged, providing the subject is so willing.

5.3.2 Pregnancy

At each follow-up visit, the research nurse or study physician queries all female subjects with childbearing potential whether there is any change to their menstrual cycle or their birth control. Urine pregnancy tests will be performed as needed at the discretion of the research team. If a urine pregnancy test result is positive, a stat serum pregnancy test (human chorionic gonadotropin, HCG) shall be performed to verify pregnancy. If pregnancy is verified, therapy must be immediately discontinued and the study termination protocol followed. Please contact the Sponsor within one working day to report a pregnancy.

5.4 Treatment Group (AspireAssist plus Lifestyle Therapy)

Those subject randomized to the treatment group will undergo endoscopic A-Tube placement, Aspiration Therapy training and treatment, along with Lifestyle Therapy. The schedule of assessments for the treatment group is detailed in **Table 1-2** and described below.

A-Tube placement must occur within 30 days of the screening visit. Subjects who do not meet this timeline will be withdrawn from the study.

5.4.1 A-Tube™ Insertion Procedure Visit

Prior to A-Tube insertion, the study coordinator shall notify the Aspire study liaison of the date of the procedure and verify that all enrollment criteria have been met. The subject must have signed and dated the consent form, met all inclusion criteria, met none of the exclusion criteria, and completed all screening and baseline procedures prior to A-Tube placement.

The subject shall be instructed to fast after midnight the night before the procedure and make arrangements to have someone drive him/her home after the procedure.

Data collected at the time of A-Tube insertion shall include:

- Body weight (using the designated study scale)
- Unidentifiable photograph of the subject taken prior to A-Tube placement (one front and one side view without the subject's head appearing in the photo); to be used by the Sponsor in scientific presentations or publications. (An additional photo will be taken at 52-weeks.)
- Any changes in health since the screening visit (these will be considered "preexisting")
- Any changes to medications (these will be considered "preexisting")

Detailed instructions for the AspireAssist A-Tube placement and use are in **Appendix D**.

An A-Tube is placed in subjects by a gastroenterologist or endoscopically-trained surgeon in an endoscopy suite. This procedure involves performing upper gastrointestinal endoscopy and close medical monitoring. The choice of specific sedative and a decision whether an anesthesiologist or anesthetist should be present during the procedure is left to the discretion of the endoscopist, based on the subject's risk of apnea and other complications. A history of disordered breathing, obstructive sleep apnea, obesity-hypoventilation syndrome, and thick neck with restricted movement are important risk factors that suggest use of short acting sedation and more careful monitoring under the supervision of an anesthesiologist or anesthetist should be considered. Pulse oximetry and heart rate are monitored throughout the procedure. A routine upper endoscopy, which includes examination of the esophagus, stomach and the proximal duodenum, is performed. The tip of the endoscope is then positioned in the gastric body or antrum of the stomach, and the A-Tube exit site is prepped and draped in sterile fashion. The site for A-Tube placement should be identified by both transillumination and finger indentation. The skin and subcutaneous tissue at the exit site area is injected with an anesthetic, and a small (<1-cm) horizontal skin incision is made by using a scalpel. The safe tract technique (no air bubbles observed after inserting a needle with syringe containing several ml of saline or anesthetic until the needle is visualized in the gastric lumen) should be used to ensure no intervening loop of bowel is present between the stomach and the anterior abdominal wall. A metal stylet with a plastic sheath is passed through the abdominal wall into the gastric lumen. After removing the inner stylet, a wire is passed through the plastic sheath into the stomach lumen. The wire is grasped with a snare, and both the endoscope and wire are removed through the mouth. The A-Tube delivery system is attached to the oral portion of the wire and pulled through the abdominal wall exit site.

The endoscope is passed into the stomach again to confirm proper placement of the tube and internal bumper. Endoscopic photographic imaging will be performed at the end of the procedure to document proper A-Tube placement.

After endoscopic A-Tube placement is completed, subjects are observed in the recovery area of the endoscopy suite or admitted to the hospital for up to 24 h, at the discretion of the physician performing the procedure.

Antibiotic prophylaxis for 24 hours is given to each subject: 1 g of cefazolin sodium intravenously approximately 30-60 minutes before A-Tube placement and subsequent oral cephalexin (500 mg q 12 hrs) for 24 hours (two doses) after endoscopy. If the subject is allergic to cefazolin, either clindamycin (900 mg intravenously) can be given followed by oral clindamycin therapy (300 mg p.o. every 8 hours) for 24 hours (three doses) after endoscopy or vancomycin (1 gram intravenously) can be given before the procedure (no post endoscopy therapy. Ultimately, the exact antibiotic regimen used in any subject is at the discretion of the study site gastroenterologist.

If the A-Tube cannot be placed safely, based on the judgment of the endoscopist, or if an exclusion criteria is discovered during endoscopy, the procedure should be terminated and subject discharged from further participation in the study.

5.4.2 Management after A-Tube Insertion

For the first 2 days after A-Tube insertion, the subject should sponge bathe and the skin around the A-Tube should be cleaned using an aseptic technique. After 2 days, the subject may shower provided that Tegaderm (or equivalent) is used to cover the A-Tube while showering during the first week. However, bathing by submersion in water should be avoided for the first 2 weeks to give the fistula time to heal. The skin around the A-Tube should be cleaned every day with a mild soap and water. The site must be dried thoroughly because moisture can contribute to infection and skin breakdown. While cleaning the skin, the subject should look for signs of infection, such as redness, swelling, tenderness, and purulent drainage. Some drainage around the tube is a normal reaction to the foreign body and is not a true infection.

5.4.2.1 Telephone Check-up

The day after A-Tube placement, a member of the research team shall call the subject to inquire about potential complications (e.g. excessive pain, excessive bleeding around the stoma site, gastrointestinal complaints).

Remind the subject to:
- Take pain medications, as prescribed
- Sponge bathe for the first 2 days, then he/she may begin showering, using a Tegaderm cover for the first week, but submersion is water should be avoided until the stoma tract has healed
- Keep the site clean and dry and protect it from potential trauma (avoid carrying children, pets, other objects against the abdomen)
- Sleep on the back or side; avoid sleeping on the belly

5.4.2.2 Day 7 Visit

Approximately 7 days after the insertion procedure, the subject shall return to the study site for a check-up visit. The following shall be assessed:
- Body weight
- Blood pressure and temperature
- Stoma site healing
- Adverse Events
- Changes to medications
- Dietary Evaluation (see **Appendix E**)

Remind the subject to
- Take pain medications, as prescribed
- Keep the site clean and dry; avoid submersion in water until the stoma tract has healed
- Protect the insertion site from potential trauma (avoid carrying children, pets, other objects against the abdomen)
- Sleep on the back or side; avoid sleeping on the belly

5.4.2.3 Day 14 Visit: Skin-Port Placement / Aspiration Initiation & Instruction

Approximately 14 days (no sooner than 10 days) after A-Tube placement, the subject shall return to the medical center for study assessments, Skin-Port

placement, and Aspiration Therapy training and initiation. The following assessments occur:

- Body weight
- Blood pressure and temperature
- Stoma site healing
- Adverse Events
- Changes to medications
- Lifestyle Therapy
- Urine protein (dipstick)

The device installation is not considered complete until the Skin-Port™ is fastened to the A-Tube. This procedure is explained in detail in the AspireAssist Skin-Port Instruction for Use (**Appendix F**). Briefly, the ideal length of the Skin-Port from the belly is determined, the subject lies down, the A-Tube is cut and the Skin-Port snapped in place. The length of tube removed shall be recorded. The entire procedure takes about 10 minutes to perform. Once the A-Tube is converted to a low profile Skin-Port, the subjects are trained to: 1) aspirate gastric contents after meals by using the specialized Companion™ aspiration device 2) maintain a clean A-Tube site, and 3) recognize signs and symptoms of potential A-Tube complications (see **Appendix I**).

Aspiration Therapy starts at the time the Skin-Port is fastened to the A-Tube. Subjects are instructed to consume a structured eating plan, which involves eating three meals a day, chewing food well, drinking a minimum of 16 ounces of non-caloric fluid with each meal, a minimum of 64 ounces of non-caloric fluid per day (including fluids ingested at meals) and limit snacking between meals. Subjects are also instructed to call their study team immediately if they are experiencing severe diarrhea or vomiting at any time with Aspiration Therapy to minimize the risk of fluid imbalances.

The aspiration procedure is performed approximately 20 minutes after finishing a meal and takes approximately 10 minutes to complete. The procedure involves connecting the Companion to the Skin-Port, which results in draining a portion of ingested food from the stomach (into a waste container or toilet), thereby preventing passage of food into the small intestine where food absorption occurs. Instructions for appropriate

aspiration of gastric contents are described in the **AspireAssist User's Manual** (**Appendix H**).

5.4.3 Phone Call at Week 0

A member of the study team shall call the subject the first day after having the Skin-Port installed to make sure the subject is aspirating satisfactorily.

5.4.4 Vitamins and Minerals

All subjects will take a multivitamin and mineral supplement daily. Additional iron supplementation (ferrous sulfate 325 mg/day taken with orange juice) should be considered in menstruating women who have a blood hemoglobin value <12 g/dL. The multivitamin and mineral supplement should be taken at night before going to sleep or least 2 hours before subjects aspirate gastric contents.

5.4.5 Medications

Subjects taking prescription or non-prescription medications related or unrelated to the study should take their medications at night before going to sleep, after aspirating, or at least 2 hours before aspirating gastric contents. If medications need to be taken with food, a snack should be consumed with the medication and not aspirated.

For subjects that have diabetes, subjects will obtain a check (by fingerstick) of their fasting blood glucose every morning and a postprandial (2-3 hours after the evening meal) every evening for the first 6 weeks after starting AT, and report this blood glucose data to the study site every week by phone call, electronically, or during the study visit. Subjects will also be instructed to contact the research site immediately if their fasting blood glucose is <70 mg/dL or >200 mg/dL, or if their postprandial blood glucose is >400 mg/dL.

After the first 6 weeks, the protocol for home blood glucose monitoring will be made at the discretion of the study site physician. All changes in diabetes medications, based on changes in glycemic control, will be made in conjunction with input from the subject's private physician to ensure medical care is coordinated.

5.5 Study Visits and Medical Monitoring

A careful medical monitoring protocol, involving regular blood tests, 12-lead electrocardiograms, and clinical follow-up visits with a research nurse or study physician, is followed (outlined in **Tables 1 and 2**) to help ensure medical safety.

5.5.1 Follow-Up Visits

The study entails one follow-up visit at 48-72 hours (denoted by week "0.5") after initiation of Aspiration Therapy and another 13 follow-up visits at weeks 2, 6, 10, 14, 20, 24, 28, 32, 36, 40, 44, 48, and 52 after initiation of Aspiration Therapy, as outlined in the study assessment schedule in **Table 1 and 2**. Follow-up visits starting at week 2 are to occur to within 7 days of scheduled visit window.

All follow-up visits will include the following assessment and procedures:

- Body weight
- Blood pressure and temperature
- Presence of normal menses in women
- Stoma site assessment
- Adverse Events
- Concomitant medications
- Document AspireAssist Connector counts
- Adherence with routine Aspiration Therapy
- Adherence with taking study-related medications (i.e. multivitamin and mineral supplements, as prescribed.)
- Dispense study supplies, as needed
- Skin-Port shortening, as needed

Additional procedures and assessments are performed at visits as shown in **Table 1 &2**:

- Lifestyle Therapy (at weeks 2, 6, 10, 14, 20, 28, 36 ,44, and 52)
- Blood tests
- Urine (dipstick) protein test
- Physical Examination
- EKG
- Eating Disorder Examination (EDE)
- DEXA

- Questionnaires (IWQOL, QEWP-R)
- Subject Photograph

If a subject develops 2+proteinuria (100mg/dL) as measured by two successive dipstick analyses, random urine shall be collected to measure protein and creatinine to calculate protein to creatinine ratio.

5.5.2 Rate of Weight Loss

The target weight loss is up to ~2% of initial body weight/week in the first 4 weeks after starting AT, and ~ 0.5 - 1% body weight loss/week thereafter, until a normal BMI is achieved. More rapid rates of weight loss or lack of adequate weight loss require interviewing the study subject and adjusting the frequency and/or technique of postprandial aspirations. The research sites decrease the frequency of aspirations, and, if needed, temporarily stop meal aspiration completely, in subjects who demonstrate excessive weekly rates of weight loss (e.g. > 2% absolute weight loss/week for more than 4 weeks). The Clinical Trial Medical Consultant will monitor weekly weight loss for each subject and instruct the research site to stop aspiration therapy in subjects who demonstrates excessively rapid rates weight loss (by temporarily removing the Connector). These subjects are able to re-start aspiration therapy after 1-2 meals per day to evaluate the rate of weight loss at a reduced frequency of aspiration.

5.5.3 Serum Potassium

A decrease in serum potassium concentration can occur with repeated aspiration of gastric contents, because of the loss of gastric acid and compensatory potassium excretion by the kidney. Therefore, serum potassium concentrations will be closely monitored in study subjects. The following protocol shall be followed to reduce the risk of hypokalemia:

a. **Ensure appropriate initial serum potassium concentrations**. Serum K concentration must be ≥3.8 mEq/L before starting Aspiration Therapy. If a potential subject has a serum K concentration that is <3.8, an attempt should be made to identify causal factors (e.g. history of diuretic therapy) so that any precipitating cause can be addressed to reduce the risk of future hypokalemia. Treatment with oral potassium supplements can be given until serum K concentration is ≥3.8 mEq/L, if Aspiration Therapy is desired in this subject.

b. **Monitoring serum potassium concentration**. Serum K concentration must be monitored regularly throughout the use of Aspiration Therapy (See Schedule of Assessments, Tables 1-3). No additional medical intervention is necessary if serum K concentrations remain ≥3.8 mEq/L and <5.6 mEq/L.

c. **Managing a decline in serum potassium to <3.8 mEq/L.**

i. **Serum potassium concentration decreases to 3.3-3.7 mEq/L.** A decline in serum K to 3.3-3.7 mEq/L requires additional monitoring and intervention. First, a medical history should be obtained to identify other possible causes for hypokalemia. If a cause for the decline in serum K is identified (e.g. non-adherence with therapy, or taking a new medication that causes hypokalemia), this problem should be addressed. Potassium supplementation should be implemented or adjusted and serum K monitored frequently (one or more times/week) until serum K concentration returns to values ≥3.8 mEq/L. Aspiration Therapy can continue while additional potassium therapy is being given.

ii. **Serum potassium concentration decreases to ≤3.2 mEq/L.** If serum K is ≤3.2 mEq/L, Aspiration Therapy shall be discontinued immediately. A 12-lead EKG should be performed to ensure there are no adverse cardiac effects that require aggressive therapy. A medical history should be obtained to identify possible causes for hypokalemia. If a cause for the decline in serum K is identified (e.g. taking a new medication that causes hypokalemia), this problem should be addressed. Potassium supplementation should be initiated or increased and serum K monitored frequently (one or more times/week) until serum K concentration returns to values ≥3.8 mEq/L. Aspiration Therapy should not be resumed until serum potassium concentration is ≥3.8 mEq/L.

5.5.4 Pain Management

Subjects are instructed to take pain medication (e.g. acetaminophen 650 mg po every 4-6 hours prn) for 1 week after A-Tube placement, as needed for pain control. In addition, at discharge from the endoscopy suite, subjects are given a 1-week prescription for pain medications that can be used to control

abdominal discomfort (e.g. tramadol [50 mg tabs] every 6 hours as needed for pain). Supplementary pain medication may be provided at the study physician's discretion.

5.5.5 Prophylactic Antibiotic Therapy

One gram of cefazolin sodium (Ancef) will be given intravenously ~1 hour before A-Tube placement and subsequent oral cephalexin (Keflex) 500 mg oral every 12 hours for 24 hours (two doses), after endoscopy. If the subject is allergic to cefazolin sodium, clindamycin (900 mg intravenously) will be given ~1 hour before A-Tube placement followed by oral clindamycin therapy (300 mg every 8 hours) for 24 hours (three doses) after endoscopy or vancomycin (1 gram intravenously) can be given before the procedure (no post endoscopy therapy). Ultimately, the exact antibiotic regimen used in any subject is at the discretion of the physician inserting the A-Tube.

5.5.6 Management of Medical Complications

Guidelines and suggested management of selected medical complications (hypokalemia, local stoma site infection, gastrointestinal complaints, dehydration, and excessive granulation tissue formation) are outlined in **Appendix I**.

5.5.7 Pregnancy

At each follow-up visit, the research nurse or study physician queries all female subjects with childbearing potential whether there is any change to their menstrual cycle or their birth control. Urine pregnancy tests will be performed as needed at the discretion of the research team. If a urine pregnancy test result is positive, a stat serum pregnancy test (human chorionic gonadotropin, HCG) shall be performed to verify pregnancy. If pregnancy is verified, Aspiration Therapy must be immediately discontinued, the A-Tube removed, and the study termination protocol followed. Please contact the Sponsor within one working day to report a pregnancy.

5.5.8 Adjustment of A-Tube Length

The length of the A-Tube needs to be shortened as subjects lose weight so that the external skin port remains within ~1 cm of the abdominal wall. This procedure will be performed by a member of the research team who (i) has

been trained, (ii) meets institutional and state licensure requirements, and (iii) is adequately qualified, in the opinion of the investigator. The frequency of length adjustment varies depending on body fat distribution and rate of weight loss, but is likely to be needed every 4-8 weeks until weight loss is stabilized. The procedure for A-Tube shortening is provided in the **AspireAssist Skin-Port Instructions for Use for Clinicians** (**Appendix F**). Data regarding the length of each A-Tube shortening is collected and recorded in the source documentation and on the Case Report Form (CRF).

5.5.9 Lifestyle Therapy

The behavioral weight loss program (see **Appendix C**) is a 10-session program delivered individually or in a group to each research subject during the first 52-weeks and includes nutritional, physical activity, and behavioral education topics. AT and Control Subjects are instructed to have a balanced 300 and 600 kcal-deficit diet, respectively. Initial daily energy requirements can be estimated by using the Mifflin-St Jeor equations[55] to estimate resting energy expenditure in men and women (see below) multiplied by an activity factor of 1.4:

Men: Resting Energy Expenditure =
(10 x weight in kg) + (6.25 x height in cm) - (5 x age in yrs) + 5

Women: Resting Energy Expenditure =
(10 x weight in kg) + (6.25 x height in cm) - (5 x age in yrs) - 161

Subjects are also instructed to establish a structured eating plan, which involves eating three meals a day, eating slowly and chewing food well, drinking a minimum of 500 mls of non-caloric fluid with each meal and at least 2000 mls of fluid per day (including the fluid consumed at meals, and limiting snacking between meals. Physical activity topics include the health benefits of physical activity and strategies for increasing lifestyle activity. The behavioral program emphasizes strategies of self-monitoring and goal-setting, and includes problem-solving, dealing with high-risk situations / cues for unhealthy eating, and stress management.

These Lifestyle Therapy sessions will be given individually during the same visit as the Medical & Study visits or regularly in group sessions.

If a subject in either intervention group is struggling with adherence or

compliance to the therapy, an individual session may be arranged between the subject and a behavioral consultant or another subject from their intervention group who has been successful with the therapy. Meetings will be considered and arranged on an individual basis with the intention of assisting subjects who may require additional attention to address a particular barrier to success with the study intervention. Any such meetings will only be held if the subject is so willing and will require permission, in advance, from the Sponsor.

5.5.10 Town Hall Meetings

Town Hall Meetings are a vital part of the PATHWAY study for both the AT and Lifestyle Therapy Group. Town Hall Meetings give the subjects the opportunity to discuss their challenges and issues, but also the opportunity to bond with other subjects. Research has shown that people who are attempting significant life-style changes do better when they can discuss their issues and challenges with other people who are attempting the same. Adherence to any regimen is also better when a person has one or more buddies who is currently attempting the same regimen or has succeeded, in the past with the same regimen.[56] [57,58]

Subjects will be invited to attend group meetings (see **Appendix J**) every other month with the other study subjects. The purpose of these meetings is to 1) provide an opportunity for subjects to share their experiences within the study and share ideas for success with the intervention and 2) provide an opportunity for study staff to interact with all subjects together to enhance retention and adherence.

5.5.11 Gastric Emptying Sub-study

A subgroup of no more than 15 Pathway AT study subjects will be recruited for a study intended to characterize the differences in gastric emptying among subjects, distribution of food bolus within the stomach, position of the A-tube in relation to the food bolus and gastric emptying at different time points. These variables are best evaluated using gastric scintigraphy (emptying) analysis. Understanding gastric emptying characteristics may lead to a better understanding of Aspiration efficiency and optimal timing of aspiration. Subjects currently enrolled in the Pathway study will be co-enrolled in this ancillary study at the Mayo Clinic.

5.5.12 Enhanced Coaching Sub-study

The Enhanced Coaching sub-study is optional for both the study sites and AT subjects. If a study site decides to participate, local IRB approval must be obtained prior to enrolling subjects in the sub-study. The objective is to improve outcomes of AT Subjects, particularly Low Responders (i.e. subjects with a total body loss at 52 weeks of 5.0% to 9.9%). Subjects who consent to the sub-study will continue Aspiration Therapy, but also receive Enhanced Coaching, as outlined in Appendix Q. The sub-study continues for as long as the subject remains enrolled in the PATHWAY study.

5.6 Withdrawal Criteria

Subjects are informed orally and in writing that they are free to withdraw from the study at any time without bias or prejudice. Subjects should be encouraged to complete the next scheduled study visit prior to withdrawal (an unscheduled visit may also be performed).

A subject who decides to stop all therapeutic interventions will have the A-Tube removed and will be followed by the study site physician until the stoma has healed, returning for three bi-monthly visits over a 6-month period.

If a subject decides to withdraw completely from the study, he/she may do so at any time. The reason for discontinuation must be recorded in the source documentation and on the Study Exit CRF. Possible reasons for premature discontinuation may include but are not limited to the following:

- Withdrawal of consent: Subject decides to withdraw from the study.
- Adverse Events: Subjects must be followed until the adverse experience resolves or until a stable clinical end-point is reached.
- Lost to follow-up: A letter will be sent to the subject when three attempts to reach the subject by telephone and/or email have failed. The subject will be considered lost to follow-up if he/she is not able to be reached within 4 months after failure to return for follow-up visits.

The Sponsor can terminate a subject's involvement in this study prior to completion for ethical or safety reasons at any time. If, at any time during the

study, a subject begins taking a weight loss medication or supplement, the subject should be withdrawn from the study.

5.7 Protocol Deviations

Protocol deviations are defined as any instance in which the subject or clinical team does not perform scheduled activities/tasks defined in the protocol and Schedule of Assessments. Examples include: missed visits, visits outside the specified visit window, missed tests, missed evaluations and missed meetings with specific members of the clinical team, enrollment of an ineligible subject, a lapse in IRB approval, invalid consent form, missing consent form, etc. The Sponsor should be notified of protocol deviations within 3 days (72 hours) of the occurrence or recognition of the deviation and the Protocol Deviation Log should be updated and kept current.

5.8 Study Termination

The study ends at 52 weeks. However, AT subjects achieving and maintaining at least a 10% absolute weight loss will be able to continue therapy for an additional 4 years provided subjects maintain ≥10% absolute weight loss (relative to baseline weight), assessed at each annual visit (i.e. years 1, 2, 3, and 4). AT subjects who achieve 5% to 9.9% WL may be considered for continuation of AT therapy after 52 weeks if they enroll in the Enhanced Coaching sub-study.

All study-related expenses, as outlined in the Schedule of Assessments (**Tables 1 - 3**), will be paid for by the Sponsor. Any participant can terminate the study at any time, or the Sponsor can terminate the study for medical reasons. If the participant or Sponsor terminates the study, the implanted A-Tube is removed according to the A-Tube Instructions for Use (IFU) procedures, and all re-usable equipment returned to the Sponsor or destroyed. In addition, the endoscopist may choose to apply an endoclip to enhance fistula closure. Subjects will be followed for 6 months after device explanation (three bi-monthly follow-up visits) to monitor fistula track closure and body weight at 2, 4, and 6 months after explantation. In addition, HbA1C will be checked in subjects with diabetes and those who lost weight and had a reduction in their diabetes medications at the time of A-Tube explantation will need additional glucose monitoring. These subjects will be expected to check their blood glucose concentrations at home at least 2 mornings each week before breakfast for up to 6 months after explantation, and provide this information to the study site every week (by FAX, email, or phone). Specific adjustments in diabetes medications needed to maintain adequate glycemic control will be left to the discretion of the study physician and the subject's primary physician.

Table 4: Schedule of Assessments: Post-Explant	**Month**			
Month Post-Explant	**2**	**4**	**6**	
Visit window (± weeks)	**1**	**1**	**1**	**Total**
Medical & Study Visit (weight, vital signs, concom meds, AE's)	**x**	**x**	**x**	**3**
Check fistula track closure	**x**	**x**	**x**	**3**
Additional procedures below for subjects with diabetes				
Hemoglobin A1C	**x**	**x**	**x**	**3**
Blood glucose monitoring (reported weekly)	**x**	**x**	**x**	
Diabetes medication adjustments, as needed	**x**	**x**	**x**	

Upon completion of all study visits, the Study Exit CRF should be completed.

5.9 Corelabs

All blood laboratory testing will be performed at Quest Diagnostics. Quest will provide uniform collection materials, sample pick-up, and sample storage. The use of a central core laboratory is expected to provide reliable and accurate blood tests and a mechanism for monitoring adherence.

6.0 Assessment of A-Tube Technical Success

Technical success is defined as successful endoscopic placement of a functional A-Tube and installation of a functional Skin-Port.

7.0 Assessment of safety

7.1 Risk Assessment

There risks of this study may be categorized into those associated with (i) endoscopic placement of the A-Tube, (ii) the presence of stomas/fistulas and A-Tube, (iii) Aspiration Therapy, (iv) behavior, and (v) concomitant drug therapy.

Each of these risk categories and the associated mitigations are discussed in **Sections 7.1.1 -7.1.5**.

7.1.1 Risks Associated with Endoscopic Placement

The risks of endoscopic placement of the A-Tube include sedation complications, discomfort, sore throat, pain, abdominal bloating, indigestion, bleeding, infection, nausea, vomiting, hypoventilation, aspiration pneumonia, perforation, and death.

The risk of infection is mitigated by the use of prophylactic antibiotics before and after the endoscopic procedure. The risk of sedation complications and aspiration pneumonia are mitigated by having the endoscopic procedure performed by a skilled and experienced medical team, who will carefully monitor the subject. The risk of perforation is mitigated by having endoscopic procedure performed by a trained endoscopist who is experienced in inserting PEG tubes. The risk of death is mitigated by all the above.

7.1.2 Risks Associated with Stomas/ Fistulas and A-Tube

Risks related having a fistula/ stoma include: 1) abdominal discomfort/pain, 2) peristomal skin irritation/ inflammation, erythema and granulation tissue formation, 3) peristomal leakage and/or bleeding, 4) infection, 5) buried bumper syndrome and gastric erosion, 6) difficulty sleeping on abdomen,

reduced range of motion at the torso, 7) persistent fistula after tube removal, and 8) scarring and/or skin depression after tube removal.

Abdominal Discomfort/Pain. It is normal for subjects to have abdominal discomfort after endoscopic A-tube (or PEG tube) insertion, which subsides over several weeks. Subjects will be instructed to take over-the-counter pain medications such as acetaminophen as needed for 1 week after A-Tube placement. In addition, at discharge from the endoscopy suite, subjects will be given a 1-week prescription for pain medications that can be used to control abdominal discomfort. Supplementary pain medication will also be provided at the physician's discretion. The experience from the Feasibility Study found that musculoskeletal or neuropathic complaints (e.g. burning, pulling) after tube placement was effectively treated with general oral pain medications and/or medications for neuropathic pain. It was thought by the Sponsor and the Study Team that discomfort after the first few weeks was primarily associated with the "old" A-Tube design (e.g., ePTFE tube with helical ridges of exterior or tube). With the new A-Tube design implemented in September 2011, subjects report significantly greater comfort.

Peristomal Skin Irritation, erythema, discharge and granulation tissue. Based upon our studies to date, skin irritation, erythema, discharge and granulation tissue formation are common, minor, and manageable, and most subjects reported at least one such complication. After the new A-Tube design was implemented in September 2011, subjects reported a marked decrease in discharge and greater comfort. Skin irritation and erythema can be treated with topical zinc oxide, or other topical creams/products and by making sure the Skin-Port is ~1 cm away from the skin to reduce irritation. It is normal for granulation tissue to form at the ostomy site of the A-Tube. If the granulation tissue is excessive, it is easily removed by topical application with silver nitrate sticks. The area should be swabbed with alcohol before and after treatment. Care should be taken to ensure that silver nitrate does not come into direct contact with normal skin tissue, fistula track, or A-Tube. In addition, subjects are taught to inspect their stomas and report any evidence of irritation, erythema, discharge and granulation tissue. The clinical team is also instructed to examine the stoma at every visit, and treat, as necessary.

Peristomal leakage. Leakage can be caused by the tube by (i) failure of the stomach stoma to heal around the tube, (ii) enlargement of the stomach stoma (sometimes caused by an infection within the tract or mechanical forces from

excessive tube manipulation), or (iii) buried bumper syndrome. The tube should be checked to make sure it can move freely in and out within the fistula tract to rule out the possibility of a buried bumper. If there is no evidence of a buried bumper, the patient should be instructed (i) not to aspirate and (ii) to avoid any manipulation of the tube to allow the stomach stoma to heal and form a tight seal. If skin irritation or excoriation occurs, skin care recommended for peristomal irritation can be started. If leakage persists after seven days, the A-Tube can be removed for several days and the tract allowed to partially close. A new A-Tube can then be placed through the same site.

Infection. The use of prophylactic antibiotics has markedly reduced the risk of bacterial infection after PEG tube insertions. If an infection occurs at the A-Tube site, it can usually be successfully treated as an outpatient: oral antibiotics for a bacterial infection or topical cream/oral antifungal agent for a fungal infection.

Buried Bumper. Buried bumper syndrome is a known complication of PEG tubes[59] that occurs when there is excess tension of the internal bumper against the intragastric wall, which causes migration of the internal bumper into the fistula tract. In the clinical studies to date, there was one such incidence of a buried bumper, which was caused by inappropriate shortening of the A-tube. The clinical team is instructed to determine Skin-Port placement when the subject's abdomen in compressed (seated) to ensure sufficient clearance (~3-10mm) between the Skin-Port and the abdominal wall. Additionally, subjects are instructed to avoid external tension on the Skin Port and to call the physician if the Skin Port feels tight against the abdominal wall.

Persistent Fistula after A-Tube Removal. Although the majority of fistulas close within a few days after tube removal, some subjects will require endoscopic or surgical closure if the fistula does not heal on its own.

Scarring after A-Tube Removal. Removal of the A-tube and fistula closure will result in a scar and skin indentation on the abdominal wall at the ostomy site.

7.1.3 Risk Associated with Aspiration Therapy

Some subjects in the Pilot and Feasibility Trials reported occasional indigestion, nausea, vomiting, constipation, and diarrhea as a result of

aspiration. Subjects may experience discomfort and/or pain when attaching the Connector to the Skin-Port for aspiration within the first several weeks after A-Tube placement, however, this subsides as the stoma tract heals. All of these reported incidents were mild in nature and fleeting.

The nutritional and metabolic risks related to Aspiration Therapy include hypokalemia, and iron (Fe) deficiency anemia.

Nutritional and Metabolic Risks

Hypokalemia. A decrease in plasma potassium concentration can occur with repeated aspiration of gastric contents, because of the loss of gastric acid and compensatory potassium bicarbonate excretion by the kidney. Plasma potassium concentrations will be closely monitored in study subjects and appropriate therapy will be initiated if plasma potassium concentration begins to decline.

Iron deficiency anemia. Serum Fe decreased in several subjects treated with Aspiration Therapy in the Feasibility Study. Several mechanisms could be responsible for the decline in serum Fe: 1) reduced dietary iron availability because of the decrease in total food intake and the aspiration of a portion of gastric contents after meal (iron) ingestion, 2) adherence with a low calorie diet and weight loss itself is associated with a decline in serum Fe; data from previous weight loss studies have found that a low-calorie diet can cause a marked reduction in serum Fe concentration within 2-4 weeks[60], 3) increased iron loss caused by increased menstruation, which often occurs with weight loss in obese women[61]. The decrease in serum Fe was associated with a decrease in hemoglobin concentration, with the development of anemia in a few subjects. Short-term treatment with iron supplementation resulted in a return of serum Fe to the normal range and was associated with an increase in hemoglobin concentration.

7.1.4 Behavioral Risks

The results from the Proof-of Principle, Feasibility and Pilot Studies did not detect any adverse behavioral effects of Aspiration Therapy. Nonetheless, there are two potential behavioral concerns with the use of this therapy: (i) excessive use of the aspiration therapy that causes excessive weight loss and nutritional/metabolic abnormalities, or (ii) adverse eating behaviors (increased food intake) because of the ability to aspirate after meals.

However, both of these potential concerns are very unlikely to occur, and we have established important safeguards to prevent and identify them (discussed below).

Overuse of Aspiration Therapy

In the studies to date, there has been no indication of excessive use of Aspiration Therapy in any subject assessed by: (i) **Connector** usage, documented by the **Counter** (on the Connector), which was consistent with normal use and (ii) rate of weight loss - no subject lost weight at a faster rate than expected.

Although there is always the possibility that a subject will attempt to over-use the therapy, this is unlikely to occur because the **Counter** prevents a subject from using the Connector more than 115 aspiration cycles, at which the point the subject would need to return to his physician to obtain a new Connector. The Connector (when it is connected to the Skin-Port opens) the normally-closed valve in the Skin-Port to allow aspiration. The Skin-Port valve automatically closes when the Connector is removed; the Connector is bulky and would protrude through clothing so that subjects want to remove it post-aspiration. There has been no evidence of subjects in the trials tampering with the Connector.

In the current study, subjects are asked to bring their connector to each study visit so the counts may be documented. If the study team suspects a subject has attempted to override the counting mechanism, that subject will be dropped from the study and his/her data will not be included in efficacy analyses, but will be included in analysis of safety data.

Abnormal Eating Behavior

The results from the Feasibility and Pilot Studies did not detect any adverse effects of aspiration therapy on eating behavior or any evidence that subjects increased the volume of food intake or frequency of eating because of the ability to aspirate. In these studies, eating behavior was evaluated by using a series of validated questionnaires and a structured psychological interview. In fact, there was evidence of improvement in eating behavioral traits (improved restraint, less disinhibition, more control over food intake, and decreased hunger).

7. 1.5 Risks Associated with Concomitant Drug Therapy

The drugs prescribed as part of the protocol include (i) prophylactic antibiotics to prevent infection after A-tube insertion, and ii) pain medication after A-Tube placements (at the physician's discretion). In addition, a multivitamin and mineral supplement will be taken throughout the duration of the study. The side effects are described below. Serious side effects of these medications are unlikely to occur because they will be given for a short period of time.

Keflex (an antibiotic given to those in the Aspiration Therapy group before and after A-Tube placement) in rare cases may cause diarrhea.

Clindamycin (an antibiotic given to subjects in the Aspiration Therapy group who are allergic to penicillin before and after A-Tube placement) may cause diarrhea, and in rare case may cause
rash, nausea, vomiting, low blood pressure, itching, inflammation of the colon.

Ultram (given to the Aspiration Therapy group for possible pain after A-Tube placement) in rare cases can cause dizziness, headache, sleepiness, restlessness, nausea, diarrhea, constipation, vomiting, stomach ache, weakness, sweating.

Silver nitrate sticks (skin product used, if necessary, to treat scar tissue around the A-Tube) may cause burning and skin irritation, and in rare case may cause skin staining.

Other medications may be prescribed at the discretion of the investigator (e.g. various pain medications); please refer to the manufacturer's label for risks associated with taking any medication.

7.1.6 Risk Management Procedures

The most important risk management procedures will be thorough subject training, meticulous A-Tube implantation procedures, and careful medical monitoring. Physicians who will perform A-Tube placement will follow the procedures outlined in the AspireAssist A-Tube™ Instructions for Use (IFU).

The inclusion and exclusion criteria and careful initial medical evaluation will help exclude potential participants who are at high risk for procedure and treatment related complications. The careful medical monitoring protocol ensures that participants are closely followed and that potential complications can be identified early and managed appropriately. Subjects will be carefully monitored by the medical staff associated with the study for the duration of the study.

7.2 Safety Criteria

All participants will be carefully monitored by a physician and research coordinator during this study. Safety will be monitored by:

1. Incidence of device-, procedure- and therapy- related adverse events
2. Incidence of device-related or unrelated serious adverse events, including unanticipated adverse device effects

7.3 Adverse Event Reporting

All adverse events must be logged on the Case Report Forms (please see **Appendix K** for **Adverse Events Guidelines**). There are special procedures for handling serious adverse events and unanticipated adverse events as described and defined in this section.

7.3.1 Adverse events (AE)

The definitions of an Adverse Event and a treatment-emergent adverse event are as follows:

Adverse event (AE): any untoward, noxious, or unintended event experienced by a subject in a clinical trial of an investigational device, whether considered related to that investigational device or not. This definition also encompasses: 1) events that result from abuse of the device, 2) symptoms reported by the subject, 3) signs detected by the investigator or other competent observer, and 4) medically important deviations from normalcy in the results of ancillary investigations.

Treatment-emergent adverse event: an AE that is new in onset or aggravated in severity or frequency following placement of the investigational

device. This includes any change from baseline physical examination findings or results of diagnostic procedures (e.g., laboratory test, ECG, X-ray) that is clinically significant, i.e., requires diagnostic or therapeutic intervention beyond confirmation alone; however, such a finding shall not be recorded as a separate AE if it is intrinsic to, or results in, a clinical diagnosis that is recorded as an AE.

a. Anticipated Adverse Device Effects

The following events have been identified as possible (anticipated) adverse events that could be related to A-Tube implantation and use:

1) Risks of endoscopic placement of the A-Tube, as outlined in Section 7.1.1, are examples of procedure-related adverse events.

2) Risks related to the presence of the A-Tube, as outlined in Section 7.1.2, are examples of device-related adverse events.

3) Risks of Aspiration Therapy, as outlined in Section 7.1.3, are examples of therapy-related adverse events.

4) Behavioral Risks, as outlined in Section 7.1.4, are examples of therapy-related adverse events.

5) Risks related to concomitant drug therapy, as outlined in Section 7.1.5, are examples of study-related concomitant medication-related adverse events.

6) Risks of weight loss include gallstone formation, bone demineralization, alopecia, dehydration, changes in bowel habits, and loose skin are examples of therapy-related adverse events.

If the subject is female, the procedure may involve unforeseeable risks to an embryo or fetus should the subject become pregnant.

Anticipated adverse events that are <u>NOT</u> deemed serious adverse events need only be recorded on the CRF.

b. Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADE) are defined as "any ***serious*** adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated ***serious*** problem associated with a device that relates to the rights, safety, or welfare of subjects'

All unanticipated adverse events and deaths must be reported by telephone and in writing immediately, or within 48 hours of knowledge of the event, to Aspire Bariatrics. The PI must also inform the relevant Institutional Review Board, Medical Ethics Committee or similar body, if applicable, per local regulations.

The telephone report must be followed by a written report that is emailed or faxed to the Sponsor within two days to include the date of occurrence, complete description of the event, severity, duration (when appropriate), action taken, outcome, and the investigator's assessment of relatedness to the endoscopic procedure or the presence of the A-Tube. The incident shall also be recorded in the CRF on the Adverse Event Form.

c. Serious Adverse Event (SAE)

Serious adverse event (SAE): any AE that is fatal, immediately life-threatening (i.e., presents an immediate risk of death at the time of the AE, not an AE that hypothetically might have caused death if it were more severe), requires inpatient hospitalization for more than 24 hours, causes permanent or significant disability, requires medical or surgical intervention to prevent permanent sequelae, or any of the outcomes listed above.

When the investigator or designee becomes aware that a serious AE has occurred, the Sponsor or designee must be notified immediately by telephone and followed by an e-mailed or faxed written report, regardless of the relationship (or lack thereof) of the AE to the study treatment. The investigator will be notified of the occurrence of serious, unexpected AEs at other study sites. If such AEs are also associated with the use of the study device (i.e., there is a reasonable possibility that the AE may have been caused by the device) and are thus deemed significant new adverse effects or

risks with respect to the investigational device, the investigator must promptly inform the relevant Institutional Review Board.

Information regarding SAEs occurring at any site will be disseminated by the Sponsor to all study sites and the information reported to the Ethical Committee as required by local regulations.

The names and telephone numbers of the individuals who shall be contacted regarding safety issues are listed in **Appendix L** ("**Sponsor Contact Information**") of this protocol.

7.3.2 Duration of Follow-up after Adverse Event

All treatment-emergent AEs must be followed until resolution or until a stable clinical end-point is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source documents and reported to Aspire Bariatrics.

7.3.3 Definitions for the Grades of Severity of Adverse Event

1) *Minimal*: Awareness of sign or symptom, but easily tolerated
2) *Mild*: tolerated w/ some difficulty
3) *Moderate*: interference with some normal daily activities
4) *Significant*: inability to perform normal daily activities
5) *Severe*: requires hospitalization

7.3.4 Definitions for Criteria of Relatedness of Adverse Events to Device

*Unrelated***:** The timing of the clinical event to the product administration makes a causal relationship not possible, or, other drugs, therapeutic interventions or underlying conditions provide a strong explanation for the observed event. Alternatively, common medical knowledge makes causal relationship implausible.

*Unlikely Related***:** The timing of the clinical event to the product administration makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event. Alternatively, common medical knowledge makes causal relationship unlikely.

Possibly Related: The timing of the clinical event to the product administration makes a causal relationship equally likely or not likely, and, other drugs, therapeutic interventions or underlying conditions provide only a low probability explanation for the observed event.

Probably Related: The timing of the clinical event to the product administration makes a causal relationship probable, and, other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event

Definitely Related: The timing of the clinical event to the product administration makes a causal relationship certain and common medical knowledge makes causal relationship highly probable.

7.3.5 Definitions for "Results" on the AE CRF

1. *Resolved*: No more evidence of the event
2. *Improved*: The symptoms associated with the event have become mild or significantly decreased
3. *Unchanged*: No reported change in the event
4. *Worsened*: The symptoms associated with the event have become significantly worse
5. *Permanent Disability*: The subject has lost a specific bodily function
6. *Death*: N/A
7. *Other*: Result or outcome that does not fit the above definitions and requires written explanation

7.4 Data and Safety Monitoring

Data from the study will be monitored on a continuous basis by the study team (PI, co-investigators, and study research nurse/coordinator). The study team will meet regularly to review subject progress, adverse events (AEs), laboratory values, and any study issues. The local IRB and the Sponsor will be notified of AEs/SAEs as stated in section E3 of this protocol. Information regarding SAEs occurring at any site will be disseminated by the Sponsor to all study sites and the information reported to the IRB. If, at any time during the study, an unanticipated significant risk to study subjects is identified, study recruitment and/or the study intervention may be stopped until such

risk has been satisfactorily resolved or corrective action taken and all study documents updated, as needed. The need to stop or interrupt study activity will be determined by the Sponsor and PI.

To ensure consistency in reporting adverse events and to meet the ethical responsibilities and standards for research subjects, a Safety Adjudication Committee (SAC) has been formed. The SAC is composed of a group of independent physicians who have no financial interest in the Sponsor (or a competitor to Sponsor) and who have expertise in gastrostomy tubes, metabolism, and obesity. The responsibilities of this committee are described in the Investigators' Brochure.

Confidentiality. All of the data will be treated confidentially and the subjects' names and identities will not be disclosed in any published reports. Subjects are assigned a study specific identifying number upon entry to the study, after which all medical information is referenced by this number. Clinic records are maintained in locked file cabinets within a locked room.

8.0 Statistical Analyses

8.1 Sample Size

Based on weight loss data and drop-out data from the prior trials involving aspiration therapy, a study size of 175 subjects, with 2:1 randomization, should adequately power the trial to demonstrate efficacy.

8.1.1 Efficacy Endpoints

The first effectiveness primary endpoint is the mean percent excess weight loss (%EWL) at 52-weeks. The hypothesis for the first primary effectiveness endpoint is that the difference in the mean percent excess weight loss (%EWL) at 52-weeks for the Aspiration Therapy (AT) group and Control group is at least 10%. %EWL is defined as absolute weight loss divided by baseline excess weight and multiplied by 100. Excess weight will be determined from ideal body weights based on a BMI=25 kg/m^2.

The second effectiveness primary endpoint is that at least 50% of the AT group at 52-weeks realizes a %EWL $\geq$ 25%. .

Sections 8.51 and 8.52 provide analysis of the sample size to meet co-primary endpoint #1 and #2, respectively with a power of 90% for each endpoint.

Since these endpoints are co-primary, the sample size is determined by the largest sample sizes required of the two primary endpoints. Co-primary endpoint #1 requires a sample size of 87 subjects (59 AT/ 29) to have a superiority margin of 10% EWL with a power of 90%, assuming an observed difference of 25% EWL and a standard deviation of both groups of 20%. Co-primary endpoint #2 requires a sample size of 99 AT subjects to realize that at least 50% of the AT groups realize >25% EWL at 52 weeks with a power of 90%, assuming an observed rate of 66% and a standard deviation of 20% of the AT group.

Co-primary endpoint #2 requires the largest sample sizes of the two primary endpoints, hence, not accounting for subject drop-out, a total of 150 subjects are needed in a 2:1 randomization (100 AT + 50 Control).

Since the primary analysis will be based on an ITT analysis using multiple imputations to estimate the missing values, the importance of over enrolling to have the exact number of evaluable patients has been lessened. However, to mitigate the effect of the imputation methodology on the control group, an over enrollment of ~15% for both groups is being proposed for a total enrollment size of 175 subjects (117 AT/58 Control).

8.1.2 Discussion on Drop-out Rate and Standard Deviation.

As 9% of the AT subjects (1 out of 11) in the Feasibility Study did not complete 52-weeks, we believe a 10% drop-out rate of the AT subjects for the Pivotal Study is a reasonable assumption. An over-enrollment of 15% (e.g., 117 AT subject versus 99 required) should readily accommodate the anticipated drop-out rate.

A lower drop-out rate for the Controls (20%) is being assumed for the Pivotal Study than what was experienced in the Feasibility Study (43%; 3 out of 7 subjects). Although 20% is still higher drop-out rate than many drug studies, we believe that this drop-out rate for Controls should be anticipated given the disappointment some of the Controls will have in not being chosen as an AT subject. Data from a recently published article that compared bariatric surgery with intensive medical therapy in obese subjects with diabetes

support our estimate of a 20% drop-out rate. In that study, subjects were randomized into three equal arms: intensive medical therapy, gastric bypass, and sleeve gastrectomy[62,] and the drop-out rate for the intensive medical therapy arm was 18% compared to 4% and 0% for the other two arms, respectively.

A standard deviation of approximately 25% in %EWL at 52-weeks was seen in both the AT and control groups. In the larger sample size associated with the Pivotal Trial, the extreme values will have a lessened impact on the variability of the observed responses. Hence, a reduction in standard deviation from 25%, as experienced in the Feasibility Trial, to an assumed 20% for the Pivotal Trial is realistic. The assumption of a 20% standard deviation is consistent with other obesity device weight loss studies. The Lap-Band PMA study had a 19% standard deviation at 1 year.[63] Similarly, the Realize Band study had nearly an 18% standard deviation at 1 year.[64]

8.1.3 Secondary Efficacy Endpoints

Only the primary endpoint of %EWL and the secondary primary endpoint of 50% of the treatment group meeting the 25% EWL success criteria will be used to make product labeling claims. The data used to support the secondary endpoints will only be listed in data tables, and will not be considered statistically significant proof of efficacy.

8.1.4 Sensitivity Analyses

The efficacy analysis will be conducted on various populations for the purpose of conducting a sensitivity analysis. The first population is the per protocol population, that is, the analysis will be conducted on all treated subjects who complete the scheduled follow-up visits. A second analysis will be conducted on an intention to treat (ITT) population where the missing values at the 12 month time period will be imputed from the return to baseline methodology (i.e. all missing values at 12 months will be given the value at baseline). A third analysis used to perform efficacy analysis will use the Last Observation Carried Forward (LOCF) to impute the missing values. A fourth analysis will also be conducted: Missing values at the 12 month time period will be imputed using the mean value at 12-months of completers from %EWL quintile group such drop-out fell into at the time of drop-out. For example, if a subject were to drop-out at the 28th week and that subject fell

into the third quintile of %EWL at the 28th week, we would impute a %EWL at 52-weeks from that drop-out subject from the mean %EWL of the completers who were in the third quintile of %EWL at the 28th week. Analyses using the best and worst case scenarios will also be conducted. Finally, an analysis using multiple imputations will be conducted. In all the analyses where data is being imputed, any subject with a device related failure, or other obvious reasons that will lead to negative outcomes, will be evaluated as worst case for the AT group.

An additional sensitivity analysis for the secondary endpoints that are binary in nature will have the subjects who are lost to follow-up in the control group counted as successes and the subjects who are lost to follow-up in the AT group counted as failures.

8.2 Statistical Methods

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software. Where not otherwise specified, the last pre-treatment (i.e. for treatment group, this is prior to the initiation of therapy) observation will be used as baseline for calculating post-treatment changes from baseline. The primary presentations and analyses will be based on data pooled across study centers. Relevant summaries for individual centers, or combinations of centers, may be presented for primary data. All testing and confidence intervals will use a significance level of 5%.

8.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be tabulated by treatment group and a test of homogeneity between the treatment groups will be conducted. For continuous variables (i.e. age, height, weight) a t-test will be used. For categorical variables (i.e. sex, race), a Fisher's exact test or chi-squared test will be used. Medical history findings, physical examinations and concomitant medications will be tabulated by treatment group.

8.4 Adverse Events

The number of subjects with at least one adverse event will be tabulated for each treatment group. Differences between the two treatment groups will be

tested using Fisher's exact test. Then number of adverse events for each treatment group will also be tabulated.

The number of subjects and the number of adverse events will be tabulated by severity, anticipated, and causality.

8.5 Statistical Analysis Plan

All safety and efficacy analyses will be conducted on the intent-to-treat (ITT) population, defined as all subjects who undergo treatment in either the AT or Control group. Primary effectiveness analyses be performed without imputation; that is the "ITT evaluable" dataset will include only the observed data from each study visit. Imputation of missing values (e.g., using the methodologies outlined above) will be performed for subjects who terminate prematurely or are lost to follow-up. Those dropout subjects that have device-related adverse events, or other obvious reasons that lead to negative outcomes, will be imputed as failures in the primary analysis. As a sensitivity analysis the primary effectiveness endpoint will be re-analyzed using only data from completers.

A poolability analysis and covariate analysis will be performed. The demographic characteristics as well as the two primary endpoints will be examined for poolability across sites. The impact of important covariates will be examined for the two primary efficacy endpoints. These covariates will include race, age, gender, and initial BMI.

An internal, 6-month analysis will be performed on all endpoints to ensure systematic data collection at all sites and to identify potential safety concerns. The results of this analysis will not affect the clinical investigation plan unless a previously unidentified risk to study participants is discovered.

8.5.1 Sample Size for Primary Endpoint #1 (Hypothesis One)

Primary endpoint #1: The observed difference in the mean excess weight loss (%EWL) at 52-weeks for the AT group and control group is > 25%. %EWL is defined as absolute weight loss divided by baseline excess weight and multiplied by 100. Excess weight will be determined from ideal body weights based on a BMI=25 kg/m2.

The first hypothesis presented is

H_0: $\mu_F - \mu_S < \delta$ versus H_A: $\mu_F - \mu_S \geq \delta$

Where μ_F is the observed %EWL for the **AT Group** and μ_S is the observed %EWL for **Control Group**. The value of δ is the clinically significant threshold value. Statistical differences between AT and Control groups will be evaluated by using a two-sample t-test. Using this hypothesis and the two-sample t-test, **Table 8.5.1** presents the sample size for the AT group (total in parenthesis) assuming a 2:1 randomization with the assumptions listed in the table. The significance level is 0.025 and the power = 90%.

Table 8.5.1 Requisite Sample Size for a 90% Power

			Observed Difference in Mean %EWL between AT and Control			
Power	**δ**	**Std.Dev**	**15%**	**20%**	**25%**	**30%**
90%	**10**	15	286 (429)	74 (111)	34 (51)	20 (30)
		20	506 (759)	128 (192)	58 (87)	34 (51)
		25	790 (1185)	200 (300)	90 (135)	52 (78)
90%	**15**	15	Na	286 (429)	74 (111)	34 (51)
		20	Na	506 (759)	128 (192)	58 (87)
		25	Na	790 (1185)	200 (300)	90 (135)

8.5.2 Sample Size for Primary Endpoint #2 (Hypothesis Two)

Primary endpoint #2: At least 50% of the AT group at 52-weeks realizes a %EWL > 25%.

Hypothesis:
H_0: $\pi_{AT} \leq 50\%$
H_a: $\pi_{AT} > 50\%$

Where π_{AT} is the proportion of patients who have a % EWL≥ 25% for the Aspiration Therapy group.

Using this hypothesis and the Fisher's exact test, the following table presents the sample size for the AT group with the assumptions listed in the table. The significance level is 0.025 and the power = 90%.

Table 8.5.2 Sample Size for Hypothesis Two

Power	Expected Proportion					
	55%	**60%**	**65%**	**66%**	**67%**	**70%**
90%	1047	259	113	99	87	62

8.5.3 Sample Size for Adverse Event Detection

Given the sample size for the AT device, **Table 8.5.3** shows the probability of detecting at least one adverse event with the given rate.

Table 8.5.3 Probability of Observing At least One AE

Probability of an AE	Probability of Observing at least one AE
1%	27%
2%	61%
3%	81%
4%	91%
5%	97%
6%	98%
7%	99%
8%	100%
9%	100%
10%	100%

8.5.4 Secondary Efficacy Endpoints

The percent change from baseline will be calculated for all major time points and the results will be summarized for each group. Within treatment group differences will be tested using a Students T-test for paired samples on the percentage change from baseline at each study visit. Difference between treatment groups will be tested by using the two-sample t-test or Wilcoxon Test whenever appropriate.

9.0 Quality Control and Quality Assurance Procedures

9.1 Data Quality Assurance

Steps taken to assure the accuracy and reliability of data include review of protocol procedures with the investigators and associated personnel prior to the study and a monitoring visit by Aspire Bariatrics Clinical Monitor to each clinical site. Electronic case report forms will be reviewed for accuracy and completeness as compared with the source documents.

9.2 Monitoring

The study will be initiated by the medical monitor (or designee) during an on-site visit after all required documents have been processed. Monitoring will be performed during the study to verify that the rights and well-being of the subjects are protected, the trial is conducted according to Good Clinical Practices (GCP), the protocol and applicable amendments are followed, and the recorded data is accurately represented according to the source documentation.

9.3 Protocol Modifications

Protocol modifications must be evaluated against FDA guidelines to determine whether prior approval is required, or 5 day notification or inclusion in annual report is sufficient.

Prior to initiating any protocol modification, the site's IRB will approve such protocol modification.

All protocol amendments must be signed and dated by the investigator prior to implementation of the amendment.

In situations requiring departure from the protocol, the investigator or other physician in attendance will contact the assigned medical monitor by fax or telephone (**Appendix L**). If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the medical monitor must be made as soon as possible in order to discuss the

situation and agree on an appropriate course of action. The CRF and source document will describe any departure from the protocol.

9.4 On-Site Audits

A Clinical Monitor, a trained and properly authorized employee of Aspire Bariatrics, may request access to all study records, including source documents, for inspection and copying. The study site will be expected to provide adequate monitoring facilities, with appropriate computer connections and work space.

10.0 Ethics and Regulatory Considerations

This study will be conducted in accordance with Good Clinical Practices and any local regulations.

10.1 Institutional Review Board/Medical Ethics Committee

The protocol will be submitted to an Institutional Review Board (and /or Medical Ethics Committee or similar body if required by local regulations) for approval prior to initiation of the study.

10.2 Informed Consent

Each subject (or legally authorized representative) shall sign and date a current informed consent (see **Appendix M**) (and other locally required documents) after the nature of the study has been fully explained. If a protocol amendment results in a change in the Informed Consent Form, a new Informed Consent Form approved by the study site Institutional Review Board will be signed by all subjects.

10.3 Clinical Investigator

The investigator selected for this clinical study will be responsible for following the protocol and providing both procedural and follow-up data.

The investigator must also:

- Agree to the requirements of this protocol by signing the Protocol Signature Page.
- Obtain subject informed consent according to local regulations.
- Provide the required data on the case report form as soon as it becomes available.

10.4 Confidentiality

Research records are marked by subject number and initials. Subject identifiers/linking information will be kept in a locked location separate from the research records. Subject identifiers will not be stored on any network drive. Subject research files, including signed consent forms, will be kept in locked storage area at the study site. All information provided to the Investigator by the Sponsor, or its designates, including non-clinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the research staff involved in conducting the study. It is recognized that this information may be related in confidence to the Institutional Review Board. Subjects' records will be made available to the Sponsor's Clinical Monitors and regulatory authorities as required.

11.0 Record Keeping/ Reporting

11.1 Required Documents

The following documents shall be submitted to Aspire Bariatrics prior to study initiation:

- Signed and dated Protocol Signature Page.
- A copy of the formal written notification of the IRB or similar body to the investigator regarding approval of the protocol.
- A copy of the informed consent form to be used in the study.
- All local regulations must be met and the necessary documentation submitted to Aspire Bariatrics.

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

11.2 Case Report Forms

Data will be entered promptly into electronic case report forms (**Appendix N**). The case report form must be electronically signed and dated by the principal investigator or designated research team member.

11.3 Record Retention

All case report forms and all source documents (i.e., laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and procedure dates, device disposition records) that support case report forms of each subject must be retained in the files of the responsible investigator for a minimum of seven years following notification by Aspire Bariatrics that all investigations of the device have been completed or discontinued.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Aspire Bariatrics must be notified in writing of the name and address of the new custodian.

11.4 Use of Information and Publication

All information concerning Aspire Bariatrics' operations, patent application, manufacturing processes, and basic scientific data supplied by Aspire Bariatrics to the investigator and not previously published, are considered confidential and remains the sole property of Aspire Bariatrics. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the written consent of Aspire Bariatrics. This includes releasing any information or comments to the media.

The investigator understands that the information developed in the clinical study will be used by Aspire Bariatrics and may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide Aspire Bariatrics with all data obtained in the study.

11.5 Reporting

Reporting will be accomplished by using an electronic Case Report Book that can be accessed via the internet by the Sponsor's Clinical Monitors. CRFs shall be completed promptly, including data from screening visits, implantation procedure, Skin-Port installation and all other visits specified in Tables 1-3.

11.6 Study Termination

The Investigator will complete the study and submit the case report forms in accordance with the agreed time frame after receipt of clinical supplies by Sponsor (or satisfactory disposal of such supplies). Either the Investigator or the Sponsor may terminate this study for good and valid reasons prior to its planned conclusion, provided reasonable notice is given in advance of the intended termination.

12.0 Clinical Supplies

Aspire will supply the AspireAssist A-Tube, the AspireAssist Starter Kit, and all AspireAssist accessories to the site.

The A-Tubes is supplied in a sterile package. The A-Tube is not currently packaged with the instruments that are commonly supplied with commercial PEG tubes, such as snares, etc. The site may use the supplies packaged with standard Ponsky-pull method gastrostomy tubes and charge Aspire for such kit. It is anticipated that by approximately April 2013, the A-Tubes will be available with the instruments that are commonly supplied with commercial PEG tubes.

All other components of the AspireAssist are supplied non-sterile as they are not used in an aseptic environment.

All investigational devices received and used by the investigator will be inventoried and accounted for throughout the study. The **AspireAssist Aspiration Therapy System** components will be stored as per the package label in a secure, locked area with restricted access separate from other medical devices.

The investigator agrees not to supply the investigational device(s) to any person except those involved in this study.

12.1 Accountability

A Device Disposition Record must be maintained by each investigator (or designee).

12.2 Instructions for Return of Damaged or Unused Devices

When instructed by Aspire Bariatrics (or designee), the investigator must return any damaged or unused devices to:

Quality Assurance
Aspire Bariatrics, Inc.
3200 Horizon Drive, Suite 100
King of Prussia, PA 19406

The Clinical Device Return Form (**Appendix O**) must be completed and returned in the box with the devices. The investigator shall keep a copy of the Clinical Device Return Form.

12.3 Instructions for Return of Used A-Tubes

After withdrawal of a treatment group subject, or potentially at the conclusion of the study, the A-Tube will be removed and, upon request, returned to the company. In addition, the company can require that a displaced A-Tube be returned.

The following procedures must be followed for return:

- Flush the A-Tube with normal (0.9%) saline or lactated Ringer's solution and immediately submerge the device in 10% neutral, buffered formalin.
- Ship the A-Tube in the 10% neutral, buffered formalin solution by using the container supplied by Aspire.
- Fill out the information on the label provided by Aspire, and place the outside of the first level of inner wrap, positioned so that it is seen immediately upon opening. Place cushioning material around inner container.

- Make sure the container is sealed tightly and apply tape around the lids as an extra precaution.

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