Spatz 3 US Pivotal Trial Protocol

Protocol Version	**V1.4e (January 11, 2017)**
Sponsor	**Spatz FGIA** 15 Cuttermill Rd, #147 Great Neck, NY 11021 Contact Person: Jeffrey Brooks, MD CEO, Spatz FGIA, Inc jeff@spatzmedical.net
Trial Title	A randomized, controlled, multicenter study comparing the Spatz3 Adjustable Balloon System plus diet and exercise to diet and exercise alone.
Device Name	Spatz3 Adjustable Balloon System® (Spatz3)
Clinical Phase	Pivotal
Trial Design	Multicenter open-label randomized controlled trial
Trial Participants	Adults with a BMI ≥ 30 and < 40 who have failed to achieve and maintain weight-loss with a weight control program
Control group	Supervised diet and exercise
Planned sample size	282 subjects randomized 2:1 to device/control
Follow-up duration	8 months for control and 14 months for treatment
Planned trial period	30 months
Primary endpoints	Percent change in total body weight (%TBL) at 32 weeks AND Clinical response, where a responder is defined as a subject with at least a 5% loss in total body weight at 32 weeks
Secondary endpoints	Maintenance of 40% of the weight loss with the balloon six months after the balloon is removed Clinical response, where a responder is defined as a subject with at least a 25% loss in excess body weight at 32 weeks

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1. ADMINISTRATIVE INFORMATION

1.1. Title

A randomized, controlled, multi-center study comparing the Spatz3 Adjustable Balloon System plus diet and exercise to diet and exercise alone.

1.2. Trial Registration

This trial protocol has been registered with clinicaltrials.gov.

1.3. Protocol Version

Version number: V1.4e

Issue date: January 11, 2017

1.4. Sponsor

Spatz FGIA
15 Cuttermill Rd, #147
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Contact Person:

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The sponsor will approve this protocol prior to study commencement.

1.5. Roles and Responsibilities

1.5.1. Sponsor Responsibility

The sponsor has the following responsibilities:

- **FDA and IRB approval**
  - The sponsor will not begin this study (or any significant change to this study) until an IRB and FDA have both approved the application or supplemental application.
- **Selecting Investigators**
  - The sponsor is responsible for selecting investigators qualified by training and experience to investigate the device. The sponsor will supply all investigators participating in the investigation with copies of the investigational plan and a report of prior investigations of the device.
- **Investigator Agreement**
  - The sponsor will obtain a signed agreement from each participating investigator that includes:

- The investigator's curriculum vitae,
- A statement of the investigator's relevant experience, including the dates, location, extent, and type of experience, where applicable,
- An explanation of the circumstances that led to termination of a study if the investigator was involved in an investigation or other research that was terminated,
- A statement of the investigator's commitment to:
  - Conduct the investigation in accordance with the agreement, the investigational plan, the IDE and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA,
  - Supervise all testing of the device involving human subjects
  - Ensure that the requirements for obtaining informed consent are met.
  - Sufficient accurate financial disclosure information to allow a sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. A sponsor shall also obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

- **Monitoring**

  The study will be monitored by the Clinical Research Organization, Clinical Development Associates Inc. (see Section 9 below).

  - *Securing Compliance*: If the sponsor discovers that an investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA, then the sponsor will promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. The sponsor will also require that the investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.
  - *Unanticipated Adverse Device Effects*: The sponsor will immediately conduct an evaluation of any unanticipated adverse device effect. If the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, then they must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination will occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.
  - *Resumption of Terminated Studies*: The sponsor will not resume a terminated investigation without IRB and FDA approval.

- **Sponsor Records (§ 812.140)**

  - The sponsor will maintain accurate and complete records relating to the investigation. These records include:
    - All correspondence including required reports,
    - Records of shipment of the device,
    - Records of disposition of the device
    - Signed investigator agreements including financial disclosure information,
    - Records concerning complaints and adverse device effects whether anticipated or not,
    - Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

- **Device Control**
  - The sponsor will ship investigational devices **only** to qualified investigators participating in the investigation.

1.5.2. Investigators

One investigator per contributing site will be nominated as a local coordinator.

Investigator responsibilities will include:

- The investigator is responsible for protecting the rights, safety, and welfare of subjects. An investigator must conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, the IDE regulations and other applicable FDA regulations, and any conditions of approval imposed by an IRB and FDA.
- While awaiting approval of an IDE application, an investigator may determine whether or not potential subjects would be interested in participating in an investigation, but cannot request written informed consent or allow any subjects to participate before obtaining IRB and FDA approval.
- An investigator is responsible for obtaining informed consent from all study subjects.
- An investigator agrees to use the investigational device only with subjects under his/her supervision and will not supply an investigational device to any person not authorized under the IDE regulations to receive it.
- **Financial Disclosure**
  - The clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the IDE applicant (or sponsor) to submit certification or disclosure of financial interests under 21 CFR 54. The investigator must update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

- **Device Disposal**
  - Upon completion or termination of a clinical investigation or the investigator's part of the investigation or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or dispose of the device as the sponsor directs.
- **Records**

  The investigator must maintain accurate and complete records relating to the investigation. These records include:
  - All correspondence including required reports,
  - Records of receipt, use, or disposition of the investigational device,
  - Records of each subject's case history and exposure to the device,
  - The protocol and documentation (date and reason) for each deviation from the protocol,
  - Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

1.5.3. Data Monitoring Committee

The Data Monitoring Committee is responsible for:

- Preparing a charter for the conduct of the committee
- Reviewing data from the study according to the schedule set out in the protocol
- Reviewing adverse events to determine if they are serious adverse events and if they are device related and evaluating any device deficiencies

2. INTRODUCTION

2.1. Background

Obesity in the United States has been increasingly cited as a major health issue in recent decades. Like the U.S., many industrialized countries have experienced similar increases, underscoring the severity of the problem. The United States had the highest rate of obesity for large countries (> 32%), until obesity rates in Mexico surpassed that of the United States in 2013[1]. Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years [1].

The American Heart Association (AHA) notes that 60-70% of the US population is either overweight or obese, putting them at risk for heart disease, stroke, high blood pressure and diabetes. According to the AHA, obesity affects nearly 78 million adults and 13 million children in the US today. The CDC found there was no decrease in obesity rate from the 2009-2010 survey to the 2011-2012 survey [3].

Among Americans age 20 and older, 154.7 million are overweight or obese (BMI of 25.0 kg/m2 and higher): - 79.9 million men and 74.8 million women. Of these 154.7 M, 78.4 million are obese (BMI of 30.0 kg/m2 and higher): 36.8 million men and 41.6 million women. If current trends in the growth of obesity continue, total healthcare costs attributable to obesity could reach $861 to $957 billion by 2030, which would account for 16% to 18% of US health expenditures (AHA) [3].

To date, treatment options for the US obese population include weight loss management programs, pharmaceuticals, and bariatric surgeries (gastric bypass, sleeve gastrectomy and gastric banding accounting for 99% of the bariatric surgeries) [4]. FDA has also recently approved the Enteromedics vagal nerve stimulator and the Orbera intragastric balloon and the Reshape Duo intragastric balloon, but it is too soon to assess the potential impact of these therapies.

2.2. Current Treatment Options

Unfortunately, the results of most weight loss management programs are rather dismal. Efficacy of behavioral changes is dependent on both a highly motivated subject and a dedicated counselor willing to maintain long-term follow-up. On average, the best weight loss programs achieve approximately 10% body weight loss, with patients compliant to diet only 20% of the time [5].

Belviq, a serotonin enhancing drug, is available in the US market and has 3-3.7% weight loss in one year. Side effects of paresthesias, fatigue, headache and dizziness have been reported. Qsymia is a combination drug containing the appetite suppressant phentermine and the seizure medicine Topiramate. 38% of users have reported weight loss of 105 or greater. Long term follow up studies to evaluate weight loss maintenance are not available in either drug [6]. Previously approved drugs include, Orlistat, which inhibits fat absorption in the intestine; Phentermine, Methamphetamine, Benzphetamine, Diethylpropion, and Phendimetrazine, which are appetite suppressants and DEA scheduled drugs [7].

Surgical therapy for obesity (bariatric surgery) is the only available therapeutic modality in the US associated with significant and sustained weight loss in the setting of subjects with morbid obesity associated with co-morbidities. Evidence is available to show that well-performed bariatric surgery in the setting of carefully selected patients and a good multidisciplinary

support team significantly ameliorates the morbidities associated with severe obesity. While bariatric surgery is the only therapeutic method associated with consistently demonstrable sustained weight loss, it is expensive, highly procedure-specific and surgeon-specific, and certainly not the only solution for the burgeoning obesity epidemic.

Among the standard bariatric procedures are roux-en-Y gastric bypass, sleeve gastrectomy and gastric banding surgeries. Gastric bypass surgeries have been available for many years and have evolved and improved, but reported mortality rates of 0.5% [8] have left a 0.6% penetration into the eligible population [9]. Reports in 16,000 Medicare beneficiaries who received roux-en-y gastric bypass surgery between 1997-2002, revealed mortalities of 2% at 30 days and 4.6% at one-year post operatively [10]. An 8-20% post-operative infection rate has led to a 25% re-operation rate within 3-5 years. As a result of these statistics, the growing population of morbidly obese patients is met with diminishing therapeutic options. Furthermore, a review of 60,000 Medicare patients who underwent roux-en-y gastric bypass surgery from 1995-2004, revealed a fourfold increase in medical expenditures in the 3-year post-op compared with the 3-year pre-op (not including the cost of surgery) [11].

Gastric banding consists of a silicone elastomer band that is placed around the upper part of the stomach to create a small stomach pouch, which can hold only a small amount of food. The diameter of the band outlet is adjustable to meet individual needs, which can change as one loses weight. Disadvantages of gastric banding include balloon leakage, band erosion/migration, band slippage, and reservoir leakage [12]. The negative impact of mortality figures and economic figures, have led the medical community to seek non-surgical bariatric solutions.

Intragastric Balloons

Intragastric Balloons (IGBs) were introduced decades ago as a minimally invasive treatment for morbid obesity. Gastric balloons fill the stomach to induce a feeling of satiety and are effective in achieving weight reduction [14 - 40]. In the 1980's the Garren-Edwards bubble for weight loss was removed from the US market due to life threatening complications of bowel obstruction from deflated bubbles (balloons). This prompted the Tarpon Springs comprehensive workshop in 1987 that delineated new standards for intragastric balloons: smooth, seamless balloons, fluid filled, adjustable, and with radio-opaque markers [13]. The next generation of IGBs, led by the BIB balloon (Bioenterics intragastric balloon) meets most of those requirements, with the exception of adjustability, and have been used OUS for the last 25 years. In the summer of 2015 both the Orbera and Reshape balloons were granted PMA approval by the FDA. These intragastric balloons are indicated for adults > 18 yrs old (or > 21 yrs old for Reshape Duo) as an adjunct to weight loss for those with BMI ≥30 and < 40 in individuals who have failed conventional weight loss therapy.

IGBs are silicone spheres filled with saline that sit in the stomach for 6 months taking up stomach volume, delaying stomach emptying and thereby decreasing appetite and preventing overeating. The deployment requires a routine endoscopy under conscious sedation which is done to be certain there are no lesions that would preclude use of the balloon. The Orbera and Re-Shape balloons are inflated at the implantation procedure and this volume remains stagnant until extraction. After 6 months, the IGBs are removed by piercing and draining balloon, and the balloon is then removed by a snare or grasping forceps. Behavior modification therapy prior, during and after balloon deployment as well as an exercise program is an essential part of the treatment.

The literature is filled with publications of the successful use of intragastric balloons outside of the US with wide ranging reports of 12-21 kg weight loss and 20-38 % EWL over 6 months, and with complication rates of up to 5 % [14 - 38]. Due to the wide range of published results, two comprehensive reviews of the BIB literature have been published in 2008 that meticulously scrutinized publications and chose studies based on multiple criteria such as controlled trials, randomization, low dropout rate, consecutive patients in series, etc [39,39]. Both review articles concluded that intragastric balloons are a "valuable" or "effective" non-surgical therapy for weight loss. Weight losses of approximately 8 to 16 kg, with 12% to 15 % weight loss and 20-30% EWL were noted in these "approved" studies. The reviewers reported 4.2% to 6.7% early balloon removals and an 8.1% deflation rate with 5 cases requiring surgery (4.1%). Studies have shown that a greater than 10% weight loss can prevent and reduce cardiovascular risks and other obesity-related diseases [41,41]. In the recently published FDA trials, the Reshape and Orbera reached their endpoints with ≥ 25% EWL in over 35% of treatment subjects with a superiority margin of > 7.5% compared with control arm subjects (sham control in the Reshape trial and diet/exercise control in the Orbera trial). In the Reshape Duo balloon SSED published by the FDA the mean weight loss was 14.3 lbs/6 months with 25.1% EWL and 6.8% TBL compared with 11.3% EWL; 3.3% TBL and 7.2 lb weight loss in the control arm. Adverse events included nausea and vomiting in 85% of patients in the first 3 days post implantation. There were 7.5% serious adverse events requiring early device removal. 39.6% ulcerations were reported, however, following design change the ulceration rate fell to 10.3%. There was one episode of UGI hemorrhage from a gastric ulcer. The extraction procedure caused one contained esophageal perforation and one esophageal tear that was closed with endoscopic clips.

In the Orbera balloon SSED published by the FDA the mean weight loss was 16 lbs/6 months with 29 % EWL and 7.6 % TBL compared with 11.1% EWL; 3.1 % TBL and 6 lb weight loss in the control arm. Adverse events included nausea and vomiting in 85% of patients in the first 3 days post implantation. There were 5.6 % serious adverse events requiring early device removal including a gastric perforation leading to sepsis and surgery.

In 1987 the Tarpon Springs comprehensive workshop on endoscopic therapy for weight loss delineated standards for IGBs: a) smooth balloon surface, b) fluid filled, c) adjustable, and d) with radio-opaque markers [13]. Unlike any other IGBs that are currently commercially available in the world, including the BIB (Orbera), Reshape Duo, Medsil, Silimed, and Medicone balloons, the Spatz3 device is the only intragastric balloon that meets all of those requirements.

3. STUDY DESIGN

3.1. Study Hypothesis

Patients who receive the Spatz3 balloon for 8 months will lose significantly more weight than those treated with diet and exercise alone.

3.2. Endpoints

3.2.1. Effectiveness

There are two co-primary effectiveness endpoints:

- Percent change in total body weight (%TBL) at 32 weeks; and
- Clinical response, where a responder is defined as a subject with at least a 5% loss in total body weight at 32 weeks

There are two secondary endpoints:

- Maintenance of 40% of the total body weight loss with the balloon six months after the balloon is removed
- Clinical response, where a responder is defined as a subject with at least a 25% loss in excess body weight at 32 weeks

3.2.2. Safety

The incidence, frequency, and severity of adverse events related to treatment with the device will be reported.

3.3. Design

The purpose of this study is to evaluate the safety and effectiveness of the Spatz3 in subjects with a BMI ≥ 30 and < 40 who have failed to achieve and maintain weight-loss with a weight control program.

Subjects will be studied in a randomized, controlled, multi-center study. The control group will receive dietary/exercise counseling for 32 weeks. The treatment group will receive dietary/exercise counseling plus the Spatz3 balloon for 32 weeks.

The study will run 32 weeks for the control group and 32 weeks followed by a 24-week follow up period for the treatment group.

282 eligible subjects will be randomized to treatment (188 subjects) or control (94 subjects) arms. All treatment group subjects will undergo endoscopy and those without endoscopic contraindications will be implanted with the Spatz3 balloon for 32 weeks. All subjects will follow a 1000-1200 kcal/day-deficit diet during their participation in the study.

At 18 weeks ± 4 weeks, treatment arm subjects will be evaluated, and those that meet the criteria described below in section 4.3.3.2.4 will undergo an adjustment procedure wherein the balloon volume will be increased to achieve extra weight loss. The balloon adjustment procedure is done with an endoscopy procedure under the same sedation as the implantation procedure. At the end of the 32-week treatment period the control subjects will be dismissed and the treatment group will be explanted and will have a 24-week follow up.

3.4. Study Setting

The study will be conducted at up to 10 US centers. The maximum enrollment at each site will be limited to 65 subjects.

3.5. Subjects

Participants will be adult patients (22 years of age or above) with a BMI ≥ 30 and <40 that meet the eligibility criteria below. All eligibility criteria must be met at the time of randomization.

3.5.1. Inclusion Criteria

1. Age 22 - 65
2. BMI ≥ 30 and <40
3. Willingness to comply with the substantial lifelong dietary restrictions required by the procedure
4. History of obesity (BMI ≥ 30) for at least 2 years
5. History of failure with non-surgical weight loss methods
6. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests, completing diet counseling
7. Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow- up visits
8. Ability to give informed consent
9. Women of childbearing potential (i.e., not post-menopausal or surgically sterilized) must agree to use adequate birth control methods. Acceptable birth control methods are limited to hormonal contraceptives (oral, flexible vaginal ring, skin patch, injection), diaphragms, IUDs, condoms with or without spermicide, and voluntary abstinence. The method of birth control must be documented and verified at follow-up. Should a treatment arm subject become pregnant during the implantation period, the balloon will be extracted during the second trimester - the timing of which will be determined via consultation with the subject's obstetrician.

3.5.2. Exclusion Criteria

1. Prior gastrointestinal surgery with sequelae, i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions.
2. Prior open or laparoscopic bariatric surgery.
3. Prior surgery of any kind on the esophagus, stomach or any type of hiatal hernia surgery.
4. Any inflammatory disease of the gastrointestinal tract including esophagitis, Barrett's esophagus, gastric ulceration, duodenal ulceration, cancer or specific inflammation such as Crohn's disease.

5. Potential upper gastrointestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasis, or other congenital anomalies of the gastrointestinal tract such as atresias or stenoses.
6. A gastric mass.
7. A hiatal hernia > 2cm or severe or intractable gastro-esophageal reflux symptoms.
8. Acid reflux symptoms to any degree that require more than one medication for symptom control.
9. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the balloon alongside the endoscope.
10. Achalasia or any other severe esophageal motility disorder that may pose a safety risk during the removal of the device
11. Severe coagulopathy.
12. Insulin-dependent diabetes (either Type 1 or Type 2) or a significant likelihood of requiring insulin treatment in the following 12 months.
13. Subjects with any serious health condition unrelated to their weight that would increase the risk of endoscopy
14. Chronic abdominal pain
15. Motility disorders of the GI tract such as gross esophageal motility disorders, gastroparesis or intractable constipation
16. Hepatic insufficiency or cirrhosis
17. Serious or uncontrolled psychiatric illness or disorder that could compromise patient understanding of or compliance with follow up visits and removal of the device after 8 months.
18. Alcoholism or drug addiction.
19. Patients unwilling to participate in an established medically-supervised diet and behavior modification program, with routine medical follow-up.
20. Patients receiving daily prescribed treatment with aspirin, anti-inflammatory agents, anticoagulants or other gastric irritants.
21. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication for the duration of the device implant.
22. Patients who are known to have, or suspected to have, an allergic reaction to materials contained in the system.
23. Patients who have ever developed a serotonin syndrome and are currently taking any drug known to affect the levels of serotonin in the body [e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs)] should not undergo placement of the device.
24. Patients who are pregnant or breast-feeding.

25. Subjects with Severe cardiopulmonary disease or other serious organic disease which might include known history of coronary artery disease, Myocardial infarction within the past 6 months, poorly-controlled hypertension, required use of NSAIDs
26. Subjects who have tested positive for H. Pylori.
27. Subjects taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications
28. Subjects who are taking corticosteroids, immunosuppressants, and narcotics
29. Subjects who are taking diet pills
30. Use of an intragastric device prior to this study due to the potential increase in risk associated with implantation of a balloon in a previously instrumented and possibly scarred stomach.
31. Participation in any clinical study which could affect weight loss within the past 6 months due to the potential to confound findings.
32. Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease.
33. Pre-existing respiratory disease such as chronic obstructive pulmonary disease (COPD), pneumonia or cancer.
34. Diagnosis of autoimmune connective tissue disorder (e.g. lupus, erythematous, scleroderma) or immunocompromised.
35. Life expectancy less than 1 year or severe renal, hepatic, pulmonary or other medical condition, in the opinion of the investigator because of an increased risk profile.
36. Specific diagnosed genetic or hormonal cause for obesity such as hypothyroidism or Prader Willi syndrome
37. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating
38. Known history of endocrine disorders affecting weight

4. TRIAL PROCEDURES

4.1. Informed Consent

Prior to being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them and per the requirements in 21CFR Part 50.20. The written informed consent document is provided in ***Appendix A*** of this protocol. Subjects are free to withdraw consent at any time, irrespective of their initial consent.

After reading the informed consent document, the participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not perform any exams or testing specifically required only for the clinical study until valid consent has been obtained.

Any use of the device without obtaining informed consent shall be promptly reported (no later than 5 working days) to the study sponsor and the IRB.

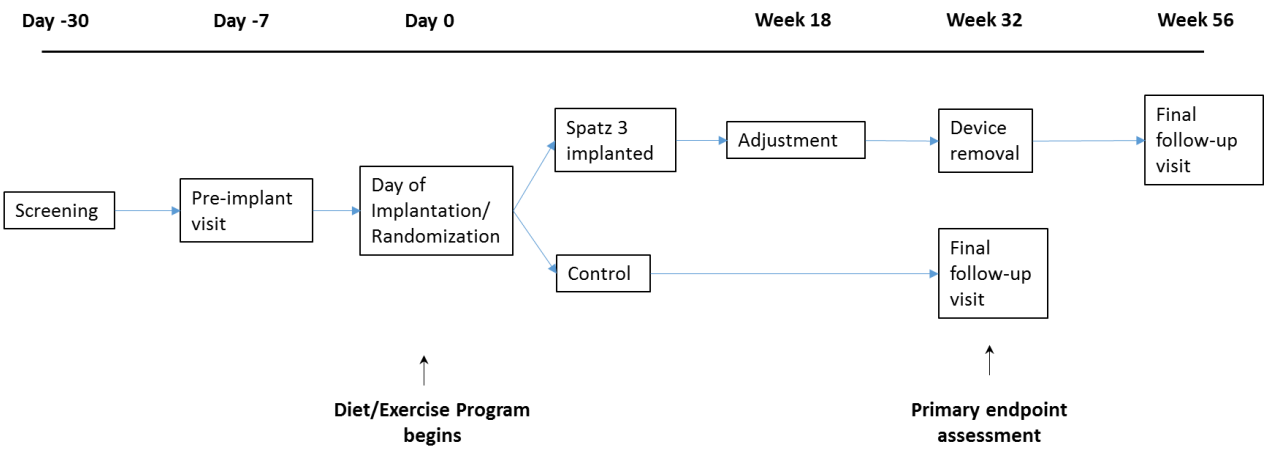
4.2. Blinding/Masking

Although it is not possible to blind the study subject or the investigator to the treatment group, weight measurements are to be performed by clinical staff who are blinded to the treatment group. Subjects will be instructed not to speak with weighing personnel and to not disclose if they are control or treatment arm.

4.3. Study Timeline

The study timeline is summarized in Figure 1:

Figure 1: Study Timeline



4.3.1. Screening and Eligibility Assessment

Screening will be conducted by the investigator or co-investigator and documented on the PI Intake form (***Appendix E2: CRF_2 PI Intake***) and Screening Labs form (***Appendix E3: CRF_3 Screening Labs***). Screening must occur no more than 30 days prior to implantation.

Screening will include the following:

1. Screening exam by investigator or co-investigator (***Appendix E2: CRF2_PI Intake***). Includes Medical history, Current medications, Record contraceptive method for female subjects, Vital signs, Body Weight and Height, Physical exam, Evaluation of inclusion/exclusion criteria.
2. Sign Informed Consent Form (***Appendix A: Informed Consent***)
3. Dietician intake - Baseline body weight, height, ideal body weight, excess weight, BMI, (***Appendix E5: CRF5_Dietician Intake***)
4. Laboratory tests* plus EKG
5. Psychological evaluation (***Appendix E10: CRF10_Consultation with Psychologist***)
6. Diabetic subject – follow up by provider or PI (***Appendix E11: CRF11_Diabetic Patient Follow Up***)

*Laboratory Tests (***Appendix E3: CRF3_Screening Labs)*** include:

CBC: Hgb, Hct, WBC, MCV, platelets

Chemistry panel: sodium, potassium, chloride, CO2, BUN, creatinine, glucose, SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin, total protein, albumin, total cholesterol, Fe/TIBC, B12, Folic Acid, 25-Hydroxy Vitamin D, TSH

Coag: Pro Time or INR, PTT

Urinalysis

$HgbA_{1C}$ (if diabetic)

H. Pylori Serology

Within 1 week of the screening tests, the PI will review the results and determine eligibility of the subject. The center will inform the subject of their results within 10 days of the tests. All potential subjects who pass the initial screening assessment must return for an additional visit within 7 days of the scheuled implantation procedure for the Pre-Implantation visit (***Appendix E4: CRF4_Preimplantation Tests and Data***). This will include an assessment of the following:

- Urine pregnancy test (women of child-bearing potential)
- Medications List
- Weight (Note: This is the baseline weight that will be used for the endpoint assessments)

Subjects with a positive pregnancy test or who are taking medications listed in the exclusion criteria will be excluded from the study at this time, and will be considered to be screening failures.

Investigators must retain study documentation for all patients who have been screened, regardless of whehter or not they are accepted as study subjects.

4.3.2. Randomization

Subject will be randomly assigned to treatment or control group with a 2:1 allocation as per a computer generated randomization schedule using variable block randomization using the following stratification factors: treatment center and then by BMI (<35 kg/m2 vs. ≥ 35 kg/m2). The randomization schedule will be created by the study statistician, and will remain confidential.

Subjects will not be informed of their randomization status until the day of implantation. Subjects randomized to the treatment group will proceed to implantation, and subjects randomized to the control group will proceed to an appointment with a dietician.

4.3.3. Trial Intervention

4.3.3.1. Control Group

The control group will be provided with dietary counselling monthly during the 32-week study. The first dietician visit will commence on the day of randomization. A diet plan will be reviewed with each subject and will be adjusted according to the needs of each subject (***Appendix C: Diet and Exercise Plan***). In addition, exercise counselling will be given by the dietician with specific exercises detailed (***Appendix D: Physical Exercise Program***). The progressive exercise plan will have 3 phases that are gradually phased in over the 32-week follow-up period.

4.3.3.2. Treatment Group

4.3.3.2.1. Implantation

The Spatz3 balloon is implanted in an outpatient setting via upper endoscopy under conscious sedation. The subject fasts from midnight the night prior to the procedure. Conscious sedation will utilize a combination of Propofol, Midazolam, and a narcotic such as Fentanyl. A standard upper endoscopy is performed to rule out contraindicating findings such as a large hiatal hernia >2 cm), esophagitis of any degree, erosive gastritis or ulceration of the stomach or duodenum.

Prior to implantation the balloon is prepared as follows: the bands are removed using “band-off” pull strings; the valve is secured to the white catheter using “valve-hold”, the Spatz3 balloon is secured to the endoscope by the insertion facilitator and finally the extension tube is connected to the valve. The scope with balloon secured to its side is passed into the throat and continues into the esophagus and stomach. Upon arrival in the stomach a retroflex maneuver confirms the presence of the balloon in the stomach and below the gastro-esophageal junction. The scope is then straightened and the balloon is inflated by connecting the 3-way stopcock at the proximal end of the extension tube to the provided 60 ml syringe and a 500 ml bag of Normal Saline. The 500 ml bag of Normal Saline will be injected with 2 cc of 1% Methylene Blue.

The balloon is initially inflated according to the following criteria:

- Initial balloon volume for subjects with height < 64 inches;

  - 450 ml (without history of GE reflux)

- 400 ml (with history of GE reflux)

- Initial balloon volume for subjects with height ≥ 64 inches;
  - 550 ml (without history of GE reflux)
  - 500 ml (with history of GE reflux)

After final balloon volume is achieved, the extension tube is pulled out of the mouth and the valve is disconnected from it and replaced with a cap. The capped valve is released and allowed to return to its position behind the balloon. The endoscope pushes the valve and catheter below the GE junction and the endoscope is then removed.

4.3.3.2.2. Diet and Exercise

The Treatment and control group will be provided with dietary counseling monthly during the 32-week study and the 24 week follow up. The first dietician visit will commence on the day of randomization. A diet plan will be reviewed with each subject and will be adjusted according to the needs of each subject (Appendix C: Diet and Exercise Plan). In addition, exercise counseling will be given by the dietician with specific exercises detailed (Appendix D: Physical Exercise Program). The progressive exercise plan will have 3 phases that are gradually phased in over the 32-week follow-up period.

4.3.3.2.3. Medications

All treatment arm subjects will receive the following oral medications for the implantation and upward adjustment procedures:

- Aprepitant (Emend) [implantation procedure only]125 mg immediately prior to or 1 hour after the procedure, 80 mg the morning after the procedure and another 80 mg two mornings after the procedure.
- Ondansetron 8 mg will be taken every 6 hours starting 1 hour after the procedure for 12 tablets (3-4 days);
- Hyoscyamine 0.125 mg prn for abdominal pain or spasm 1-2 tablets every 4 hours sublingually (maximum 12 tablets/ 24 hours)
- Percocet 10 mg will be provided for subjects who have abdominal pain that is not relieved by Hyoscyamine.
- A PPI (proton pump inhibitor such as Nexium 20 mg, Protonix 40 mg or Prevacid 30 mg) will be taken daily for the entire 8 months to reduce acid in the stomach. This helps preserve the silicone and also controls acid reflux symptoms, should they arise.
- Probiotic, Acidophilus, 8-10 Billion CFU will be taken once daily for the 8-month period.

During the 8-month implantation period, different symptoms may arise such as constipation, nausea, vomiting, bloating, abdominal pressure, heartburn, and diarrhea. These can be treated as discussed below.

Constipation is expected in the first week after implantation. It generally resolves after oral intake increases in the first 2 weeks. If it persists, standard treatments such as a teaspoon of mineral oil daily, Milk of Magnesia, or Miralax (OTC med) 17 gram+ 8 oz water twice daily.

Nausea and/or vomiting or bloating or abdominal pressure can be treated with metoclopramide – 10 mg orally up to 4 times in 24 hours.

Heartburn can be treated by increasing the PPI medication to twice daily; addition of antacids such as Maalox, Mylanta, Gaviscon – 30 ml or 2 tablets every 3-4 hours; or addition of Sucralfate suspension 1,000 mg 4 times daily

Diarrhea is expected in about 20-25% of patients and is due to a mild case of bacterial overgrowth in the stomach and small intestine. Should diarrhea develop, the probiotic Acidophilus will be increased to 4 pills daily for 4 days and during those 4 days the PPI will not be taken. In the event those measures do not alleviate the diarrhea, treatment with Metronidazole 500 mg 3 times daily for 5 days will commence - generally the diarrhea improves on the first day of treatment. Some subjects have recurrence and require repeat treatment.

Foul-smelling belches may occur in 20% of subjects as a result of continuous administration of daily PPI medications in combination with balloon induced delayed gastric emptying. At the discretion of the investigator, these subjects may benefit from a 3-day holiday from the daily dose of PPI. No more than two such PPI holidays should be prescribed in any month. Gastro-esophageal reflux symptoms can be managed by use of antacids at a dose of 30 ml PO QID prn during the 3-day holiday.

For subjects intolerant to PPI medications (headache, diarrhea, abdominal pain, nausea, vomiting), the investigator will have the option of discontinuing the PPI and substituting any H2 Blocker medication at a twice daily dosing (Ranitidine 150 PO BID; Famotodine 20 mg PO BID ; Nizatidine 150 mg PO BID).

4.3.3.2.4. Gastric Ulcers and H. Pylori treatment

For the purposes of this study, a *gastric ulcer* is defined as a gastric lesion ≥ 5mm in diameter with unequivocal depth by endoscopy.

A gastric ulcer is defined as *endoscopically significant* if it is ≥ 3cm in length and ≥ 1cm in width. Dimensions should be confirmed by capturing clear images with an accessory of known dimensions next to the lesion.

Gastric ulcers/gastritis require biopsy for H.pylori (urease test) and treatment with “triple” regimen for 14 days if positive.

- PPI BID
- Amoxicillin 1 gram PO BID
    - (Pcn allergic – substitute metronidazole 500 mg PO BID)
- Clarithromycin 500 mg PO BID

Blood hemoglobin will be monitored during scheduled or unscheduled endoscopies in patients who have ulcers or report signs of upper GI bleeding (hematemesis or melena).

4.3.3.2.5. Adjustments

1. *Adjustments for Intolerance*

The PI may make an adjustment to the balloon volume at any time if the patient has symptoms of continued nausea, vomiting, uncontrolled GE reflux or abdominal pain in spite of conservative symptomatic treatment.

For intolerance that continues more than 7-10 days beyond the first 5 days after implantation or that occurs at any time during the 8 months, the investigator should:

- remove 150 ml from balloon (when initial volume is 450-550ml)
- remove 100 ml from balloon (when initial volume is 400ml)

The final volume should not be reduced below 300ml. If medications and balloon volume down adjustment do not alleviate the intolerance, the balloon should be extracted.

2. *Unscheduled endoscopy*

An unscheduled endoscopy may be performed at any time at the discretion of the investigator.

The following procedures will be applied to subjects who present with endoscopic findings based on an unscheduled endoscopy.

Gastric Ulceration

Subjects who present with an endoscopically confirmed gastric ulcer will be treated as follows:

- **Ulcers whose smallest dimension (S) is ≥ 2cm, or if there are any stigmata of increased risk of bleeding, such as visible vessels or clots**

  The balloon should be extracted. Biopsy for H.pylori will be performed and treatment prescribed if positive.

  These subjects should be treated with the following regimen: with sucralfate 1,000 mg PO Qid, and PPI medication twice daily for 3 months, followed by endoscopic evaluation after 3 months to confirm healing.

- **Ulcers whose smallest dimension (S) is ≥ 1 cm and < 2 cm**

  The balloon volume should be decreased by 150 ml (or 100 ml if starting volume is 400 ml) and subjects should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

  Endoscopic follow up will be performed at 8 weeks and if not healed at 8 weeks, an additional endoscopy at 16 weeks to confirm healing.

  - At the 8-week follow-up, if signs of healing defined by a 25% reduction in either length or width are not observed, then the balloon should be extracted.
  - At the 16-week follow-up, if signs of healing defined by a 50% reduction from baseline in either length or width are not observed, then the balloon should be extracted, and healing confirmed at follow up endoscopy 2-3 months after extraction.

  These subjects will not undergo adjustment at 18±4 weeks.

- **Ulcers whose largest dimension is ≥ 1 cm and whose smallest dimension (S) is < 1 cm.**

The balloon volume should be decreased by 150 ml (or 100 ml if starting volume is 400 ml) and subjects should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

Endoscopic follow up will be performed at 12 weeks and if not healed at 12 weeks, an additional endoscopy at 20 weeks to confirm healing.

- At the 12-week follow-up, if signs of healing defined by a 25% reduction in either length or width are not observed, then the balloon should be extracted.
- At the 20-week follow-up, if signs of healing defined by a 50% reduction from baseline in either length or width are not observed, then the balloon should be extracted.

These subjects will not undergo adjustment at 18±4 weeks.

These recommendations are summarized in the following table:

		L – Largest Dimension (cm)				
		0 – 0.5	**0.5 – <1.0**	**1 –<2**	**2 – <3**	**≥ 3**
S - Smallest Dimension (cm)	**0 – 0.5**	Not ulcer	Increase Medication	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks
	0.5 - <1		Increase Medication	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks
	1 - <2			Decrease balloon volume Follow-up 8 and 16 weeks	Decrease balloon volume Follow-up 8 and 16 weeks	Decrease balloon volume Follow-up at 8 and 16 weeks*
	≥ 2				Remove Device	Remove Device*

*Endoscopically Significant

All subjects in whom a gastric ulcer is confirmed will have endoscopic confirmation of complete healing 2-3 months after the balloon extraction.

Erosive gastritis, and Small Ulcers

Subjects with ulcers < 1 cm in diameter in all dimensions (< 0.5 cm is not considered an ulcer) and erosive gastritis should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive. Balloon volume reduction at the discretion of the PI.

Endoscopic follow-up of these subjects prior to the 8-month extraction is not needed if they are asymptomatic. These subjects will not undergo adjustment at 18±4 weeks.

Non-Erosive Gastritis

If non-erosive gastritis is found at endoscopy, subjects will be treated with increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be performed and treatment prescribed if positive.

Endoscopic follow up and healing confirmation (and H.pylori eradication, if positive) will be deferred until the adjustment endoscopy at week 18±4 weeks or extraction endoscopy at 8 months, whichever comes first (must be at least 2 months after this unscheduled endoscopy), unless symptomatic.

Esophagitis

Subjects who present with esophagitis will be treated as follows:

- For subjects with esophagitis grade 3 or 4 at endoscopy, the balloon will be extracted, with the following medication regimen given:
    - Increase PPI to BID
    - Add Reglan 10 mg ac and Qhs
    - Add Gaviscon or Maalox 30 ml Q4h prn
    - Add Sucralfate Suspension 1,000 mg PO QID

  Endoscopic evaluation will be conducted after 3 months to confirm healing.

- For subjects with esophagitis grade 1 or 2 at endoscopy, the balloon may be left in place, with the following medication regimen given for 2-3 months:
    - Increase PPI to BID
    - Add Reglan 10 mg ac and Qhs
    - Add Gaviscon or Maalox 30 ml Q4h prn
    - Add Sucralfate Suspension 1,000 mg PO QID

  Endoscopic follow-up of these subjects prior to the 8-month extraction is not needed if they are asymptomatic. These subjects will not undergo adjustment at 18±4 weeks.

3. *Early Adjustments for lack of effect*

For patients without any balloon effect from days 4-14 after the implantation, defined as lacking all of the following symptoms - nausea, vomiting, abdominal pressure, post prandial fullness, abdominal pain, heartburn, and eructation - an additional 250 ml will be added to the balloon.

4. *18- week adjustment*

At 18 weeks ± 4 weeks, all treatment arm subjects whose balloon has not been removed will be evaluated to determine if an upward adjustment is clinically appropriate. The following algorithm will be followed:

1. Subjects who have reached goal weight (calculated by BMI of 25) ***and*** are without any symptoms of gastroesophageal reflux or symptoms suggestive of gastritis or gastric ulcer, will not receive a balloon volume adjustment, and endoscopy at 18± 4 weeks will not be performed.
2. Subjects who underwent a prior unscheduled endoscopy with findings of a gastric ulcer will not receive an adjustment at 18± 4 weeks and no additional endoscopy beyond that described in section 2 above will be performed.
3. For all other subjects, endoscopy will be performed, and adjustments/treatment decisions will reflect the following algorithm:
    a. For subjects with gastric ulceration found at endoscopy, **no upward adjustment** and PI will decide if balloon requires extraction based on endoscopic findings as described below.

Subjects who present with an endoscopically confirmed gastric ulcer will be treated as follows:

- **Ulcers whose smallest dimension (S) is ≥ 2cm, or if there are any stigmata of increased risk of bleeding, such as visible vessels or clots**

  The balloon should be extracted. Biopsy for H.pylori will be performed and treatment prescribed if positive.

  These subjects should be treated with the following regimen: with sucralfate 1,000 mg PO Qid, and PPI medication twice daily for 3 months, followed by endoscopic evaluation after 3 months to confirm healing.

- **Ulcers whose smallest dimension (S) is ≥ 1 cm and < 2 cm**

  The balloon volume should be decreased by 150 ml (or 100 ml if starting volume is 400 ml) and subjects should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

  Endoscopic follow up will be performed at 8 weeks and if not healed at 8 weeks, an additional endoscopy at 16 weeks to confirm healing.

    - At the 8-week follow-up, if signs of healing defined by a 25% reduction in either length or width are not observed, then the balloon should be extracted.
    - At the 16-week follow-up, if signs of healing defined by a 50% reduction from baseline in either length or width are not observed, then the balloon should be extracted, and healing confirmed at follow up endoscopy 2-3 months after extraction.

- **Ulcers whose largest dimension is ≥ 1 cm and whose smallest dimension (S) is < 1 cm.**

  The balloon volume should be decreased by 150 ml (or 100 ml if starting volume is 400 ml) and subjects should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

  Endoscopic follow up will be performed at 12 weeks and if not healed at 12 weeks, an additional endoscopy at 20 weeks to confirm healing.

- At the 12-week follow-up, if signs of healing defined by a 25% reduction in either length or width are not observed, then the balloon should be extracted.
- At the 20-week follow-up, if signs of healing defined by a 50% reduction from baseline in either length or width are not observed, then the balloon should be extracted.

These recommendations are summarized in the following table:

		L – Largest Dimension (cm)				
		0 – 0.5	**0.5 – <1.0**	**1 –<2**	**2 – <3**	**≥ 3**
S - Smallest Dimension (cm)	**0 – 0.5**	Not ulcer	Increase Medication	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks
	0.5 - <1		Increase Medication	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks	Decrease balloon volume Follow-up 12 and 20 weeks
	1 - <2			Decrease balloon volume Follow-up 8 and 16 weeks	Decrease balloon volume Follow-up 8 and 16 weeks	Decrease balloon volume Follow-up at 8 and 16 weeks*
	≥ 2				Remove Device	Remove Device*

*Endoscopically Significant

All subjects in whom a gastric ulcer is confirmed will have endoscopic confirmation of complete healing 2-3 months after the balloon extraction.

Erosive gastritis, and Small Ulcers

Subjects with ulcers < 1 cm in diameter in all dimensions (< 0.5 cm is not considered an ulcer) and erosive gastritis should be treated with the following regimen: sucralfate 1,000 mg PO Qid and increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive. Balloon volume reduction at the discretion of the PI.

Endoscopic follow-up of these subjects prior to the 8-month extraction is not needed if they are asymptomatic.

b. For subjects with Esophagitis grade 3 or 4, the balloon will be extracted, with the following medication regimen given for 3 months:

- Increase PPI to BID
- Add Reglan 10 mg ac and Qhs
- Add Gaviscon or Maalox 30 ml Q4h
- Add Sucralfate Suspension 1,000 mg PO QID

Endoscopic evaluation after 3 months to confirm healing.

c. For subjects with esophagitis grade 1 or 2, no volume addition is given and the balloon may be left in place, with the following medication regimen given for 2-3 months:

- Increase PPI to BID
- Add Reglan 10 mg ac and Qhs
- Add Gaviscon or Maalox 30 ml Q4h prn
- Add Sucralfate Suspension 1,000 mg PO QID

If asymptomatic, endoscopic follow-up deferred until the extraction endoscopy at 8 months.

d. For subjects with non-erosive gastritis found at endoscopy, balloon volume addition can be performed as per parameters below. These subjects will be treated with increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be performed and treatment prescribed if positive. Endoscopic follow up and healing confirmation (and H.pylori eradication, if positive) deferred until the extraction endoscopy at 8 months, unless symptomatic.

4. For subjects without gastric ulceration, erosive gastritis or esophagitis (any grade), the following volume addition parameters should be followed:

- No addition for GE reflux symptoms not controlled by medication
- 200 ml for subjects who previously received down adjustment for intolerance, but are currently asymptomatic
- 200 ml for any height with GE reflux symptoms controlled by medication
- 250 ml for height < 64 inches without GE reflux symptoms
- 300 ml for height ≥ 64 inches without GE reflux symptoms

Note: The Maximum final volume of the balloon must not exceed 1,000 ml.
Subjects who received an additional 250 ml in the first month for lack of any balloon effect will undergo an 18-week adjustment; however, their maximum final volume cannot exceed 1,000 ml. For example, a subject who started with 550 ml and then received 250 ml addition after 2 weeks due to lack of effect, cannot receive more than 200 ml addition at 18 weeks even if they do not have GE reflux symptoms and are ≥ 64 inches.

5. *Adjustment procedure*

The balloon adjustment procedure is done with an endoscopy procedure under the same sedation as the implantation procedure.

The adjustment procedure requires the patient to be on the following dietary restrictions:

- 72 hours prior to the procedure: Soft food only, no meat or vegetables in any form.
- 48 hours prior to the procedure: Full liquids only.
- 24 hours prior to the procedure: Clear liquids only.
- 12 hours prior to the procedure: No food or liquids by mouth.

The adjustment procedure is performed under conscious sedation by the anesthetist similar to the implantation procedure. The endoscope is introduced in the usual manner. The capped valve is identified and the suture loop is grasped with a standard rat tooth grasping forceps. The scope and cap are pulled out of the mouth, (the inflation tube stretches and reaches the mouth – see section 5.1) wherein the cap is twisted off and replaced with the extension tube (provided). The extension tube is lowered down the throat into the esophagus followed by the scope. The adjustment commences by utilizing the 3-way stopcock on the proximal end of the extension tube. Following completion of the adjustment, the extension tube is pulled out of the mouth and is replaced by the cap. The cap is lowered back into the throat and allowed to pull itself back to its position touching the white catheter. The scope then pushes it down into the stomach.

6. *Follow-up Endoscopy*

All study subjects whose final adjusted volume is >900 ml will receive a follow-up endoscopic mucosal evaluation 4 weeks following the adjustment.

4.3.3.2.6. Extraction

The extraction procedure requires the patient to be on the following dietary restrictions:

- 72 hours prior to the procedure: Soft food only, no meat or vegetables in any form.
- 48 hours prior to the procedure: Full liquids only.
- 24 hours prior to the procedure: Clear liquids only.
- 12 hours prior to the procedure: No food or liquids by mouth.

The extraction procedure is performed under conscious sedation by the anesthetist similar to the implantation procedure. The endoscope is introduced in the usual manner. The capped valve is identified and the suture loop is grasped with a standard rat tooth grasping forceps. The scope and cap are pulled out of the mouth, wherein the cap is twisted off. A large polypectomy snare is inserted into the biopsy channel of the scope and the snare is opened and placed on the valve. Then the extension tube (provided) is connected to the valve. The scope (with snare closed on the valve) and the extension tube are lowered down the throat into the esophagus. The balloon deflation commences by utilizing the 3-way stopcock on the proximal end of the extension tube. Following completion of the deflation, the scope is pushed down to the gastro-esophageal junction to confirm complete deflation of the balloon. The snare is opened as the extension tube is pulled until the valve exits the mouth- this will bring the distal white catheter and deflated balloon edge into the open snare. The snare is closed. The scope (with snare secured around balloon/white catheter) and the stretched inflation tube are pulled out together with the balloon in tow. The scope is then reinserted to inspect for any mucosal damage.

Following the extraction procedure, all treatment subjects will be followed for an additional 24 weeks.

4.3.3.2.7. Device Failures

If a balloon deflation or other device failure due to device malfunction or operator error occurs during the implantation or adjustment procedures or follow-up period, the investigator will replace the failed device with a new device unless doing so is not in the best interest of the patient. All device failures will be reported to the Data Monitoring Committee. The number of

device failures and the circumstances under which they occurred will be included in the final Study Report.

4.3.3.2.8. Pancreatitis

New onset abdominal pain (developed after acute accommodative balloon symptoms of balloon placement and adjustment has resolved) suggestive of pancreatitis (epigastric / RUQ in location with or without radiation to the back, persistent (>3 hours in duration), and associated with nausea, vomiting, or new poor PO tolerance justify checking pancreas enzymes (amylase and lipase).

- If pancreas enzymes (amylase and lipase) are > 3X upper limit of normal for institution,
    - In a systemically ill patient with evidence of moderately severe or severe acute pancreatitis (requiring > 3 days hospitalization, OR evidence of end organ damage [e.g., acute renal failure, respiratory distress, or meeting SIRS (systemic inflammatory response syndrome) criteria for sepsis], OR cross sectional imaging suggestive of severe acute pancreatitis [peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected)] -- **Balloon removal** and close clinical follow-up of these severely ill patients
    - In a patient who does not meet the criteria of severe pancreatitis-- **Balloon volume adjustment** with removal of 150 ml (or 100 ml for a 400 ml balloon) and repeat pancreas enzymes 48 hours after adjustment with clinical follow-up.

- If pancreas enzymes (amylase and lipase) are < 3X upper limit of normal for institution,
    - In a systemically ill patient with evidence of moderately severe or severe acute pancreatitis (requiring > 3 days hospitalization, OR evidence of end organ damage [e.g., acute renal failure, respiratory distress, or meeting SIRS (systemic inflammatory response syndrome) criteria for sepsis], OR cross sectional imaging suggestive of severe acute pancreatitis [peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected)] -- **Balloon removal** and close clinical follow-up of these severely ill patients
    - If typical pain persists for > 48-72 hours -- **Balloon volume adjustment** with removal of 150 ml (or 100 ml for a 400 ml balloon) and repeat pancreas enzymes 48 hours after adjustment with clinical follow-up
    - If pain resolves and within 48-72 hours -- no further action needed clinical follow-up only.

4.3.4. Follow-Up Schedule

Follow-up visits for treatment and control patients will occur according to the following schedule: Visits at 1 week, 2 weeks, and 4 weeks (± 3 days), and thereafter every 4 weeks (± 2 weeks) until primary endpoint assessment at 32 weeks. In addition, 1-2 weeks after the adjustment procedure the subject will have a follow up appointment with the PI/NP.

Each follow-up visit will include:

1. Clinical assessment by PI or nurse practitioner or physician's assistant for both the treatment group and control group (***Appendix E6: CRF6_Control Group PI Follow Up*** or ***Appendix E7: CRF7_Treatment Group PI Follow Up***)
2. Satiety and Dietary Assessment for both the treatment group and control group - limited to 30-45 minutes per session (***Appendix E8: CRF8_Control Group Dietician Follow Up*** or ***Appendix E9: CRF9_Treatment Group Dietician Follow Up***))
3. Record adverse events, device complications, concomitant medication (***Appendix E6: CRF6_Control Group PI Follow Up*** or ***Appendix E7: CRF7_Treatment Group PI Follow Up***)
4. Weight to be done by staff (patient may not speak with weighing personnel and may not disclose if they are control or treatment arm)

Control patients will exit the study at Week 32. Treatment patients will have the device explanted and will be followed for an additional 24 weeks according to the following schedule: Visits at Week 36 (± 3 days) and thereafter every 4 weeks (± 2 weeks) until 56 weeks. Treatment patients who undergo balloon extraction prior to 32 weeks will be followed from the time of balloon extraction an additional 24 weeks according to the following schedule: Visits at 4 Weeks post extraction (± 3 days) and thereafter every 4 weeks (± 2 weeks) until 24 weeks after the extraction.

These follow-up visits for the treatment group only, will include:

1. Clinical Assessment - only at the visit 4 weeks post extraction(***Appendix E7***: ***CRF7_Treatment Group PI Follow Up)***
2. Satiety and Dietary Assessment (***Appendix E9: CRF9_Treatment Group Dietician Follow Up***)

A summary of required visits and procedures for subjects who do not require an unscheduled endoscopy is shown in the following table and provided in ***Appendix B: Study Visits and Master Schedule***:

Assessment / Procedure	**Screening Assessments**	**7 Days Prior to implant**	**Implantation**	**Adjustment**	**Explantation**	**Follow-Up Assessment weeks 1-32**	**WEEKS 36 - 56**
Informed Consent	X						
Date of birth/gender	X						
Body Weight	X	X	X	X	X	X	X
Body Height	X						
BMI	X	X	X			X* (week 32)	X * (week 56, or 24 weeks after extraction)
Ideal weight/ Excess Weight	X				X	X* (week 32)	X * (week 56, or 24 weeks

Assessment / Procedure	Screening Assessments	7 Days Prior to implant	Implantation	Adjustment	Explantation	Follow-Up Assessment weeks 1-32	WEEKS 36 - 56
							after extraction)
Medical History	X						
Physical Exam[1]	X			X	X		Week 36, or 4 weeks after extraction
Blood Pressure	x		X	X	X	X	Week 36, or 4 weeks after extraction
CBC[2] Coag[2] (Coag @ screen only)	X						Week 36, or 4 weeks after extraction
H. Pylori Serology	X						
Chemistry Panel[2]	X						X Week 36, or 4 weeks after extraction
HgbA1C2 IF DIABETIC	X						X Week 36, or 4 weeks after extraction
EKG*(Females and Males >40 y/o	X						
Psychological Evaluation	X						
Inclusion and Exclusion Criteria	X						
Develop/Review Dietary Plan	X						
Satiety and Dietary Assessment						X	X (or 24 weeks after extraction)
Investigator or Nurse follow up				X	X	X	X (or 24 weeks after extraction)
Medications List	X	X				X	X Week 36, or 4 weeks

[1] Investigator or co-investigator must perform physical exam.
[2] See section 4.3.1 for required tests

Assessment / Procedure	Screening Assessments	7 Days Prior to implant	Implantation	Adjustment	Explantation	Follow-Up Assessment weeks 1-32	WEEKS 36 - 56
							after extraction
Urine Pregnancy Test women of child bearing potential*	X	X					
Adverse Events/Device Complications			X	X	X	X	X
Verify Birth Control for Females	X						

4.4. Participant Retention

All patients will be encouraged to complete study follow-up, and all reasonable efforts will be made to ensure completeness of follow-up

It is understood that study participants may withdraw consent for study participation at any time irrespective of their reasons. The investigators may also withdraw a recipient from the study in order to protect their safety and/or if they are unwilling or unable to comply with the required study procedures.

In the event of a patient withdrawing from the trial, the reason for withdrawal must be documented on the CRF.

4.5. Definition of the End of the Trial

The trial will end after completion of the 56-week visit for the last subject treatment group subject enrolled in the trial and a final study report will be generated.

5. SPATZ 3 DEVICE

5.1. Device Description

5.1.1. Spatz3

The Spatz3 device (Figure 2) consists of a balloon positioned around a curved catheter inside the balloon, and whose catheter continues and exits outside of the balloon. The external catheter houses the stretchable inflation tubing.

Figure 2: Spatz3 Prior to Implant

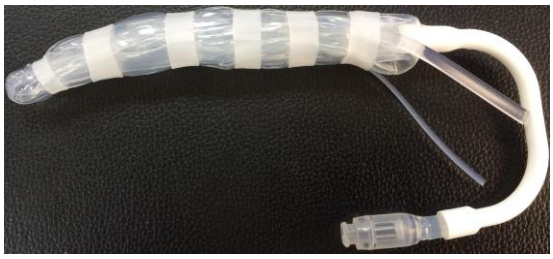
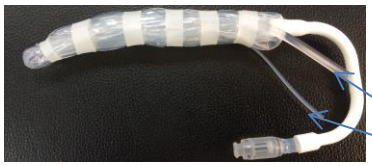


Figure 3: Spatz3 during Implantation

The Spatz3 balloon is wrapped by 6 silicone bands during shelf life, which gives it a tapered profile. The bands are removed using the "band-off" silicone pull strings prior to implantation.

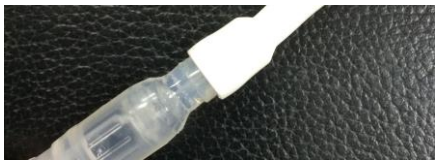


Pull both silicone strings to the left to remove all bands

The valve is secured to the white catheter with "valve-hold."

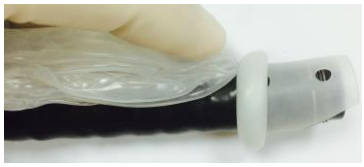
Valve Hold


Pushing Valve Hold into White catheter

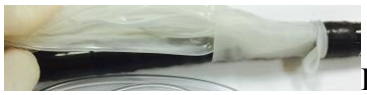

Valve Hold inside white catheter

The balloon is secured to the scope with the insertion facilitator.


Insertion Facilitator (as supplied)


Dressed on distal tip of scope w/ balloon ready to be secured


Rolled over balloon (2 holes to be used to secure to scope)


Balloon secured and insertion facilitator secured to scope

The balloon is inflated, adjusted and deflated via connection to an extension tube which has a 3-way stopcock at its proximal end. The extension tube is connected to the valve for all procedures and is provided in the packaging along with a 60 ml syringe (section 4.3.3.2 for details of all procedures).

The stretchable inflation tube design of the Spatz3 device permits balloon volume adjustment at the time of placement, and at a later time. Initial balloon volumes range from 400 cc to 550 ml. The minimum and maximum balloon volumes will range from 300 ml (an initial balloon volume of 400 or 450 ml that has been adjusted down to 300 ml due to intolerance) to 900 ml (an initial balloon volume of 550 ml that has been adjusted upward to 900 ml due to lack of any balloon effect in the first 2 weeks after implantation).

Figure 4: Inflation tube at rest

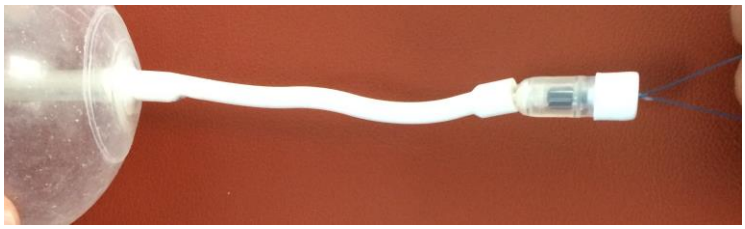
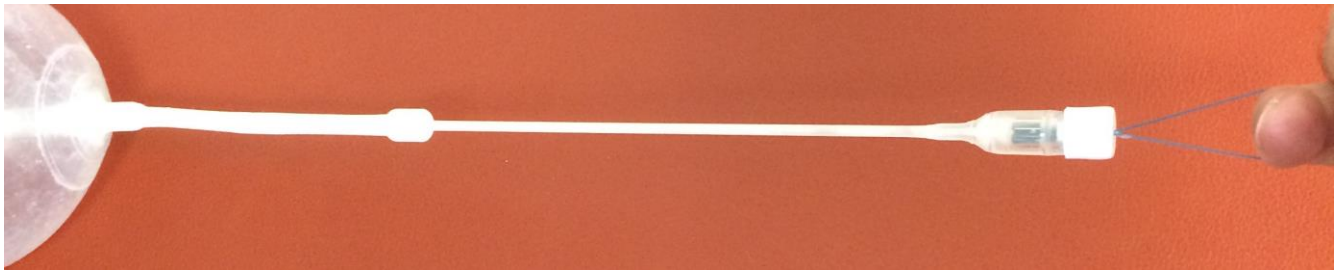


Figure 5: Inflation Tube partially stretched



A retractable/stretchable silicone inflation tube allows the balloon to have its volume adjusted after initial insertion, while the balloon remains in the stomach (Figure 4 and Figure 5). The inflation tube is a 10cm long stretchable soft silicone tubing with an inner diameter of 2mm and an outer diameter of 4mm. The stretchable inflation tube is attached to the distal end of the catheter that resides within the balloon and exits the catheter just behind the balloon and is accessible for future adjustments. The inflation tube travels within the soft catheter outside of the balloon and exits where it is attached to a luer-lock valve. The valve is closed with a cap. The valve has within it a silicone piece that prevents fluid escape even when the cap is off. The balloon is filled with saline and methylene blue (in the event of a balloon deflation the urine turns blue).

5.1.2. Additional Components and Adjunct Devices

The following additional items are not supplied by Spatz FGIA, but are used during the implantation, adjustment, and extraction procedures.

Sterile Saline Solution

Sterile saline solution is used to fill the balloon to the desired volume.

Methylene Blue

USP 1% methylene blue (Akorn 1% Methylene Blue Injection, NDC 17478-504-01) is added to the saline to provide a visual indicator to the patient (i.e., blue-green urine) when saline solution is released from a deflated balloon.

Endoscopic Rat Tooth Grasping Forceps

Rat tooth grasping forceps are recommended for use during the balloon adjustment and removal procedures to grab the suture loop at the top of the cap.

Large Polypectomy Snare

A large polypectomy snare is used during the balloon removal procedure to grab the valve.

5.2. Device Labeling

All components of the Spatz3 device will be labeled "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use". Labeling will also include the Sponsor name and contact details.

5.3. Device Accountability

The study site coordinator will maintain a log for tracking study devices, and a final reconciliation of study devices will be performed at the study end. Unused devices will be returned to the sponsor. The lot number for each device will be recorded on the case report forms (CRFs).

6. DATA MONITORING AND SAFETY REPORTING

6.1. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will serve as an autonomous advisory group for Spatz FGIA, Inc., the sponsor of this trial. The DMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, adjudication of Adverse Events, and for monitoring the overall conduct of the clinical trial. The DMC may also provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC members appointed for this trial consist of individuals who collectively have experience and expertise in the management of patients with obesity, experience in randomized clinical trials with experimental agents/devices, experience in safety monitoring and absence of significant conflicts of interest.

The first DMC meeting will occur once 25 subjects have either been implanted for at least 2 months or have terminated from the trial. Subsequent DMC meetings will be scheduled based on the following assessment of gastric ulcer rates.

> At each DMC meeting, the crude rate of gastric ulcers will be calculated using as its denominator only subjects who have been implanted for at least 2 months plus all subjects implanted less than 2 months but had experienced a gastric ulcer event. A gastric ulcer is defined as a gastric lesion ≥ 5mm in diameter with unequivocal depth by endoscopy. The date of the event will be the date of the confirmatory endoscopy. If this rate exceeds 10% then a Kaplan-Meier curve will be calculated that includes all implanted subjects. Subjects who are ongoing at this time without having experienced a gastric ulcer event will be censored at the data cutoff date, and subjects who terminated from the trial due to any reason other than a gastric ulcer event will be censored at the time of explant. Rates at each monthly interval for which a minimum of 25 subjects have been implanted will be calculated. For example, if 30 subjects have been implanted for at least 3 months, but only 20 for at least 4 months then rates will be calculated for 1, 2, and 3 months only.

If all of the monthly rates of gastric ulcers are below 10%, the DMC will meet every two months. If any of the monthly rates of gastric ulcers exceeds 10%, the DMC will meet every month.

A separate DMC charter will contain full details of the committee and its roles and reporting structure.

6.2. Adverse Events

6.2.1. Definitions

The following definitions will be used:

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) whether or not related to the study intervention.

Serious Adverse Event (SAE)

An adverse event that meets one of the following criteria

- Led to death
- Resulted in serious deterioration in the health of the subject that results in:
- Life-threatening illness or injury
- Permanent impairment of a body structure or a body function
- The need for in-patient care or prolongation of hospitalization
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Planned hospitalization for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event.

Device-Related Adverse Event (DRAE)

An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or from intentional misuse of the investigational device.

Serious Device-Related Adverse Event (SDRAE)

Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

Unanticipated Adverse Device Effects (UADE)

Any adverse device effect which, by its nature, incidence, severity or outcome, has not been identified in Section 6.2.2.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies resulting in SADEs will be managed as detailed in Section 6.2.3.

Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate will also be managed as detailed in section 8.2.3.

Severity Definitions

The following definitions will be used to determine the severity rating for all adverse events:

Mild: awareness of signs or symptoms, that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae.

Moderate: a sign or symptom, which interferes with the subject's usual activity.

Severe: incapacity with inability to do work or perform usual activities.

6.2.2. Anticipated Adverse Events

The following are anticipated adverse events related to the device and procedure that will be documented:

Table 1: Anticipated Adverse Events

Event	Comment	Consequence
Aspiration pneumonia	During procedure	Treat with antibiotics
Nausea, vomiting, abdominal pain, abdominal spasms, hiccups, heartburn, belching	all expected symptoms that can occur in varying degrees in almost all balloon patients	Mild dehydration Occasionally requires IV hydration
Blood tinged vomitus	Small amounts less than a tablespoon	None
Vomiting blood	Large amounts due to esophageal tear – "Mallory-Weiss Tear" - or due to ulcer of esophagus or stomach.	Requires balloon extraction and possible endoscopic clips to close tear or stop bleeding from ulcer
Superficial mucosal bleed	Tongue, esophagus or stomach during procedure	Small amounts – evaluated by PI and generally not clinically significant
Heartburn, acid reflux	Treated with medications (PPI, antacids, metoclopramide, sucralfate)	If uncontrolled, balloon down volume adjustment can help
Diarrhea	Due to bacterial overgrowth-like syndrome. Occurs in 20% of subjects and may recur	Treat with metronidazole 500 mg 3 times daily for 5 days
Esophageal or stomach ulcer	Superficial ulcers can be treated with medications (PPI, antacids, sucralfate)	Larger ulcers may require balloon extraction
Esophageal tear	During implantation or extraction	May require endoscopic clips
Balloon deflation	Urine turns blue alerting subject to deflation	Deflated balloon will remain in stomach or pass in bowels uneventfully. Rarely the balloon will obstruct intestine
Bowel Obstruction	Deflated balloon that obstructs intestine on its way out	Requires endoscopic extraction or surgery
Perforation of esophagus	Dr error- Balloon inflated in esophagus, or perforation during extraction	Requires endoscopic clips or surgery
Perforated stomach	Spontaneous ischemic perforation or perforated ulcer	Requires endoscopic clips or surgery

Event	Comment	Consequence
Infected balloon fluid	Unexpected dilation of balloon with air/fluid level in balloon	Requires balloon removal and culture of fluid

The investigator will document the clinical significance of all abnormal laboratory findings in the source documents throughout the study. The investigator will exercise his/her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. However, if in the opinion of the investigator, the frequency or severity of the event is greater than would be expected then it must be reported as an AE.

6.2.3. Procedures for recording adverse events

It is the responsibility of the local investigator to ensure that all adverse events (AEs, ADEs, and device deficiencies) occurring during the course of the study are recorded. This may include but not be limited to:

- A description of the event
- The dates of the onset and resolution
- Action taken
- Outcome
- Initial assessment of relatedness to the device (final adjudication will be made by the DMC)
    a. Whether the AE is serious or not
    b. Whether the AE arises from device deficiency
    c. Whether the AE arises from user error

Adverse events that occur during the course of the study should be treated by established standards of care that will protect the life and health of the study subjects

It is the responsibility of the local investigator to collect all directly observed adverse events and all adverse events spontaneously reported by the subject. In addition, each subject should be questioned about adverse events at each visit. Adverse events should be recorded on provided serious adverse event data collection forms.

6.2.4. Reporting Procedures for Adverse Events and Serious Adverse Events

It is the responsibility of the local investigator to ensure that all adverse events which fall into the categories of SAEs, DRAEs, SDRAEs and any device deficiencies are reported to the sponsor as soon as possible after becoming aware of the event but no later than 24 hours, via e-mail to the sponsor at jeff@spatzmedical.net (cc to office@spatzmedical.net) using the provided SAE form.

A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

6.3. Study Suspension or Early Termination

6.3.1. General

The DMC or sponsor may recommend suspension or termination of the study either at an individual investigation site or the entire study for significant and documented reasons. An investigator, IRB or FDA may suspend or prematurely terminate participation in the study at the investigation sites for which they are responsible. If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by the IRB or regulatory authorities, the sponsor shall suspend the study while the risk is assessed. The sponsor shall terminate the study if an unacceptable risk is confirmed.

6.3.2. Stopping Rule for Gastric Ulcer

At each DMC meeting, the crude rate of gastric ulcers will be calculated using as its denominator only subjects who have been implanted for at least 2 months plus all subjects implanted less than 2 months but had experienced a gastric ulcer event. A gastric ulcer event is defined as a gastric lesion ≥ 5mm in diameter with unequivocal depth by endoscopy. The date of the event will be the date of the confirmatory endoscopy.

If the crude gastric ulcer rate exceeds 10% then a Kaplan-Meier curve will be calculated that includes all implanted subjects. Subjects who are ongoing at this time without having experienced a gastric ulcer event will be censored at the data cutoff date, and subjects who terminated from the trial due to any reason other than a gastric ulcer event will be censored at the time of explant. Rates at each monthly interval for which a minimum of 25 subjects have been implanted will be calculated. For example, if 30 subjects have been implanted for at least 3 months, but only 20 for at least 4 months then rates will be calculated for 1, 2, and 3 months only. If the monthly Kaplan-Meier rate exceeds 20% for any month, then the study will be suspended and the IRB and FDA will be notified.

6.4. Protocol Deviations

All protocol deviations will be documented with the subject number and date of the protocol deviation. The following information will be documented for each protocol deviation:

- Inclusion/Exclusion exceptions or violations, including subject did not sign informed consent prior to study admission
- Follow-up visit not performed or Follow-up outside of window
- Required testing or questionnaire not performed
- Other (Describe)

7. STATISTICS

7.1. Description of Statistical Methods

7.1.1. Study cohorts for analyses

The primary analysis will be based on the intent-to-treat dataset, which will include all randomized subjects according to their randomized treatment. However, any subject with an absolute contraindication to balloon implantation which was only revealed at the endoscopy procedure, and who therefore did not receive a balloon, will not be considered in analysis of efficacy.

7.1.2. Primary Endpoints

The co-primary hypotheses are as follows:

1. The mean %TBL in the Spatz3 group exceeds that in the control group by 4.5%. In formal terms, this is:

$$H_O: \mu_S - \mu_C \leq 4.5\%$$
$$\text{vs.}$$
$$H_A: \mu_S - \mu_C > 4.5\%,$$

   where μ_S and μ_C are the population mean %TBL for the Spatz3 and control groups, respectively.

2. The response rate in the Spatz3 group is superior to a performance goal of 50%, where a responder is defined as a ≥5% loss in total body weight at 32 weeks. In formal terms, this is:

$$H_O: \pi \leq 50\%$$
$$\text{vs.}$$
$$H_A: \pi > 50\%,$$

   where π is the population response rate in the Spatz3 group.

All missing body weight data will first be imputed as follows. Initially, all interim missing data (missing data for which there is at least one subsequent non-missing body weight) will be linearly interpolated based on the last and subsequent non-missing body weight. If a subject in the Spatz3 group has the balloon explanted, the body weight immediately preceding the explant will be used and the subject will be treated as a dropout from that time forward, even though the subject will be followed for another 24 weeks. After the interim missing data have been interpolated, all additional missing data will be imputed using a regression method for multiple imputation. Baseline body weight, baseline BMI, subject's gender, study center, treatment group, and all non-missing body weight measurements through Week 32 will be included in the imputation model. A total of five imputed datasets will be created. The first primary endpoint, %TBL at 32 weeks, will be analyzed by an analysis of covariance that includes the effects of treatment group, study center, baseline BMI group (<35 kg/m^2 vs. ≥ 35 kg/m^2) and subject's gender as covariates. The parameter estimates from the five imputations

will be used to estimate a one-sided lower 97.5% confidence bound on the difference in mean %TBL (Spatz3 mean minus control mean). If this lower confidence bound exceeds the super-superiority margin of 4.5% the Spatz3 will be deemed to have super-superiority over the control group in %TBL.

The second primary endpoint will be analyzed using the same five imputed datasets created for testing the first primary endpoint, but only the data from subjects in the active treatment group. The estimated proportion of subjects with a ≥5% weight loss at Week 32, along with their associated variance, from each dataset will then be combined using Rubin's method to estimate the overall proportion and its variance. This proportion and its variance will then be used to estimate the one-sided lower 97.5% confidence bound on the proportion of subjects with a ≥5% weight loss at Week 32. If this lower confidence bound exceeds 0.50 the second primary hypothesis will be rejected, and the Spatz3 will be deemed to have met its second primary hypothesis.

As a sensitivity analysis of each co-primary endpoint, an LOCF imputation procedure will be employed in which all missing data among subjects with at least one post-randomization body weight measurement are replaced by the last non-missing value.

Secondary analyses of the primary endpoints will be per protocol and will include subjects according to the actual treatment received and will exclude subjects who did not meet the inclusion criterion of baseline BMI ≥ 30 kg/m^2 and < 40 kg/m^2.

7.1.3. Secondary endpoints

The observed rate of subjects who maintain 40% of the weight loss with the balloon at six months will be compared to a performance goal of 50%.

Percent change in excess weight loss (%EWL) will be calculated by first calculating the excess weight based on a BMI of 25 kg/m^2. This endpoint will be analyzed by averaging the mean 32-week changes in body weight for each subject across the five imputations described for the primary endpoint to determine which subjects had a clinical response of a ≥25% loss in excess body weight. This response rate will be compared to a performance goal of 35%.

7.1.4. Subgroup Analyses

The following subgroup analyses will be performed:

- Study site
- Gender
- Baseline BMI (<35 kg/m^2 vs. ≥ 35 kg/m^2)
- Age (<45 years vs. ≥45 years)
- Race (white vs. all others)

Subgroup analyses of the first primary endpoint will be performed on the average of the five imputed datasets. For each subgroup, the subgroup and its interaction with treatment group will be added to the primary analysis model. A significant interaction with treatment group ($p<0.05$) will indicate that the mean %TBL differences between the Spatz3 and the control were not comparable between (among) the levels of the subgroup. If a significant interaction is found for any subgroup, additional analyses will be performed in an attempt to determine the cause of the interaction.

It should be noted that a formal subgroup analysis to compare subjects who did and did not receive a change in balloon volume must be assessed with caution. This is because the decision to have the change is optional and a meaningful comparison of its effect could only be done if subjects were randomized to volume addition or not. However, to characterize the risk profile of the Spatz3 and on its effect on weight loss, sub-group analyses by number of adjustments and on balloon volumes will be performed based on the following balloon volume sub-groups:

- 400-600 cc - includes mostly study subjects with initial filling volume only
- 601-800 cc – includes subjects who have had one additional adjustment
- 801-1000cc – includes subjects who have had at least 2 upward adjustments

These analyses will evaluate their effects on the first primary endpoint and on adverse events.

7.1.5. Missing data

Missing data will be imputed as described above in Section 7.1.2.

7.2. Sample size

The true population mean %TBL in the control group is assumed to be 3.3% based on the Orbera and ReShape PMA studies. The standard deviation of %TBL is assumed to be approximately 6.6%, based on 6-month data from the Orbera PMA study. Based on these two assumptions, and a true population mean %TBL in the Spatz3 group of 10.34%, a total sample size of 240 subjects randomized 2:1 (160 in the Spatz3 group and 80 in the control group) will provide 80% power to demonstrate super-superiority of 4.5% TBL over the control at a one-sided significance of 2.5%. To account for a potential dropout rate of 15%, the final total sample size is 282 subjects randomized 2:1 (188 in the Spatz3 group and 94 in the control group).

7.3. Safety

All adverse events and all serious adverse events will be summarized by treatment group as the first occurrence for each subject. These adverse events will also be presented by causality. In addition, the number and percent of subjects with balloon deflation will be summarized.

8. DATA COLLECTION AND MANAGEMENT

8.1. Data Recording

Data collection will be electronic using a commercially available and validated EDC system that is compliant with 21 CFR Part 11 pertaining to the use of electronic records and signatures. The investigator will be authorized to review and sign each eCRF with an electronic signature. Data will be input by local study investigators/coordinators trained in the use of the EDC system prior to receiving log-in details.

The database will reside on a server hosted by the data center. The CRO, Clinical Development Associates Inc. (CDA), will subcontract the data management to Technical Resources International Inc. of Rockville, Maryland. All changes made to the data will be captured in an electronic audit trail and available for review. Database backups are performed regularly.

Access to the database will be controlled by username and password. The Database Administrator will be responsible for assigning usernames and passwords to individuals requiring access to the EDC database. The Database Administrator will revoke access for the users who are no longer required to use the database. At regular intervals passwords will be changed.

8.2. Source Data

Source documents include all information obtained in the study to verify all data collected in the EDC system. This includes patient reported documents (i.e. diaries), medical records, surgical procedural information, all clinic visits and any supporting information related to a device malfunction or adverse event. Source documents are where data are first recorded, and from which participants' eCRF data are obtained. eCRF entries will be considered source data if the eCRF is the site of original recording (e.g. there is no other written or electronic record of the data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

The standardized case report forms are provided in ***Appendix E*** of this protocol. Information regarding the relevant patient history and physical examination will be obtained from the medical chart and recorded. Completed CRFs will be submitted to the datacenter within10 days of the patient visit. Instructions and on-line training will be provided via WebEx by the data center staff prior to site initiation. EDC training of all staff responsible for data collection using an EDC system that is compliant with 21 CFR Part 11 will be documented and filed in the Investigator Site File (ISF).

Study data will be stored and analyzed in an anonymous fashion (no patient identifiers). Data will be stored at the data center in accordance with ICH/GCP and all local and federal regulations. Study data (paper and electronic) will be archived by the sponsor for a minimum of 5 years following completion of the study.

9. MONITORING

The Contract Research Organization (Clinical Development Associates Inc. Richmond, VA) will be responsible for monitoring of compliance with the trial protocol, GCPs, the Spatz3 Protocol Monitoring Plan and all applicable federal regulations concerning human subject research. The study monitors will perform on-site monitoring visits, including source document verification, device accountability, and assess compliance with safety reporting in accordance with Clinical Development Associates, Inc. (CDA) procedures and all applicable regulatory requirements. The investigator will agree to give full access of all study data, site procedures, and other relevant information to the study monitor (and auditor if needed) during each site visit.

At the site initiation visit the sponsor will review the study protocol and all associated study documentation and procedures with the investigator and study personnel. All local site personnel will receive training for device use and use of the data collection tool, as appropriate to their role, as described in section 11.3. In addition, study-specific GCP training will be given by the Contract Research Organization.

During the course of the study, the Contract Research Organization will maintain regular contact with the investigative sites and conduct central monitoring, on-site monitoring visits and source data verification (100% for adverse events and other critical variables) on a regular basis to ensure compliance with this study protocol. All patient consent forms will be reviewed for compliance with GCP and all applicable regulatory requirements.

The investigators shall conduct this study in accordance with this protocol and any conditions of approval/notification imposed by the FDA. Failure to comply with and/or inability to meet these regulations may jeopardize further participation of the investigator or investigative site in this and future clinical studies.

Investigators must report major protocol deviations which affect the safety and welfare of subjects or affect integrity of study (or if the investigator deviated from the protocol in order to save a life or prevent further harm to the subject) to the Sponsor within 5 working days of investigational site knowledge of the deviation. All protocol deviations must be recorded and reported to the Data Monitoring Committee. The DMC will review all deviations and assess their impact on patient safety.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. IRB and FDA approval

This protocol and associated documents will be submitted for approval by the FDA and host institutions. Before the study can begin, each investigator must have written evidence of IRB approval and the sponsor must have approval from the FDA.

Once approval has been granted, the Investigator is responsible for ensuring that he/she complies with the terms of the approval, namely with adverse event reporting, notification of amendments, interim, annual and final reports on the progress of the study.

10.2. Protocol amendments

Any change or addition to this study protocol which may impact on the conduct of the study, potential benefit to the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal written amendment to the study protocol.

All amendments to the protocol will be submitted as appropriate to FDA and the IRBs. Approved amendments will be circulated promptly to all investigators by the coordinating center.

10.3. Reporting

10.3.1. Sponsor Reports

The following reports are required by the sponsor under §812.150. All reports to FDA will be identified as IDE Reports.

Unanticipated Adverse Device Effects

The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

Withdrawal of IRB Approval

The sponsor must notify FDA and all reviewing IRBs and participating investigators of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval.

Withdrawal of FDA Approval

The sponsor must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval within 5 working days after receipt of the notice.

Current List of Investigators

Every six months the sponsor must submit to FDA a current list of the names and addresses of all investigators participating in a significant risk device investigation.

Progress Reports (or Annual Reports)

At regular intervals and at least yearly, the sponsor must provide progress reports to all reviewing IRBs. For a significant risk device, the sponsor must also submit the progress report to FDA. A suggested format is provided below.

Recalls and Device Disposition

The sponsor must notify FDA and all reviewing IRB's of any request that an investigator return, repair, or dispose of any unit of an investigational device. The notice must be made within 30 working days after the request is made and must state why the request was made.

Final Report

The sponsor must notify FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor must also submit a final report to FDA and all reviewing IRBs and participating investigators within 6 months after the completion or termination of the investigation. A suggested format is provided by FDA.

10.3.2. Investigator Reports

The investigator must provide the following reports to the sponsor in a timely manner under §812.150.

Unanticipated Adverse Device Effects

The investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible but no later than 10 working days after the investigator first learns of the effect.

Withdrawal of IRB Approval

The investigator must report to the sponsor a withdrawal of approval of the reviewing IRB within 5 working days.

Deviations from the Investigational Plan

The investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. The notice must be provided as soon as possible but no later than 5 working days after the emergency occurred. If it is not an emergency, prior approval from the sponsor is required for changes in or deviations from the investigational plan. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the sponsor is required to obtain prior IRB approval and also to obtain FDA approval for a significant risk device investigation by submitting an IDE supplement.

Other Reports: The investigator must provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA.

10.4. Participant confidentiality

All study-related information will be stored securely both at the study sites and the coordinating center. Written information will be stored in locked filing cabinets in areas with limited access. All documentation and specimens will be identified by a unique study ID number to maintain participant confidentiality. Where this is not possible (e.g. informed consent forms), these will be stored separately from any study records identified by the unique study ID.

Participant's information will not be released outside of the study without the written consent of the participant, except as necessary by regulatory authorities.

11. DISSEMINATION POLICY

11.1. Data analysis and release of results

By conducting the study, the local investigators agree that all information provided by the sponsor and coordinating center will be maintained by the local investigators and the site personnel in strict confidence. It is understood that the confidential information provided to local investigators will not be disclosed to others without authorization from the sponsor and/or coordinating center.

The scientific integrity of the study requires that all data must be analyzed study-wide and reported as such.

11.2. Primary outcome publications

Any publication arising from data collected as part of this study will be subjected to the agreed publication policies of the sponsor. Publications will reflect the input of every center. Reports relating to primary outcomes will be published in peer-reviewed journals of appropriate relevance. Individual centers will undertake not to report any trial data independently. A final report on the primary outcomes of the study will be compiled by the chief investigator and coordinating center, and approved and signed off by each local investigator.

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13. PROTOCOL AMENDMENTS

Version	Date	Amendments
1.0	3/21/2016	Original Version
1.1	4/11/2016	Modified to reflect FDA feedback
1.1a	4/14/2016	Added 3 exclusion criteria requested by FDA
1.1b	4/18/2016	Add H. Pylori test
1.2	5/27/2016	Revised version submitted as FDA Amendment 1
1.2a	6/24/2016	Modified to reflect FDA feedback (clarify monitoring, add f/u endoscopy for balloons >900ml)
1.3	7/7/2016	Modified in response to FDA feedback to add stopping rule for ulcers and clarify f/u based on endoscopy (FDA Amendment 2)
1.3a	7/22/2016	Modified section procedures for subjects with gastric ulcers
1.3b	7/27/2016	Remove Forrest class ulcers from DMC sections
1.3c	8/10/2016	Add TSH to baseline screening
1.3d	8/23/2016	Add belch protocol
1.4	8/26/2016	Modifications to statistical analysis
1.4a	9/21/2016	Modified statistical analysis per FDA feedback (Rubin's method)
1.4b	10/10/2016	Emend not given after upward adjustments. Clarification of Ondansetron dose-8 mg PO Q6h after implantation and upward adjustment procedures – this is not a change.
1.4c	12/8/2016	Expand window of upward adjustment from 18±2 weeks to 18±4 weeks. Treatment subjects who undergo early extraction will be followed for 24 weeks after extraction.
1.4d	1/3/2017	Pancreatitis protocol
1.4e	1/11/2017	Increase maximum enrollment per site