Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Clinical Management with SmartPill Motility Monitoring System and Validation of the SmartPill Five Hour Cutoff in Patients with Symptoms of Gastroparesis (**MA-501 Study**)
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Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 [Final]	• First SAP generated	Mathilde Lourd, Sr Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CRA	Clinical Research Associate
eCRF	electronic Case Report Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
FAS	Full Analysis Set
GCP	Good Clinical practice
GCSI	Gastroparesis Cardinal Symptom Index
GET	Gastric Emptying Time
GES	Gastric Emptying Scintigraphy
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index
PI	Principal Investigator
PPAS	Per Protocol Analysis Set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SPM	Smartpill Motility Monitoring System
UM	User Manual

3. Introduction

Gastroparesis is a common gastro-intestinal disorder with a range of clinical manifestations including nausea, vomiting, bloating, postprandial fullness, early satiety, and abdominal discomfort in association with demonstrable delays in gastric emptying. Gastroparesis has profound impact on the lives of affected patients, impairing quality of life, and produces a significant health care burden, leading to extensive emergency department visits and inpatient stays.

A range of therapies has been proposed for use in gastroparesis to reduce symptoms and promote adequate nutrient intake. Determination of the rate of gastric emptying is commonly employed to facilitate the decision to prescribe one of these therapies for a gastroparesis patient with significant symptoms.

For many years, Gastric scintigraphy is the standard of clinical practice for diagnosis of gastroparesis. However, it has been apparent that this method has a number of serious drawbacks including variability in methods between clinical centers, the choice of meal for clinical assessment, timing of image acquisition from scintigraphy, which call into question its validity to discriminate those with versus those without disease ; as a consequence, a standardized protocol has been advocated that employs a standard test meal with measurement of emptying in the late postprandial time period (4 hours) when most emptying is complete in healthy controls (Guidelines published by both the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine) but - to date - a small minority of medical centers in the United States have adopted this protocol. Additional drawbacks of gastric scintigraphy include the requirements to have access to a qualified nuclear medicine department and the potential for radiation exposure to individuals who may already have undergone extensive radiographic testing.

Because of the well-documented deficiencies of gastric scintigraphy, other methods for determination of gastric emptying have been proposed (e.g. Breath testing after consumption of different meals labeled with a non-radioactive isotope (^{13}C) (16, 17)), but such methods have also

some limits.

The SmartPill Motility Monitoring System (SPM) employs an ingested capsule that measures pH and pressure activity within the gastrointestinal lumen. The SPM gastric emptying time (GET) is determined when the capsule pH increases at least 2 units from the acidic environment of the stomach to the more neutral proximal duodenum. Some data comparing SMP vs gastric scintigraphy in healthy patients and in patients with established gastroparesis have recently been published with good performance and excellent safety results.

As a consequence of this trial, the SPM system was approved by the United States Food and Drug Administration (FDA) in July 2006 for determination of delayed gastric emptying and for measurement of whole gut transit, even if concerns have been raised by clinicians and insurance providers in response to this initial clinical trial that mandate additional investigation (related to small sample size, targeted population and gastric empty-time cutoff considered in this trial).

In this context, this trial is designed to study the intended population in which the device will be used, subjects with suspected gastroparesis based on their self-reported symptom profile. The study will compare patient management decisions based on results of gastric emptying scintigraphy tests to decisions based on SmartPill Motility Monitoring System study to assess both impact on patient management and diagnostic gain associated with the latter test.

4. Study Objectives and Endpoints

The study population consists of patients with symptoms of gastroparesis.

a. Primary objective

To evaluate per-device agreement in the diagnosis of delayed gastric emptying between SmartPill Motility Monitoring System (SPM) gastric emptying time (GET >5 hours) and the non-reference standard gastric scintigraphy test (>10% retention of a solid meal at 4 hours) in patients with symptoms of gastroparesis.

b. Secondary objectives

Several secondary hypotheses can be tested from data generated by this investigation which include but are not exclusive to:

1. To assess the device agreement of SPM with GES for detection of severe gastroparises *Hypothesis:* Severe gastric delay identified with scintigraphy (>35% at 4 hours) (35) is associated with severe prolongation of SPM GET (>8 hours) and impaired contractility (36)

2. To assess the correlation of gastroparetic symptoms measured by the PAGI-SYM symptom survey and PAGI-QUL survey instruments with SPM transit and fed response contractility parameters and with gastric emptying scintigraphy. *Hypothesis: G*astroparetic symptoms correlate with discreet SPM measures

3. To quantify the additional abnormal motility (diagnostic gain) detected with SPM relative to GES . *Hypothesis:* The GI transit and contractility measures provided with SPM result are additional abnormal motility findings (diagnostic gain) over the conventional test gastric emptying scintigraphy in the symptomatic gastroparetic population

4. To assess the impact of the diagnostic gain associated with SPM on patient management *Hypothesis:* The diagnostic gain realized with SPM results impact patient management decisions.

Study Endpoints

1. Primary Endpoint

Per patient device agreement for the diagnosis of delayed gastric emptying between SmartPill Motility Monitoring System (SPM) gastric emptying time (GET >5 hours) (18) and

the non-reference standard, gastric Emptying scintigraphy test (>10% retention of a solid meal at 4 hours)(13) in patients with symptoms of gastroparesis

2. Secondary Endpoints

2.1. Agreement between Gastric emptying time of smartpill capsule (GET>8hrs= severe) and gastroduodenal contractility and percent of radiolabeled meal retained at 4 hours on scintigraphy (>35% = severe)

2.2. Correlation between total GCSI scores, GCSI subscale scores for nausea/vomiting, postprandial fullness/early satiety, bloating , PAGI-SYM score for upper abdominal pain, PAGI-QOL score and SPM GET, SPM SBTT, SPM CTT, SPM fed response gastroduodenal contractility (frequency and AUC) and percent retention of radiolabeled meal measured with scintigraphic camera at 4 hours,

2.3. Number of abnormal SPM GET, SBTT,CTT and antroduodenal contractility findings (contraction frequency and AUC) and number of abnormal radiolabeled meal emptying findings measured with scintigraphic camera.

2.4. Documented patient management plans recording therapy, Dx tests, nutrition, and surgery decisions based on SPM results and based on GES and assessment of patient management change in accordance with following guidelines:

a. Change in Therapy: A change in category of drug therapy or the addition of a new category of drug therapy constitutes a change in management. Thus a change in treatment from prokinetic to antiemetic, neuromodulator or laxative category constitutes a change in patient management. A change of therapy within category such as switching from one prokinetic drug to another prokinetic drug does not constitute a change in patient management unless the drug is intended to impact a different GI region.

b. Dietary guidelines: Changes to diet constituting a change in patient management include: recommendation of diets specific for gastroparesis, recommendation of a liquid diet, initiation of TPN or G or J feeding tube.

c. Surgery: Relocation of feeding tube to new location (G tube changed to J Tube) constitutes change in management but not relocation of G tube to new gastric location. Either initiation or elimination of surgical referral constitutes change in management.

d. Diagnostic Testing: Any avoidance or additional diagnostic testing related to patient GI symptoms whether to detect abnormal motility or rule out alarm conditions constitute a change in management.

5. Investigation Plan

This is a multi-center, prospective study which aims to evaluate positive and negative device agreement in the diagnosis of delayed gastric emptying between SPM system gastric emptying time (GET >5 hours) and the non-reference standard gastric emptying scintigraphy test (>10% retention of a solid meal at 4 hours) in patients with symptoms of gastroparesis.

The study will include approximately 275 patients with symptoms of gastroparesis aged 18-80 years, who have no evidence of metabolic and/or organic disease.

Each subject will go through a Gastric scintigraphy test concurrently conducted with SPM testing after an overnight fast. The subject will be instructed to maintain a diary of times of meal consumption, bowel movements, and sleep.

Patient and physician will complete survey instruments (detailed in section 7 of protocol).

Subject will return the SPM receiver 5+2 days after ingestion day.

Physician will complete 4 management plans:

- Between 5-28 days (visit 4) after SPM and gastric scintigraphy test day- 3 management plans based first on one motility test blinded to the second test and then independently based on second test but not blinded to the first test result. The PI will then develop a third patient management plan based on both test results. This plan will be presented to the patient at the follow-up visit (visit 4)

Subjects will be contacted at 3 and 6 months post SPM procedure for follow-up assessment of symptoms.

Subjects will be compensated for completing the study.

All observations/ assessments to be conducted are displayed in the Trial Flow Chart (Appendix- A of Protocol) and detailed in the sections below

Study Duration: each subject is expected to participate in the study for two to five weeks (including medication wash) and up to 6 months follow up. Each subject will report to the study site for at least 4 visits and up to 6 visits.

Up to 16 months will be required to enroll 275 patients following IRB approval of the study. The completion of the study will require 20 months due to data collection and validation, data analysis, and the final clinical report.

Inclusion criteria

- Males and females between ages of 18-80 years of age with symptoms of gastroparesis for at least 12 weeks.
- Presenting with 2 or more of the following symptoms or signs which, in the opinion of the site investigator, are suggestive of a diagnosis of gastroparesis:
  - .1 Nausea, vomiting, or retching (dry heaves)
  - .2 Postprandial fullness or early satiety
  - .3 Bloating or visible abdominal distention
  - .4 Postprandial discomfort or pain
- Ability to stop proton pump inhibitors for 7 days and histamine$_2$ receptor antagonists, prokinetic agents, narcotic agents, anticholinergic drugs, and cannabinoids 3 days prior to SPM and gastric scintigraphy testing.
- No evidence of metabolic disease (hypothyroidism, uncontrolled diabetes [hemoglobin A1c >10% within the past 6 months], electrolyte imbalance).
- An upper endoscopy or upper gastrointestinal barium series within the past 2 years showing no organic disease that is potentially causative of symptoms.
- High probability of compliance and completion of study.

Exclusion criteria

- Participation in previous SmartPill clinical trials.
- Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
- Dysphagia to solid food or pills.
- Prior surgery involving the luminal gastrointestinal tract (cholecystectomy, appendectomy, and hysterectomy are permitted if performed > 3 months prior to SPM test).
- Any abdominal or pelvic surgery within the past 3 months
- Known or history of inflammatory bowel disease.
- History of diverticulitis, diverticular stricture, and other intestinal strictures.
- Chronic daily use of nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, etc.)
- Tobacco or alcohol use within eight hours prior to capsule ingestion.
- BMI > 40 kg/m^2.
- Allergies to eggs, bread, or jam.
- Females of childbearing age who are not practicing birth control and/or are pregnant or lactating. (Urine pregnancy testing will be performed on female subjects of child-bearing potential prior to capsule ingestion and gastric scintigraphy).
- Use of cardiac medical devices such as pacemakers and defibrillators (gastric stimulators, bladder stimulators, spinal stimulators, medication infusion devices, insulin pumps, continuous glucose monitors are permitted).
- Uncontrolled diabetes with a hemoglobin A1c >10%.
- Patient is expected to undergo MRI examination within 7 days after ingestion of the capsule

Prohibited Medications

Medications Which May Alter Gastric pH:

(i) Proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, dexlansoprazole, pantoprazole, rabeprazole) for 7 days prior to study including the day of SPM ingestion.

(ii) Histamine$_2$ receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) for 3 days prior to study including the day of SPM ingestion.

(iii) Antacids (containing magnesium, aluminium, or calcium carbonate) for 1 day prior to study including the day of SPM ingestion.

Medications That May Affect Gastrointestinal Motility: The following medications must be discontinued for 3 days prior to study including the day of SPM ingestion (if subject develops nausea to the degree that study discontinuation is contemplated, he or she may take promethazine, prochlorperazine, or ondansetron as rescue antiemetics in doses recommended by the site investigator):

(i) Prokinetic agents (metoclopramide, domperidone, erythromycin, azithromycin, bethanechol, pyridostigmine)

(ii) Narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, fentanyl, etc.)

(iii) Anticholinergic agents (dicyclomine, hyoscyamine, scopolamine)

(iv) Cannabinoids (dronabinol, marijuana)

Permitted Medications

Prescription medications for maintenance of stabilized conditions (e.g., hyperlipidemia, thyroid disease, chronic anxiety or depression, birth control, etc.) are permitted if the condition and the dose are stable for three months prior to study participation.

6. Determination of Sample Size

In that accurate assessment of PPA · and NPA · is of utmost importance in this study, the sample size of 275 is based on the expected precision associated with our estimates expressed in terms of confidence interval width and 10% additional patients in order to compensate for 1 interim analysis performed. It is expected that 10% of data will be lost to follow-up or not evaluable resulting in an effective sample size of approximately 248. The precision associated with each estimate is a function of the true unknown

value of the parameter being estimated, and the percentage of delayed diagnoses by the predicate in the case of positive percent agreement and the percentage of negative diagnoses by the predicate in the case of negative percent agreement. For the purpose of our calculations of the expected confidence interval half width, it is assumed that 40% of patients will be delayed by the predicate. A range of possible scenarios for the true value of the parameter were considered for PPA · and NPA · and calculations of the expected interval half width appear in the table below:

True value	50%	60%	70%	80%	90%
PPA	10.3	10.1	9.5	8.3	6.2

Note that a true value for π_{PPA} or π_{NPA} of 50% represents the worst-case scenario with regards to precision and therefore may be taken as an upper bound of expected accuracy. Calculations reveal that both confidence intervals will have a half width of at most 9.8

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Enrolled patients (Full Analysis Set) will be summarized using frequencies and percentages from the screened population.

Protocol deviations will be summarized and listed, and per-protocol patients will be summarized (frequency and percentage from Full Analysis Set population).

Frequency and percentage of FAS patients with full follow-up will be reported, as well as patients with early withdrawal from the study, and the related reasons. Please refer to section 7.1.3

7.1.2. Clinical Investigation Plan (CIP) Deviations

Any deviation from specified statistical plan will be in addition to "per protocol" analysis and will be reported as such. Post-hoc analysis will be conducted according to the existing data gathered, if necessary.

Full-list of protocol deviations will be provided in a separate file; protocol deviations to be excluded from PPAS1 and PPAS2 (refer to section 7.1.3) will be discussed and validated with the study team prior to run statistical analysis.

7.1.3. Analysis Sets

Two analysis sets will be created for study purpose:

1. **Full Analysis Set (FAS)**. FAS includes all enrolled subjects:
    - who signed the informed consent and
    - who satisfied to the eligibility criteria

FAS will be used for subjects disposition, population description, and for Safety analysis.

2. **Per Protocol Analysis set (PPAS)**: PPAS is a subset of the FAS, restricted to subjects who adhere to the protocol, in terms of SPM and Scintigraphy procedures, and minimal follow-up.

   Two subsets of the PPAS - according to follow-up- will be created and used for Performance analysis purpose:
    - PPAS1: Subjects who completed the full study follow up to 6 months FU
    - PPAS2: Subjects who completed visit 4 with 3 patient management plans- this group will be larger than the above and will have all data for study end points, even though not completed full study flow.

   Listing of major protocol deviations to be excluded from the PPAS1 and 2 will be provided by the study team prior to run statistical analysis.

   Per protocol Analysis Sets (PPAS1 and PPAS2) will be used for Performance analyses.

7.2. General Methodology

Continuous variables will be summarized using tables of descriptive statistics: number of patients with recorded observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using counts and percentages. Descriptive statistics will be presented by diagnosis and clinical center. Diagnostic outcome will be tabulated and compared for SPM and conventional test and percentage gain determined. Frequency of patient management change resulting from SPM test relative to conventional test will be recorded for categories of: therapy, elimination of diagnostic testing, diet and surgery.

Statistical analysis will consist in:

- Descriptive analysis of patients characteristics and assessments before and after study procedures.
- Agreement analyses between SmartPill Motility Monitoring System and Gastric Scintigraphy (GS)
- Correlation analysis between PAGI-SYM, PAGI-QOL and SPM and GES.
- Descriptive and Comparative analysis of safety parameters related to procedures, between SPM and GES.

Parameters ascribed to the safety of patients will be summarized by diagnosis and clinical center.

All available data from patients who fail to complete this study will be included in all safety summaries.

Agreement analysis (primary and secondary endpoints) will be run to provide % of agreement (overall, positive and negative agreement) between both procedures, as well as Kappa coefficient, p-value and 95% confidence interval.

Correlation analysis (between two quantitative parameters) will be run: Pearson coefficient, p-value and 95% confidence interval will be calculated.

For other analyses:

- Continuous variables will be summarized using descriptive statistics, specifically the mean, standard deviation, median, minimum and maximum. Comparison of continuous parameters between two group will be performed using T-test or Wilcoxon Man-Whitney U test, or Wilcoxon signed rank test (non-parametric) for paired data, as appropriate.

- Categorical variables will be summarized using frequencies and percentages, and compared between two groups using Chi-Square or Fisher exact test, or Mac Nemar Chi-square test for paired data, as appropriate.

Subject disposition and follow-up, as well as demographic and baseline characteristics of patients, results related to SPM and GES , or to any questionnaire will be described for each clinical center.

Reporting outputs

All outputs will be produced using SAS® version 9.4 and Minitab v15.0.

Tables and listings will be produced as PDF files and Courier New font size 9 bold.

Outputs will be ordered in the order that they appear in the textual sections of the plan i.e. disposition outputs first, followed by protocol deviations, baseline outputs, compliance outputs, effectiveness outputs and safety outputs.

The listings will be ordered by site, subject and visit as applicable, unless otherwise stated.

7.3. Center Pooling

Descriptive statistics will be presented by diagnosis and clinical center. Parameters ascribed to the safety of patients will be summarized by diagnosis and clinical center.

7.4. Handling of Missing Data and Dropouts

No method of imputation will be used for missing data. A summary of missing data will be provided according to the number of subjects, the time points where the data are missing and

clinical center. For each clinical center, number and percent of subjects with no missing data will be presented in tabular form.

7.5. Adjustments for Multiple Comparisons

No adjustment will be made.

7.6. Demographic and Other Baseline Characteristics

Patient's characteristics and other baseline data will be summarized and reported using statistical methods described above (see section 7.2 General Methodology).

7.7. Treatment Characteristics

Scintigraphy procedure and SPM procedure completions will be evaluated; all event or technical failure occurring during procedures will be described and reported in data-listing.

Patients with medications (Y/N) will be summarized at baseline and at each follow-up ; details on medications will be provided using data-Listing, for each visit.

7.8. Interim Analyses

One (partial) interim analysis Interim analyses has already been performed (June 2015) on primary endpoint, on N=130 patients. Final analysis will occur on 167 enrolled at the end of the study.

7.9. Evaluation of Objectives

III.2 Primary analysis

Since a clearly defined universally accepted physiological definition of disease in this population does not exist, the diagnostic test under evaluation (SPM GET) will be compared to a non-reference standard test method, the percent retention of a radiolabelled solid meal at 4 hours on gastric scintiscanning. Device agreement will be examined through use of the positive percent agreement (PPA) and negative percent agreement (NPA). (38), the Statistical Evaluation of

Medical Tests for Classification and Prediction. Oxford University Press Inc, New York. Let π_{PPA} represent the true positive percent agreement defined as the probability of a positive SPM test result given the non-reference is positive and let π_{NPA} represent the probability of a negative SPM test result given the non-reference is negative. The primary analyses of this trial is estimation of these parameters in order to assess the equivalence between the diagnostic test under evaluation and the non-reference standard. Maximum likelihood estimates of π_{PPA} and π_{NPA} will be computed based on collected data i.e., conditional relative frequencies in addition to corresponding 95% confidence intervals based on the methodology of Clopper and Pearson (28). Additional measures such as estimates of the overall percent agreement and Cohen's kappa will be calculated.

Primary endpoint analysis will be run on PPAS1 and PPAS2.

III.2 Secondary analyses

1. The correlation between diagnoses of profound gastric retention on scintigraphy (>35% at 4 hours) with severe prolongation of SPM GET (>8 hours) and impaired contractility will be examined using relative frequencies. 95% confidence intervals will also be provided.

2. Total GCSI scores as well as GCSI nausea/vomiting, GCSI postprandial fullness/early satiety, and GCSI bloating subscale scores, PAGI-SYM upper abdominal pain scores and PAGI-QOL scores will be correlated with SPM GET, SPM SBTT, SPM CTT scintigraphy gastric retention at 4 hours and SPM gastroduodenal and fed response contractility profiles. Since validity of the standard confidence interval corresponding to the Pearson correlation requires distributional assumption which will not be met based on the nature of the data to be collected, bootstrap methodologies will be utilized alternatively to construct said intervals.

3. The relative frequency will be computed for SPM transit and contractility results that provide diagnostic gain (additional abnormal motility findings) compared to conventional test results. A corresponding 95 percent confidence interval will also be provided.

4. The percent of changes to patient management plans will be estimated. Frequencies of the types of changes will be summarize and presented in tabular form.

Secondary performance endpoints will be run on both PPAS1 and PPAS2.

7.10. Safety Evaluation

To monitor safety, subjects will be asked at each visit and during telephone contacts about changes in their medical conditions. Adverse events should be assessed in terms of their seriousness, duration, intensity, and relationship to the study device. All anticipated and unanticipated adverse events will be collected. Subjects will be able to contact the investigator at any time during the study if they note any change in their medical condition. The outcome of each adverse event will be observed and documented.

Safety analysis, including adverse events and device deficiencies incidence and description will be run on FAS only.

a. Adverse Events Definitions and Reporting Requirements

An adverse event (AE) is any complaint or untoward medical occurrence that is an unintended disease or injury or untoward clinical sign (including abnormal laboratory findings) in a subject, users or other persons, whether or not related to the investigational medical device. AEs are non device related, non serious medical occurrences.

A Serious adverse event (SAE) is an untoward medical occurrence in a subject that is not related to the investigational device, comparator, or trial procedures, but that meet the criteria of "serious". A Serious Adverse event is one that:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
    - resulted a life-threatening illness or injury;

- resulted in permanent impairment of a body structure or body function and required inpatient hospitalization or prolongation of existing hospitalization;
- resulted in medical or surgical intervention to prevent life threatening illness or permanent impairment to body structure or body function.

- Led to fetal distress, fetal death, congenital abnormality or birth defect.

An Adverse Device Effect (ADE) is an occurrence related to or caused by the investigational device, procedure or comparator that is not serious.

A Serious Adverse Device Effect (SADE) is an adverse device effect, comparator, or procedure that has resulted in any of the consequences characteristic of a serious adverse event and is serious, but is not unanticipated.

An Unanticipated Serious Adverse Device Effect (USADE) (also called an unanticipated device effect in per 21 CFR Part 812) is any medical occurrence or unintended disease or injury or serious adverse effect (including abnormal laboratory findings) on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subject.

Adverse events will be collected and documented until the end of the study.

All adverse events will be graded as follows:

- Mild: Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
- Moderate: Sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
- Severe: Sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures and the discontinuation of the study device

may be required.

The relationship of the adverse event to the study is defined as follows:

- Definitely: an adverse event was shown to be related to the study device
- Probable: an adverse event has a strong temporal relationship to study device, and another etiology is unlikely or significantly less likely.
- Possible: an adverse event has a strong temporal relationship to the study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.
- Unlikely: an adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
- Not assessable: Given the information available, sequence and timing of events, it is unknown or impossible to determine the relationship of the adverse event with the study device.
- None: an adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

b. Device Deficiency

Since device deficiencies are not captured on study eCRF they will not be included in this analysis

7.11. Health Outcomes Analyses

Health outcomes have been previously described.

7.12. Changes to Planned Analysis

Per protocol, final statistical analysis was scheduled once N=275 patients were enrolled and completed the study ; due to sponsor decision upon interim analysis primary endpoint results, decision have been taken to early stop the enrollment at N=167 subjects. So, final statistical analysis will be run on N=167 enrolled subjects.

8. Validation Requirements

Original Statistical Programmer performs a visual inspection of the code and output to confirm functionality (Level III as per 056-Wi 181).

9. References

1. Revicki DA, Rentz AM, Tack J, Stanghellini V, Talley NJ, Kahrilas P, De La Loge C, Trudeau E, Dubois D. Responsiveness and interpretation of a symptom severity index specific to upper gastrointestinal disorders. Clin Gastroenterol Hepatol. 2004 Sep;2(9):769-77.

2. De La Loge C, Trudeau E, Marquis P et al. Responsiveness and interpretation of a quality of life questionnaire specific to upper gastrointestinal disorders. Clin Gastroenterol Hepatol. 2004 Sep;2(9):778-86.

10. Statistical Appendices

N/A