Clinical Trial Protocol

MA-501

Clinical Management with SmartPill Motility Monitoring System and Validation of the SmartPill Five Hour Cutoff in Patients with Symptoms of Gastroparesis

Principal Investigator:	Dr. Braden Kuo
Test Product:	Given SmartPill Motility Monitoring Capsule
Sponsor Name:	Given Imaging Inc.
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Sponsor Telephone:	
Study Number:	MA-501
Version Number and date:	Version 3- March 15 2015

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol:

Investigator

Signature: _____

Date:

SPONSOR

VP Medical and Regulatory Affairs

Tim Thomas **Signature:** _____

Date:

Table of Contents

Glossary

SPM- SmartPill Motility Monitoring System

GET- Gastric Emptying Time

GES- Gastric Emptying Scintigraphy

UM - User Manual

CRA - Clinical Research Associate

IEC - Independent Ethics Committee

IRB- Institutional Review Board

eCRF - electronic Case Report Form

AE - Adverse Event

SAE - Serious Adverse Event

ADE- Adverse Device Effect

USADE - Unanticipated serious Adverse Device Effect

SQA - Software Quality Assurance

GCP - Good Clinical Practice

PI - Principal Investigator

Study Summary

Purpose of study	To evaluate the agreement between gastric emptying scintigraphy tests and SmartPill Motility Monitoring System (SPM) study and to assess both impact on patient management and diagnostic gain associated with the SPM test.
Study design	Comparative study
Number of subjects	275
Subject population	Patients with symptoms of Gastroparesis
No of centers	Up to 12
Duration of enrollment	Up to 24 months from IRB approval to enroll study subjects
Procedure Duration	Two to five weeks (including medication wash) + 6 months follow up
Primary objectives	To evaluate 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

1. Introduction

Gastroparesis—Clinical Manifestations and Management

Gastroparesis presents with a range of gastrointestinal manifestations including nausea, vomiting, bloating, postprandial fullness, early satiety, and abdominal discomfort in association with demonstrable delays in gastric emptying (1). In the largest accumulated series to date, approximately two thirds of patients exhibited gastroparesis of an idiopathic nature while approximately 25% developed the disease as a consequence of long-standing diabetes mellitus (2). Even in smaller single center series, the predominant etiology of disease appears to be idiopathic (3). 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 (1, 4, 5, 6, 7, 8). 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.

***Gastroparesis* - Survey Tools**

Patient Assessment of Gastrointestinal Disorders—Symptoms (PAGI-SYM) - The PAGI-SYM survey consists of 22 questions which encompass a broad range of symptoms pertinent to organic and functional disorders of the gut (22). Contained within the PAGI-SYM is the Gastroparesis Cardinal Symptom Index (GCSI). The GCSI is comprised on 9 symptoms relevant to gastroparesis and has been stratified

into three subscales—nausea/vomiting (3 questions), postprandial fullness/early satiety (4 questions), and bloating (2 questions) (23). The GCSI has been validated in seven university-based clinical practices in the United States which correlates well with patient and physician ratings of gastric symptom severity with an internal consistency reliability score of 0.84. GCSI scores are responsive to changes in overall gastroparesis symptoms reported by both clinicians and affected patients.

Patient Assessment of Gastrointestinal Disorders—Quality of Life (PAGI-QOL)- The PAGI-QOL has been validated in two large longitudinal, multicenter, multinational trials to reliably assess quality of life in upper gastrointestinal disorders (24). The survey exhibits a high sensitivity to change with therapy in eight week observation studies. The PAGI-QOL consists of 30 options, which each are answered on a scale ranging from 0=lowest to 5=highest. Items are grouped into: daily activities (10 items), clothing (2 items), diet and food habits (7 items), relationship (3 items), and psychological well-being and distress (8 items).

Short Form-36 version 2 (SF-36v2) - The SF-36v2 is a validated survey consisting of 36 questions which rates quality of life in 4 mental and 4 physical health scores (25). In contrast to the PAGI-QOL, it is a generic measure, which relates quality of life in this population to that of patients with unrelated conditions to provide perspective on the degree of impact conferred by gastroparesis.

Rome III Modules - The Rome III modules for (1) nausea, vomiting, and belching and (2) functional dyspepsia to assess upper functional symptoms and (3) all functional bowel disorders to assess lower functional symptoms are validated measures developed by the Rome Foundation to quantify symptoms and to suggest

the presence of functional disorders involving the upper and lower gastrointestinal tracts, respectively (26, 27).

Visual Analog Scales (VAS): VAS will be completed for 8 symptoms which are quantifiable in a continuous fashion before scintigraphic meal ingestion and after each hour of scanning. The VAS form will also provide 3 options for assessing the severity of retching and vomiting. The VAS is a non-validated measure specifically designed for this protocol.

Bristol Stool Form Scale: The Bristol Stool Form Scale provides a measure of stool hardness based on a scale of 1- 7 to describe hardest to loosest stool form. The scale provides a visual image along with descriptive text for each successively looser stool type (38).

Status of Diagnostic Testing in Gastroparesis—Emerging Role of SmartPill Wireless Motility Capsule

For many years, the standard of clinical practice mandated performance of gastric scintigraphy for diagnosis of gastroparesis. However, it has been apparent that this method has a number of serious drawbacks which call into question its validity to discriminate those with versus those without disease. Firstly, there are significant variations in methodology between centers which raise the possibility that what might be delayed emptying in one institution would be normal at another. One source of variability has been the choice of meal; many hospitals employ scrambled eggs while others use oatmeal, chicken liver, beef stew, pancakes, or water (9, 10, 11). A second factor in the variability of scintigraphy results has been

the timing of image acquisition. The majority of centers measure gastric emptying early in the postprandial period (90-120 minutes after eating), when emptying is incomplete even in healthy individuals. A commonly reported measure, the half time of emptying, in many instances is an extrapolated value that is calculated from the very little emptying that occurs in the early postcibal phase and is likely fraught with inaccuracy. Because of these variabilities in meal- and image timing-related factors, it has been difficult for many institutions to define their range for normal gastric emptying. In a recent survey, 40% of academic and non-academic centers did not have experimental data to support the diagnostic cutoff for delayed gastric emptying at their hospitals (12). As a consequence, a standardized protocol has been advocated that employs a standard test meal (Egg Beaters®, bread, jam) with measurement of emptying in the late postprandial time period (4 hours) when most emptying is complete in healthy controls (13). Guidelines published by both the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine recommended this method in an effort to standardize diagnosis of the disease across all centers (14, 15). However 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). Such measures can be influenced by small bowel and pancreatic diseases that impair digestion and by pulmonary conditions that disrupt gas exchange. Furthermore, most studies of gastric emptying breath tests to date have been validated against non-standardized scintigraphic measures of gastric emptying such as the half time of emptying or emptying rates in the early postprandial period (90-150 minutes).

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. In an initial published comparison trial versus gastric scintigraphy in 87 healthy subjects and 61 patients with a previously established scintigraphic diagnosis of gastroparesis, correlation of the percent retention of an Egg Beaters® meal at 4 hours by scintigraphy and the GET of the SPM capsule at 4 hours was 0.73 (18). The diagnostic accuracy of the SPM GET (0.83) was comparable to that of the standardized 4 hour scintigraphy method (0.82). Using a cutoff of 5 hours, the sensitivity and specificity of the SPM were 65% and 87%, respectively, for diagnosis of gastroparesis. These values are comparable or superior to those of scintigraphy at 4 hours (sensitivity 44%, specificity 93%). These findings support an equivalency of the SPM GET with the scintigraphy methodology advocated by the recent consensus guidelines. As a consequence of this trial and after presentation of data suggesting an excellent safety profile of the method, 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.

Concerns have been raised by clinicians and insurance providers in response to this initial clinical trial that mandate additional investigation. The first critique relates to the sample size of the gastroparesis patients recruited for this study. Although all 61 patients had undergone prior scintigraphy demonstrating delays in gastric emptying, pH data was reliably acquired in only 48 individuals. Of these patients, only 24 exhibited >10% retention of a solid meal on scintigraphy at 4 hours. It has been suggested that this small cohort may be inadequate to support the routine use of the SPM for determination of delayed gastric emptying. A second issue pertains to the cutoff to discriminate normal from delayed gastric emptying. The FDA has approved the SPM for measurement of gastric emptying based on a cutoff of 4 hours; this value was determined by optimizing both the sensitivity and specificity from the ROC curves from the initial study. However after review of the raw data from this initial trial, it was elected to emphasize the specificity of the SPM GET to minimize the numbers of falsely positive delays in emptying that would be diagnosed using the 4 hour cutoff. Taking this approach, a GET cutoff of 5 hours was found to provide a specificity of 87% for diagnosing gastroparesis based on a prior diagnosis of the condition. Also in the initial study, subjects with confirmed gastroparesis on prior scintigraphy were recruited.

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. Finally published payer policies call for evidence that conduct of a SmartPill

Motility Monitoring System test will impact patient management. 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.

Study Purpose and Rationale

This protocol is designed to validate use of the SPM for diagnosis of delayed gastric emptying in patients with symptoms of gastroparesis and assess impact of a SmartPill study on patient management in the gastroparetic populations. Patients with symptoms of gastroparesis will be recruited.

Patients will undergo concurrent gastric scintigraphy and SPM testing to determine the presence or absence of delayed gastric emptying based on predetermined diagnostic cutoffs for each technique.

24 months will be required in order to enroll 275 subjects eligible for the trial.

2. Tested Device

.2.1 Intended purpose

The SmartPill GI Monitoring System measures whole gut and regional gut (stomach, small bowel, and colon) transit times. Measurements of gastrointestinal (GI) tract transit times are used for evaluating motility disorders.

The system measures pH, pressure, and temperature throughout the GI tract. Pressure contraction data from the antrum and duodenum can be used to calculate motility indices.

.2.2 Device Description

The SmartPill Motility Monitoring System was cleared by the United States Food and Drug Administration (FDA) and caries a CE mark, from July 2006. The SPM system includes an ingestible capsule, a receiver, a laptop computer and analysis software. .

pH

pH is measured every 5 seconds for the first 24 hours, every 10 seconds from 24-48 hours, and every 2.5 minutes after 48 hours. pH changes from 0.05-9.0 are detected with a sensitivity of +0.5 pH units.

Pressure

Pressure measurements from 0-350 mmHg are acquired every 0.5 seconds during the first 24 hours and every 1 second thereafter and are accurate to +5 mmHg for values <100 mmHg and +10% for pressures >100 mmHg.

Temperatures

Temperatures from 25-49oC are obtained every 20 seconds in the first 24 hours and every 40 seconds thereafter and are accurate to +1°C.

Data is uploaded and stored on the laptop computer. Transit data is analyzed using MotiliGI Monitoring System software, while pressure data is quantified using GIMS Data Viewer software.

The device does not incorporate any medicinal product, human blood derivative or tissues of animal origin.

The SPM system is fully compliant with all safety and radio standards and regulations similar to the currently marketed Platform Systems.

SmartPill Capsule Pack

Each capsule pack contains a single-use capsule, calibration buffer, instructions for use and a patient diary

The SPM capsule measures 26.8 x 11.7 mm and houses sensors for pH, pressure, and temperature and transmits data at a carrier frequency of 434 MHz to a receiver worn by the subject

Data Receiver

The data receiver records biomedical data sent by the capsule. It is worn by the patient on a belt clip or a lanyard (around the neck). The data receiver features an

Event button that when pushed places a marker in the electronic data. A patient diary for recording the time and reason for the event button use is stored on the backside of the receiver. The data receiver weighs approximately 225g (0.5 lb).

Docking Station

The docking station establishes electronic communication between the data receiver and the system computer for data download and serves as a charging stand for the data receiver. The docking station weighs approximately 200 grams (0.45 lbs).

Activation Fixture

The activation fixture turns the capsule on and off using strong magnets that interact with the capsule's internal power switch.

System Computer and MotiliGI Software

MotiliGI software version 3.0 comes installed on the system computer. MotiliGI receives and processes downloaded data from the data receiver, stores test data, provides data analysis tools, and graphically displays test results. MotiliGI features algorithms that calculate GET, SBTT, CTT, WGTT, and motility indices of the antrum and duodenum.

.2.3 Packaging, distribution, labeling and caution statements

Caution

SPM should not be used in patients with the following diseases or conditions:

- history of gastric bezoar
- swallowing disorders
- suspected or known strictures, fistulas, or physiological/mechanical GI obstruction
- GI surgery within the past 3 months
- severe dysphagia to food or pills
- Crohn's disease or diverticulitis
- implanted or portable electro-mechanical medical device such as a cardiac pacemaker, defibrillator or infusion pump
- younger than 18 years old.

Data transmission from the capsule to the data receiver is influenced by patient BMI. Significant data dropout can occur in severely obese patients (>40 BMI).

Labeling

All equipment associated with the clinical trial will be identified with visible markings stating "Exclusively for clinical investigations MA-501 only"

Packaging and storage

The SPM should be stored in a dry place, at ambient room temperature (-15-40°C) and humidity (rH 30-90%) and away from magnetic sources. To prevent capsule activation, the SPM capsule should be kept in the box until use.

Even if stored in their original containers and according to recommendations, the SPM capsule should not be used past the expiration date on the capsules.

.2.4 Inventory Control

Sponsor will initiate shipment of product from the sponsor to the site upon receiving all required documents. (e.g. approval/favorable opinion from IRB/IEC). The sponsor will maintain tracking for all shipment documentation. Prior to any shipment, the site will be informed by the sponsor on the upcoming shipment, expected arrival date and content of the shipment. The site should confirm receipt of the shipment. The site will file Sponsor's Shipping Receipt in the Sponsor's Study File.

An Investigator's Device Accountability form will be conducted under the Regulatory Binder at each site and will be monitored by the site's CRA.

In case of technical failure the site will approach the technical support team which will help solve the problem and will notify the site's CRA.

For each dispensed capsule, the following information should be recorded: the subject study number, date dispensed and the capsule ID number. At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by Given Imaging.

.2.5 Findings from non-clinical and clinical trials

In an initial published comparison trial versus gastric scintigraphy in 87 healthy subjects and 61 patients with a previously established scintigraphic diagnosis of gastroparesis, correlation of the percent retention of an Egg Beaters® meal at 4 hours by scintigraphy and the GET of the SPM capsule at 4 hours was 0.73 (18). The diagnostic accuracy of the SPM GET (0.83) was comparable to that of the standardized 4 hour scintigraphy

method (0.82). Using a cutoff of 5 hours, the sensitivity and specificity of the SPM were 65% and 87%, respectively, for diagnosis of gastroparesis. These values are comparable or superior to those of scintigraphy at 4 hours (sensitivity 44%, specificity 93%). These findings support an equivalency of the SPM GET with the scintigraphy methodology advocated by the recent consensus guidelines. As a consequence of this trial and after presentation of data suggesting an excellent safety profile of the method, 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.

.2.6 Manufacturer of investigational device

Given Imaging Ltd. is the manufacturer of the investigational device

.2.7 Description of & justification for route of administration & treatment period(s)

SPM capsule is ingested by the patient after an 8 hour fast and consumption of the technetium radiolabeled eggbeater meal, two pieces of toast with jam[13] . with 50ml of water. The test requires fasting for accurate results.

Procedure will take up to two weeks + 6 months follow up.

.2.8 Training and experience needed to use the investigational device

The medical staff and investigators who will perform the SPM procedure will go through a training session on the SPM system and Procedure, performed by the sponsor of the study.

.2.9 Risk Anlysis

Benefits-There may be no direct benefit to patients with possible gastroparesis from participation in this study. However, some patients may receive diagnostic information that helps the care provider plan a treatment program. Indirect benefits of this study include improved insight into the importance of gastric emptying disorders in patients with symptoms of gastroparesis and the role of different methods in the diagnosis of impaired gastric motor function in this disorder.

Alternatives to Study Participation- Participation in the study is voluntary. Subjects may discontinue the study at any time without penalty or loss of any benefits to which they are otherwise entitled

The SPM capsule is in compliance with relevant medical device standards. Our facilities have been certified to relevant medical device quality system requirements. Internal Verification and Validation testing has been successfully completed. All required Certifications and test reports are on file and have been reviewed for acceptability. The risk management summary demonstrates that the risks associated with the SPM capsule products are well mitigated and are as low as reasonably practicable as defined by the applicable standards.

3. Objectives

The study population consists of patients with symptoms of gastroparesis

.3.1 Primary objective

To evaluate 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

.3.2 Secondary objectives

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

1. *Objective:* 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. *Objective:* 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. Objective: 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. Objective: 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.

4. Study Endpoints

.4.1 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

.4.2 Secondary Endpoint

1. Agreement between Gastric emptying time of smartpill capsule (GET>8hrs= severe) and gastroduodenal contractility (36) and percent of radiolabeled meal retained at 4 hours on scintigraphy (>35% = severe) (35)

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,

3. Number of abnormal SPM GET, SBTT,CTT(20) and antroduodenal contractility findings (36) (contraction frequency and AUC) and number of abnormal radiolabeled meal emptying findings measured with scintigraphic camera(13)
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. Study Design

.5.1 Overall design

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 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 this protocol).

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

Physician will complete 3 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 followup assement 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) 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 3 visits and up to 6 visits.
Up to 24 months will be required to enroll 275 patients following IRB approval of the study. The completion of the study will require 30 months due to data collection and validation, data analysis, and the final clinical report.

6. Subject Eligibility

Patients must meet all the inclusion criteria and none of the exclusion criteria in order to be eligible for the study.

.6.1 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 3 years showing no organic disease that is potentially causative of symptoms.
- High probability of compliance and completion of study.

.6.2 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.

.6.3 Withdrawal criteria

Patients may withdraw from the study for the following reasons:

- At their own request, or at the request of their legally acceptable representative.

The investigator may withdraw a patient from the study at any time for the following reasons*:*

- Severe side effects clearly related to the study device.
- Presence or appearance of exclusion criteria.
- Appearance of accompanying diseases rendering further participation in the study impossible.
- A significant protocol violation, as determined either by the sponsor or the investigator
- Subject noncompliant with investigational procedures
- Subject noncompliant with visits
- At the specific reasonable request of the sponsor

The sponsor must be informed in each withdrawal case. The reason for withdrawal must be recorded in the case report form and in the patient file. The study can be stopped

following unforeseen events or other factors that do not permit continuation of the study. The Investigator and/or Given Imaging and/or local ethics committee and/or regulatory authority can decide whether the study is to be terminated. The appropriate ethics committees will be notified of discontinuation of the trial for any reason no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor receives a notice from the ethics committee and/or regulatory authority.

7. Study Plan

7.1 Enrollment of participants

Eligibility to participate in the study will be assessed by the investigator based on inclusion and exclusion criteria.

7.2 Informed Consent Process

Each subject will receive a full oral explanation of the study and will receive a copy of the subject Informed Consent Form. The subject will be requested by the investigator or his designee to sign the Informed Consent Form. Informed consent will be obtained before or during visit 1, prior to any study procedures being conducted including medication wash out period.

Consent to participate in this study must be given in writing. The signed informed consent will remain in the file of the subject; a signed copy will be given to the subject.

An enrollment log will be kept at the site listing all subjects who signed an informed consent for participating in the trial. The log will include the subject's full name, ID, subject's study code and date of enrollment.

In case that new information shall be provided to the subject a new informed consent form, which will include the new information, will be signed by the subject

In case of a subject who is unable to give a written informed consent an independent witness will sign the Informed consent on behalf of the subject, considering the subject gave his oral consent.

7.3 Survey Instruments

Brief Rapid Assessment of Subject History (BRASH) - Appendix B

The BRASH is a protocol-specific document that will be completed by a site investigator on the day of the screening visit. The survey consists of several items that provide details into demographic factors (age, gender, ethnicity, race) as well as factors related to the subject's symptoms prompting evaluation to measure gastric emptying. This will include the investigator's assessment of the presumed etiology of disease (idiopathic, diabetic [including type 1 vs. type 2, insulin requirements, and age of onset], other) and the profile of disease (duration of symptoms, acuity of onset, infectious prodrome, prior gastric scintigraphy or SmartPill testing, use of marijuana, use of opiates). A complete medication list will be included in the BRASH including doses and timing and whether they are to be taken on a scheduled or as needed basis.

Patient Assessment of Gastrointestinal Disorders—Symptoms (PAGI-SYM) - Appendix C

The PAGI-SYM will be completed by the patient at visits 1and 2 and again at the 3 and 6 month follow up time points (visits 5 and 6). For this study, symptoms will be quantified by total GCSI scores, GCSI nausea/vomiting subscale scores, GCSI postprandial fullness/early satiety scores, GCSI bloating scores, and PAGI-SYM upper abdominal pain and discomfort scores.

Patient Assessment of Gastrointestinal Disorders—Quality of Life (PAGI-QOL)- Appendix D

The PAGI-QOL will be completed by the patient at visits 1and 2, and at the scheduled 3 and 6 month follow up time point (visits 5 and 6).

Rome III Modules - Appendix F

The Rome III Modules will be completed by the patient at visit 1

Visual Analog Scales (VAS) - Appendix G:

The VAS will be completed by the patient at visits 1 and 2. During visit 2 subjects will complete a separate VAS after each set of images at 0, 1, 2 and 4 hours

Bristol Stool Form Scale Appendix H:

The Bristol Stool Form Scale will be completed by the patient at visits 1 and 2.

7.4 Screening- Assessment of eligibility (Visit 1)

After obtaining the consent, subjects will be assessed for eligibility to participate based on the inclusion and exclusion criteria.

Subject baseline condition will be assessed to include:

- Date of birth, gender, height, weight, BMI index, prior abdominal surgery, G.I symptoms, and reason for referral.
- General medical history will be assessed based on clinical condition categorized by category codes specified in the case report form
- Concomitant medications will be assessed to include name, frequency, dose and duration.
- Documentation of previous GI procedure
- Review of prior hemoglobin A1c levels to exclude values >10%
- Female subjects will be assessed for childbearing potential, and if they do have childbearing potential, they will undergo a urine pregnancy test at visit one and prior to the SPM and gastric scintigraphy procedure. If the test is positive, they will be excluded from the study. If the pregnancy test is negative, the subjects will be eligible to participate, but must agree to use medically accepted contraceptive methods, throughout the course of their study participation.
- Complete BRASH document symptom surveys, PAGI-SYM and PAGI-QOL questionnaires (see appendix B, C, D)
- Full ROME III along with Rome III criteria worksheet (see appendix F)

- Diabetic patients will have blood drawn to provide an updated measure of hemoglobin A1c.

Wash Out Period

1. Subjects will be instructed to discontinue agents that affect intragastric acidity including proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole) for 7 days prior to study including the day of SPM ingestion, histamine$_2$ receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) for 3 days prior to study including the day of SPM ingestion, and antacids (containing magnesium, aluminum, or calcium carbonate) for 1 day prior to study including the day of SPM ingestion. Several medications with the potential to alter gut motility will be discontinued for 3 days prior to study including the day of SPM ingestion including prokinetic agents (metoclopramide, domperidone, erythromycin, azithromycin, bethanechol, pyridostigmine), narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, fentanyl, etc.), anticholinergic agents (dicyclomine, hyoscyamine, scopolamine), and cannabinoids (dronabinol, marijuana).
2. Patients will stop treatments for constipation at least 3 days (a full 72 hours) prior to Day 1, Ingestion Day and continuing for the duration of the monitoring period (4 to 7 days). These treatments include enemas, cathartics, PEG solutions (including Miralax, Enulose).

3. Patients may take medications to help stimulate a bowel movement with either milk of magnesia, 2.4 to 4.8 grams (30-60 ml), or magnesium citrate, 11 to 25 grams daily in 1 or more doses, up to 48 hours prior to SmartPill ingestion.

7.5 SmartPill Testing and Gastric Scintigraphy (Visit 2)

The following protocol will be followed on the day of study:

- The subject will report to the study center after overnight fasting and will be asked to void his/her bladder prior to study.
- Women of childbearing potential will undergo urine pregnancy testing to exclude pregnancy.
- Diabetic patients will undergo finger stick testing of blood glucose. If this value exceeds 270 mg/dl, the study will be postponed and rescheduled.
- Prior to testing, the subject will complete the PAGI-SYM, and the PAGI-QOL (appendices C,D respectively)
- The SmartPill capsule will be activated and calibrated.
- Radiolabelled EggBeaters sandwich will be prepared by study team containing egg substitute (120 grams Egg Beaters®), 2 slices of bread, 30 grams strawberry jam (255 kcal, 72% carbohydrates, 24% protein, 2% fat, 2% fiber). To prepare the meal, the Egg Beaters® will be poured into a bowl, sprinkled with 0.5-1 mCi 99mTc-sulfur colloid marker, mixed, and cooked in a microwave oven with stirring until the mixture achieves the consistency of an omelet. Jam will be

spread on the bread and a sandwich will be made using the bread and cooked Egg Beaters®.

- The subject will then consume the radiolabelled EggBeaters sandwich with 70 ml water within 20 minutes.
- Immediately after meal completion, the subject will swallow the SPM capsule with 50 ml water. Additional water may be provided if necessary to swallow the SPM capsule.
- One minute anterior and posterior images will be obtained in the ^{99m}Tc window (140 keV±10%) with the patient sitting or standing immediately after meal completion and at 1, 2, and 4, hours afterwards. Additional GES scans will be allowed according to site standard of care. Results of 0, 1, 2 and 4 scans will be collected and recorded for this study.
- Subjects will complete a separate VAS (appendix G) after each set of images at 0, 1, 2, and 4 hours.
- During free time in the 4 hour scintigraphy study, subjects also will complete the Bristol Stool Form Scale (appendix H)
- During the initial 6 hours after capsule ingestion, the subject will be permitted to sit, stand, or walk in close proximity to the nuclear medicine department and gastroenterology laboratory. The subject will not be permitted to sleep to prevent its inhibitory effects on gut motor function. After 6 hours, the subject will be discharged from the study site.
- The subject will be asked to continue to avoid solid food intake until 8 hours after capsule ingestion. Then, the subject will be instructed to consume 240 ml

Ensure® (1 can supplied by clinical site) and one hour later can resume a normal diet. Fifty ml of water will be permitted every hour after completion of the 4 hour scintigraphy period up to 9 hours after capsule ingestion if desired by the subject; liquid intake will be unrestricted thereafter.

- The subject will be instructed to maintain a diary of times of meal consumption, bowel movements, and sleep. An event marker on the receiver will be depressed for each diary entry. The subject will be told to maintain the receiver in close proximity at all times over the next 5 to 7 days to ensure adequate signal acquisition from the SPM capsule. After each bowel movement, the subject will be asked not to flush to toilet for 5 minutes to ensure that accurate temperature measurements can be obtained by the SPM capsule after evacuation.
- The subject will be given contact information and instructed to notify the site investigator if he/she experiences abdominal pain, nausea, vomiting, fever, or rectal bleeding prior to the follow-up visit.
- The subject will be scheduled for the follow-up visit 5-7 days after the study visit performed either on study clinic or by phone.

Diabetic patients on insulin will be instructed to use half of their normal long-acting dose the morning prior to testing and to refrain from use of short-acting insulin until directed by the site investigator. Finger stick glucose levels will be obtained prior to meal ingestion and 4 hours after consuming the Egg Beaters® meal. Hypoglycemia (glucose <70 mg/dl) or hyperglycemia (glucose >270 mg/dl) will be treated in accordance with the usual practice for each subject and recommended by his/her personal care provider.

7.6 Follow up visit (Visit 3)

The subject will return to the study site, or contacted by phone, for a follow-up visit 5+2 days after Visit 2. At that time, the subject will turn in the receiver and completed diary forms. In case the visit performed by phone receiver will be sent to study site by Fedex. The subject will confirm if capsule passage was visualized during defecation. The SmartPill receiver will be examined for the presence of a signal from the capsule. If no signal is detected, the subject can be discharged. If a capsule signal is detected with a pH >4.5 and the subject in not on a proton pump inhibitor, this suggests the capsule has passed into the small intestine or colon. In this instance, the subject can be discharged. If a capsule signal is detected at 5-7 days after capsule ingestion and shows a pH <4.5 suggestive of gastric retention in the stomach, the subject will be prescribed erythromycin liquid suspension to be taken at a dose of 250 mg orally before meals and at bedtime for the next 7-9 days (if not allergic). In case of patient allergic to Erythromycin patient will be followed up per instructions in visit 4.

7.7 Follow up visit (Visit 4)

All subjects return to the study site between day 14 to day 28, from capsule ingestion, to receive their patient management plans. Subjects who did not report or the MotiliGI data does not demonstrate capsule expulsion will receive an abdominal plain radiograph to assess for capsule retention according to PI discretion. If the radiography shows capsule retention, or if the subject reports symptoms or exhibits signs of mechanical

obstruction, the site Principal Investigator or another qualified gastroenterologist will perform a comprehensive evaluation and suggest appropriate management.

Management Plan

Between day 5 and days 14 to 28 the PI completes patient management plan 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 alternate between the conventional test result and SmartPill test result for bases of initial blinded patient management plan with each successive patient. 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).

The PI will select a patient management plan from a maximum of two of six categories listed below consistent with guidelines described in section 9.2.

1. Prokinetic
2. Antiemetic
3. Neuromodulator
4. Laxative
5. Enteral feedings
6. Surgery
7. Is additional diagnostic testing required? Yes__ No__

Management of test results data to assure blinding of PI to test results

The Scintigraphy test results (delayed or normal emptying) and the SmartPill GDF file will be supplied to the sponsor Data Management (DM) team within a timely manner of

SPM test completion. The sponsor DM team will provide the SmartPill data along with the patient study code (initials and number) to a central reader for data extraction. Upon receiving the SPM results from the central reader the sponsor DM team will then provide both test results (SPM &GES) to the site PI per the order described above assuring the second test result is not available to the PI until the management plan is complete based on the first test result. All above procedures should take place in a timely manner in order to assure 3 management plans ready by patient visit 4 scheduled visit, 14-28 days from capsule ingestion.

7.8 3 month follow-up (visit 5)

At 3 months ±7 days after visit 4 each site will conduct a follow up interview with their patients. Patients may be called or return to their respective clinical study sites to report their current GI symptom profiles using the survey instruments (PAGI-SYM, PAGI-QOL, forms appendices C, D,). The prior three month patient history will be documented including additional diagnostic tests for GI symptoms, emergency room visits, GI specialist visits and medication use. Data will be confirmed where possible with patient medical records.

7.9 6 Month Follow UP (Visit 6)

At 6 months ±7 days after visit 4 each site will conduct a follow up interview with their patients. Patients may be called or will return to their respective clinical study sites and report current GI symptom profiles using the survey instruments (PAGI-SYM, PAGI-

QOL, forms appendices C, D). The prior three month patient history will be documented including additional diagnostic tests for GI symptoms, emergency room visits, GI specialist visits and medication use. Data will be confirmed where possible with patient medical records.

An Economic Analysis survey (appendix I) will be filled by study team, if applicable)

7.10 Data organization and shipment

For each patient the following information will be sent to the sponsor:

a. Completed CRF

b. Completed BRASH

c. 4 completed PAGI-SYM

d. 4 completed PAGI-QOL

f. 1 completed ROME III modules

g. 5 completed VAS

h. 2 Bristol stool form indexes

i. 3 patient management plans (1 from visit #1 and 3 from visit #4)

j. SPM raw data (.GDF files)

k. SPM report

l. Gastric scintigraphy report

m. Economic Analysis survey, if applicable

All data recorded on the eCRF will be supported by a source document

8. Assesments of the SPM and Gastric Scintigraphy systems

This is a non-randomized prospective study of 275 patients with symptoms of gastroparesis designed to assess the agreement between SmartPill and the predicate, gastric emptying scintigraphy (% retention at 4 hours), through characterization of the device agreement for delayed versus normal gastric emptying. As part of the review of collected data, all quantification of SPM results will be performed by central readers and scintigraphic gastric emptying results will be performed by radiologists at each study site. The principal investigators will create initial patient management plans based on the results of either the scintigraphy or SPM test while blinded to the alternate test result. The test the PI is blinded to will alternate with each successive patient and be managed by the sponsor DM team.

The following parameters will be measured;

8.1 Assessment of efficay

SmartPill

Several parameters will be quantified for this study:

SPM gastric emptying time (GET) will be calculated from the time the capsule is ingested to the time it passes into the duodenum. Capsule passage into the duodenum is defined when pH abruptly rises ≥2 units from the lowest postprandial value to ≥4 and does not decrease to <4 for >10 minutes at any subsequent time.

Small intestine and colon transit values, for secondary outcomes, will be calculated. Ileocecal capsule passage is defined when pH decreases ≥1.0 unit at least 30 minutes after gastric capsule evacuation; such a pH decrease has been observed in >95% of patients in the recent colon transit validation trial (19). Small intestine transit will be calculated from the time of duodenal entry to the time of ileocecal passage. Anal capsule expulsion is determined by abrupt 0.045°F/second decreases. Colon transit will be calculated from the time of ileocecal passage to anal expulsion as described previously (20). In cases where ileocecal passage cannot be detected secondary to a lack of a well-defined ≥1 pH unit decrease, combined small intestine-colon transit will be calculated.

Whole gut transit times will be calculated from the time of capsule ingestion to the time of anal expulsion.

Two validated pressure parameters will be calculated for this study (21). Numbers of contractions >10mmHg in the stomach and small bowel and >25 mmHg in the colon amplitude will be standardized to contractions per minute and per 15 minutes respectively to compare recording periods of different length. Areas under pressure curves (AUC) >10mmHg in the stomach and small bowel per minute and >25 mmHg per 15 minutes in the colon will be calculated in units of mmHg x minutes.

Gastric Scintigraphy

Scintigraphic images will be acquired after meal consumption and then at 1, 2 and 4 hour intervals. For scintigraphic testing, the subject will be placed in front of a gamma camera and 1 minute anterior and 1 minute posterior images will be taken in the 140

keV ^{99m}Tc peak with a 20% window (140 keV ± 10%). Regions of interest will be drawn around gastric images for each time frame. Geometric means will be calculated as square roots of the product of the counts measured on the anterior and posterior images.

8.2 Assessment of Saftey

Safety parameters

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.

8.3 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.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety and performance.

Adverse events will be collected and documented until the end of CE procedure follow up period, which will be considered to be 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

Probably: An adverse event has a strong temporal relationship to study device, and another etiology is unlikely or significantly less likely.

Possibly: 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.

Probably not: An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.

Unrelated: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

8.4 Anticipated adverse events reactions associated with SPM ans Gastric Scintigraphy

The potential risks of this study include those related to the SmartPill capsule, those occurring during gastric scintigraphy, and those related to radiation exposure from abdominal radiography.

Capsule Retention: The risk of retention of the SmartPill capsule is minimal. Other FDA released medical capsule devices such as the Given PillCam and the Heidelberg pH capsule are similar in size and shape and are considered to pose similar risk. In 435 healthy and 443 non-healthy individuals who ingested the Heidelberg pH capsule, there were no complications in the healthy subjects and one complication in a non-healthy subject with pyloric stenosis (29). In this individual, the retained capsule in the stomach was retrieved using upper endoscopy. More than 1,500,000 capsule endoscopies have been performed since Given Imaging introduced the first ingestible video capsule for human use in 2000. Today, capsule endoscopy is considered to be well tolerated and safe. Capsule retention has not been reported in normal volunteers or patients with diverticulosis and no history of diverticulitis (30). Less than 1% of patients with localized diseases develop capsule retention (31, 32). However, the risk of capsule retention may be as high as 13% in patients with a history of Crohn's disease and also is reportedly increased in individuals on chronic use of non-steroidal anti-inflammatory drugs (33, 34).

Thirty one potential adverse events were logged in shipments of 8451 SmartPill capsules including twenty eight for prolonged retention (>5days). Two of the remaining events involved retention of SPM in the esophagus and one incident involved an episode of vomiting after capsule ingestion. Retention in the colon accounted for seventeen of the twenty-eight incidents of prolonged retention, three incidents involved retention in the small bowel and the capsule was retained in the stomach in the remaining eight subjects. Subjects with prolonged retention in colon all resolved without intervention beyond laxative therapy. One small bowel retention, resolved with administration of bowel prep, resulted in detection of a malignancy prompting surgery to remove a previously undetected tumor that had created a stricture in the small bowel. The second small bowel retention passed without incident. A third incident of small bowel retention required surgery for resolution and also resulted in detection of a previously undetected tumor. Endoscopic intervention was used to retrieve the capsule in seven of the eight cases of gastric retention and prokinetic therapy was used to stimulate peristalsis and move the capsule out of the stomach into the small bowel in the remaining case where it then passed naturally from the body on its own. In the two incidents of capsule retention in the esophagus patients reported no difficulty breathing and the capsules were removed with routine endoscopy without further incident. In summary, there were 31 potential adverse events out of shipments of 8451 capsules for a potential adverse event rate of 0.4% with intervention beyond laxatives required in 11 cases or 0.1% .

In three prior multicenter clinical studies involving administration of SmartPill to 175 healthy subjects, 59 subjects with gastroparesis, and 260 subjects with chronic constipation, one adverse event involving capsule retention in the stomach in a gastroparetic subject was reported. The capsule emptied from the stomach after IV erythromycin administration and passed normally. In this study, subjects will be instructed to examine their stools for evidence of capsule passage. Capsule excretion verification will be performed as described in sections number 7.6 and 7.7.

Other Capsule Risks: Other potential adverse events considered in prior clinical trials of the SmartPill capsule included nausea, vomiting, aspiration of the capsule or test meal, abdominal pain, diarrhea or constipation. Technical issues that can occur include premature battery termination (failure) of either the capsule or receiver, signal loss within 6 hours or before the capsule emptying from the stomach, signal loss after 6 hours but before 48 hours, loss of capsular structural integrity, and failures to receiver or capsule electronics. In previous studies with adult subjects (N=326), 28 adverse events were reported: 19 were not device related, 7 were probably not device related, 1 was possibly related (substernal pain), and 1 was definitely related (19, 20). In this individual, the capsule failed to exit the stomach 9 days after its ingestion secondary to entrapment in a bulking agent consumed by the subject. Capsule evacuation from the stomach was effected within 24 hours by administration of the prokinetic agent erythromycin as described above; no endoscopic or surgical intervention was required for this related adverse event.

Scintigraphy Risks: The risks associated with gastric scintigraphy include radiation exposure and allergy to the test meal components. The total effective radiation dose

equivalent for gastric scintigraphy is <200 millirem. The organ with the greatest exposure (860 millirem) during testing is the upper small intestine. This degree of radiation exposure is less than the yearly background exposure received by a typical resident of the United States. The risks of allergic reaction to the egg substitute, bread, and jam are slight. Any subject with such an allergy will be prohibited from study participation.

Radiography Risk: Those individuals undergoing abdominal radiography to confirm capsule expulsion will be exposed to a whole body radiation dose of 127 millirem. This value is less than the yearly background exposure received by a typical resident of the United States.

An unanticipated Adverse Event, which, based on the investigator's judgment, is device related should be notified to Given Imaging within 24 hours after the investigator is made aware of the event.

A subject will be followed up after an occurrence of an adverse event until the resolution of the event and/or the investigator's decision.

Recording and documentation of adverse events

Every adverse event should be recorded in the case report form. The following data must be documented:

- Type of event
- Subject number
- Time of occurrence: date, time

- Time of resolution: date, time
- Severity degree: mild / moderate / severe / unknown
- Relationship to study device: probable/possible/unlikely/not related

Measures taken

- Outcome of event: unchanged / worsened / improved / resolved / unknown / death

Reporting responsibilities:

• An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated serious adverse events, adverse device effect and device deficiencies that could have led to a serious adverse device effect occurring during an investigation within 24 hours of learning of the event, but in no event later than 10 working days after the investigator first learns of the effect.

• 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. (21 CFR Part 812.150)

8.5 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety and performance. Given Imaging Customer service is responsible to manage and document all device deficiencies related to the identity,

quality, durability, reliability safety or performance of an investigational medical device throughout the clinical investigation

9. Statistical consideration

9.1 Determination of Sample size

In that accurate assessment of π_{PPA} and π_{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 π_{PPA} and π_{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

NPA	8.4	8.3	7.7	6.7	5.1

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

9.2 Interim Analysis

Upon enrollment of 150 subjects an intermediate analysis for primary end point will be performed

9.3 Description of statistical methods

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

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. Parameters ascribed to the safety of patients will be summarized by diagnosis and clinical center. No method of imputation will be used for missing data. All available data from patients who fail to complete this study will be included in all safety summaries. 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.

Primary Analyses

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.

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. Ninety-five percent 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 scintigraphic 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.

Primary Safety Stopping Rule

A decision for discontinuation of the study may be made in consultation with the investigator if more than 5 patients require a gastroenterologist consultation for evaluation and removal of a retained capsule within the gastrointestinal tract.

9.4 Adverse Events

Individual listings of adverse events including type of device, age, weight, height, gender, adverse events (reported term), start, duration, relationship to device and severity will be provided

10. Suspension or premature termination

The study can be terminated following unforeseen events or other aspects that do not permit continuation of the study. Given Imaging and/or local ethics committee and/or regulatory authority can decide whether the study is to be terminated. The appropriate ethics committees will be notified of discontinuation of the trial for any reason no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor receives a notice from the ethics committee and/or regulatory authority.

11. Data collection and quality control

11.1 Data collection

It is the responsibility of the investigator to ensure the completeness and accuracy of the case report forms. One case report form must exist for each subject participating in the study. Each clinical site may receive validated electronic case report form (eCRF) software for electronic capture of data. The CRA will maintain eCRF validation records or provide access to them. Electronic case report form entries will be user-identifiable and will include an audit trail. Erroneous values and/or text must not be obliterated. Instead, the error must be crossed out with a single line in black ink, the correct value/text added, and the correction signed, initialized and dated by the clinical coordinator.

Once CRFs have been collected by the study monitor no changes should be made to the CRFs. In case that corrections are required due to Illogical data, missing data / empty fields, misspellings, contradictory data or other reasons, the data analysis team will generate a query on designated forms and sent it to the CRA for resolution.

As the queries are resolved:

the study coordinator correct the CRF at the site and send the corrected CRF's to the data analysis team or return sign and complete data query sheet back to the data analysis team for data entry.

All CRF's will be verified against source data by a dedicated study monitor.

11.2 Archiving

All source documents and case report forms will be kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or

completed or; the date that the records are no longer required supporting marketing applications.

11.3 Monitoring Plan

The study will be monitored in accordance with the site recruitment rate for data verification and data collection.

12. Ethical and legal aspectes

12.1 Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee will be obtained prior to study start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained. The Ethics Committees must supply to the sponsor, a list of the Ethics Committee membership and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

12.2 Ethical conduct of the study

This clinical investigation shall not begin until the required approval/ favorable opinion from the IRB or regulatory authority have been obtained. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines (GCP in the appropriate current version) and that this clinical investigation will be conducted in accordance with the ethical principles that have their

origin in the Declaration of Helsinki. The study will also be carried out in keeping with ISO 14155 and applicable local law(s) and regulation(s). This may include an inspection by Given Imaging representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/Given Imaging representatives, and must allow direct access to source documents to the Regulatory Authority/ Given Imaging representatives. Regulatory Authority approvals/ authorizations/ notifications, where required, will also be in place and fully documented prior to study start.
Furthermore, any additional requirements imposed by the IRB or regulatory authority shall be followed.

12.3 Amendments and Deviations from clinical investiagtion plan

- Protocol changes will be approved by the sponsor, investigator/s and ethical committee before change is implemented in the study.
- The investigator is not allowed to deviate from the CIP, except for sponsored approved deviations and under emergency circumstances and deviations to protect the rights, safety and well-being of human subjects
- Deviations, deviations for emergency use, and violations will be analyzed by the sponsor and their significance assessed and reported by the sponsor to competent authority.
- Deviation for emergency use for non-significant risk study will be reported to IRB within five days or as required by national law

- Corrective and preventive actions and PI disqualification criteria: as per section 2.3 of the study investigator agreement

12.4 Subject Information and Consent

A core information and consent form will be provided. Prior to the beginning of the trial, the investigator must have the Ethics Committee written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects. The written approval of the Ethics Committee together with the approved subject information/informed consent forms must be filed in the study files.

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s), and must adhere to GCP and to the ethical principles originating in the Declaration of Helsinki. Written informed consent must be obtained before any study specific procedure takes place. Participation in the trial and date of informed consent given by the subject should be documented appropriately in the subject files.

12.5 Insurance

All subjects participating in the trial will have insurance coverage by the Sponsor, which is in line with applicable local laws

12.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will be kept confidential. Only the subject number and initials will be recorded in the case report form, and if the subject name appears on any other document (e.g. GES report), it must be obliterated. In cases where the local low does not allow using the subject initials serial number will be appointed (e.g. AAA, BBB). Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IEC or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Subjects will also be informed that information regarding the study that does not include patient identifiers will be posted on clinicaltrials.gov.

If the results of the trial are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

12.7 Use of Data and Publications

All data and results and all intellectual property rights in the data and results derived from the study will be the property of Given Imaging, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators, educational, further product development and marketing uses. The investigator acknowledges that the system tested in the study, the Given SmartPill Motility Monitoring System is a product available commercially in the United States.

The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written

consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor forty-five days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

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14. Appendices

Appendix A: Schedule of Assessment

Visit	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	screening visit	Med Wash	SPM and GES	Return SPM receiver	Management plan	3 months follow up	6 months follow up
Days	Day (-14)-(-1)	Day (-7)-0	Day 0	Day 5+2	Day 14-28	90±7 after visit 4	180±7 after visit 4
Informed Consent[1]	X						
Assess Inclusion/ Exclusion criteria	X						
Urine pregnancy test	O		O				
Previous hemoglobin A1c levels	O						
Previous GI procedures	X						
BRASH	X						
PAGI-SYM	X		X			X	X
PAGI-QOL	X		X			X	X

Visit	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	screening visit	Med Wash	SPM and GES	Return SPM receiver	Management plan	3 months follow up	6 months follow up
Days	Day (-14)-(-1)	Day (-7)-0	Day 0	Day 5+2	Day 14-28	90±7 after visit 4	180±7 after visit 4
ROME III MODULES	X						
VAS	X		X*				
Bristol Stool Form Scale	X		X				
Patient management plan	X				X**		
blood drawn to provide hemoglobin A1c measure	O						
finger stick testing of blood glucose			O				
SPM test			X				
Gastric scintigraphy			X				

Visit	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	screening visit	Med Wash	SPM and GES	Return SPM receiver	Management plan	3 months follow up	6 months follow up
Days	Day (-14)-(-1)	Day (-7)-0	Day 0	Day 5+2	Day 14-28	90±7 after visit 4	180±7 after visit 4
return receiver & diary				X			
Verify capsule excretion				X	O		
abdominal plain radiograph					O		
prior three month patient history						X	
prior six month patient history							X
Follow-up telephone call						X	X
Adverse events	O	O	O	O	O	O	O

1 Informed concent will be obtained prior to the conduct of any study procedure

O If applicable

****Subjects will complete a separate VAS after each set of images at 0, 1, 2 and 4 hours***

PI will complete 3 managemnet plans and present to the patinet the one based on both SPM and Scintigraphy

Appendix B: BRIEF RAPID ASSESSMENT OF SUBJECT HISTORY (BRASH)

Query	Response
Subject ID number	
Date of study	
Age	
Gender	
Ethnicity	Hispanic _____ Not Hispanic _____
Race	White _____ Black/African-American _____ Asian _____ American Indian/Alaskan Native _____ Hawaiian/Pacific Islander _____ Refused _____
Height (inches)	
Weight (pounds)	
1. Is subject diabetic?	1. Yes-type 1 _____ Yes-type 2 _____ No _____ 2. Yes _____ No _____ 3. Yes _____ No _____

Query	Response
2. Is diabetes etiologic (in opinion of investigator)? 3. Does subject take insulin? 4. Age of onset of diabetes?	4.. _____ years
Are other diseases potentially etiologic?	Yes _____ No _____ Potential etiology _____
Duration of symptoms	Years _____ Months _____
Was the onset of symptoms acute?	Yes _____ No _____
1. Was symptom onset preceded by an infectious prodrome? 2. If so, characterize the infection.	1. Yes _____ No _____ 2. Respiratory ____ Upper GI ____ Lower GI ____ Other _____

Query	Response
Results of prior gastric scintigraphy	Delayed _____ Normal _____ Rapid _____ Never done _____
Results of prior SmartPill gastric emptying time measurement	Delayed _____ Normal _____ Rapid _____ Never done _____
Marijuana use	Yes _____ If so, quantity _____ No _____
Opiate use	Yes _____ No _____
Medications	**Drug** **Dose** **Scheduled vs. PRN** 1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____

Query	Response
	8. _____ 9. _____ 10. _____ 11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____ 17. _____ 18. _____ 19. _____ 20. _____

Appendix C: PATIENT ASSESSMENT OF UPPER GASTROINTESTINAL DISORDERS—SYMPTOMS (PAGI-SYM)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. For each symptom, please circle the number that best describes how severe the symptom has been during the prior 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. There are no right or wrong answers. Please answer each question as accurately as possible. Please be sure to answer every question.

	None	**Very Mild**	**Mild**	**Moderate**	**Severe**	**Very Severe**
Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
Retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
Vomiting	0	1	2	3	4	5
Stomach fullness	0	1	2	3	4	5
Not able to finish a normal-sized meal	0	1	2	3	4	5

	None	Very Mild	Mild	Moderate	Severe	Very Severe
Feeling excessively full after meals	0	1	2	3	4	5
Loss of appetite	0	1	2	3	4	5
Bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
Stomach or belly visibly larger	0	1	2	3	4	5
Upper abdominal pain (above the Navel)	0	1	2	3	4	5
Upper abdominal discomfort (above the navel)	0	1	2	3	4	5
Lower abdominal pain (below the navel)	0	1	2	3	4	5
Lower abdominal discomfort (below the navel)	0	1	2	3	4	5
Heartburn during the day (burning pain rising in your chest or throat)	0	1	2	3	4	5

	None	Very Mild	Mild	Moderate	Severe	Very Severe
Heartburn when lying down (burning pain rising in your chest or throat)	0	1	2	3	4	5
Feeling of discomfort inside your chest during the day	0	1	2	3	4	5
Feeling of discomfort inside your chest at night (during your sleep time)	0	1	2	3	4	5
Regurgitation or reflux during the day (fluid or liquid from your stomach coming up into your throat)	0	1	2	3	4	5
Regurgitation or reflux when lying down (fluid or liquid from your stomach coming up into your throat)	0	1	2	3	4	5
Bitter, acid or sour taste in your mouth	0	1	2	3	4	5

	None	Very Mild	Mild	Moderate	Severe	Very Severe
Constipation	0	1	2	3	4	5
Diarrhea	0	1	2	3	4	5

Appendix D: PATIENT ASSESSMENT OF UPPER GASTROINTESTINAL DISORDERS—QUALITY OF LIFE (PAGI-QOL)

The following questions ask about how some of the gastrointestinal problems you may be experiencing (such as pain, discomfort or other problems) may have affected your overall quality of life and well-being in the past 2 weeks. Please answer every question by circling the number that best represents your opinion. There are no right or wrong answers.

During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Had to depend on others for daily activities?	0	1	2	3	4	5
Have you avoided daily activities?	0	1	2	3	4	5
Had difficulty concentrating?	0	1	2	3	4	5
Has it taken longer than usual to perform daily activities?	0	1	2	3	4	5

During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you felt tired?	0	1	2	3	4	5
Have you lost desire to socialize?	0	1	2	3	4	5
Have you worried about stomach symptoms in public?	0	1	2	3	4	5
Have you avoided physical activities or sports?	0	1	2	3	4	5
Have you avoided travelling?	0	1	2	3	4	5
Have you felt frustrated about limitations?	0	1	2	3	4	5
Have you felt constricted in the clothes you wear?	0	1	2	3	4	5

During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you felt frustrated about not dressing as you like?	0	1	2	3	4	5
Have you felt concerned about what you can eat?	0	1	2	3	4	5
Have you avoided certain foods?	0	1	2	3	4	5
Have you restricted eating out?	0	1	2	3	4	5
Have you felt less enjoyment in food?	0	1	2	3	4	5
Have you felt changing foods could trigger your symptoms?	0	1	2	3	4	5

During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you felt frustrated about not being able to choose your foods?	0	1	2	3	4	5
Have you felt frustrated about not being able to choose your drinks?	0	1	2	3	4	5
Has your relationship with your spouse or partner been disturbed?	0	1	2	3	4	5
Has your relationship with your children or relatives been disturbed?	0	1	2	3	4	5
Has your relationship with your friends been disturbed?	0	1	2	3	4	5

During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you been in a bad mood?	0	1	2	3	4	5
Have you been depressed?	0	1	2	3	4	5
Have you felt anxious?	0	1	2	3	4	5
Have you felt angry?	0	1	2	3	4	5
Have you felt irritable?	0	1	2	3	4	5
Have you felt discouraged?	0	1	2	3	4	5
Have you been stressed	0	1	2	3	4	5
Have you felt helpless?	0	1	2	3	4	5

Appendix F: ROME III MODULES

Nausea, Vomiting, and Belching Disorders Module		
1. In the last 3 months, how often did you have bothersome nausea?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 3*
2. Did this nausea start more than 6 months ago?	☐ No ☐ Yes	
3. In the last 3 months, how often did you vomit?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 8*
4. Have you had this vomiting 6 months or longer?	☐ No ☐ Yes	
5. Did you make yourself vomit?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
6. Did you have vomiting in the last year that occurred in separate episodes of a few days and then stopped?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	*Skip to question 8*
7. Did you have at least three episodes during the past year?	☐ No ☐ Yes	
8. In the last 3 months, how often did food come back up into your mouth?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 12*
9. Have you had this problem (food coming back up into your mouth) 6 months or longer?	☐ No ☐ Yes	
10. When food came back up into your mouth, did it usually stay in your mouth for a while before you swallowed it or spit it out?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	

11. Did you have retching (heaving) before food came into your mouth?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
12. In the last 3 months, how often did you experience bothersome belching?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip remaining question*
13. Did this bothersome belching start more than 6 months ago?	☐ No ☐ Yes	

B2a: Aerophagia

Diagnostic criteria*

Must include all of the following:

1. Troublesome repetitive belching at least several times a week

   Bothersome belching more than 1 day a week (question12>4)

2. Air swallowing that is objectively observed or measured

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

   Yes. (question 13=1)

B3a: Chronic Idiopathic Nausea (CIN)

Diagnostic criteria*

Must include all of the following:

1. Bothersome nausea, occurring at least several times per week

   Nausea more than once a week (question 1>4)

2. Not usually associated with vomiting

   Vomiting less than one day a week (question 3<4)

3. Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea

   No question.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

   Yes. (question 2=1)

B3b: Functional vomiting

Diagnostic criteria*

Must include all of the following:

1. On average one or more episodes of vomiting per week

   Vomiting occurs at least once a week (question 3>3)

2

2. Absence of criteria for an eating disorder, rumination, or major psychiatric disease according by DSM-IV

   Patient does not meet criteria for Rumination Disorder (RUMINATE=0)

   No questions for eating disorder or major psychiatric disease.

3. Absence of self-induced induced vomiting and chronic cannabinoid use and absence of abnormalities in the central nervous system or metabolic diseases to explain the recurrent vomiting

   Never or rarely make yourself vomit (question 5=0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

  Yes. (question 4=1)

B3c: Cyclic Vomiting Syndrome (CVS)

Diagnostic criteria*

Must include all of the following:

1. Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)

   Vomiting occurs more often than 'never or rarely' (question 3>0
   (other criteria implied by criteria 2 & 3)

2. Three or more discrete episodes in the prior year

   At least 3 episodes during the year. Yes. (question 7=1)

3. Absence of nausea and vomiting between episodes

   Occurred in separate episodes and then stopped more often than 'never or rarely' (question 6>0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

  Yes. (question 4=1)

B4: Rumination Syndrome in Adults

Diagnostic criteria*

Must include all of the following:

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing

   Bring up food at least 1 day/week (question 8>3)

   Hold food in mouth before spitting or swallowing often (question 10>1)

2. Regurgitation is not preceded by retching

   Was bringing up food preceded by retching? No. (question 11=0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

  Yes. (question 9=1)

Functional Dyspepsia Module		
1. In the last 3 months, how often did you have pain or discomfort in the middle of your chest (not related to heart problems)?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	
2. In the last 3 months, how often did you have heartburn (a burning discomfort or burning pain in your chest)?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	
3. In the last 3 months, how often did you feel uncomfortably full after a regular-sized meal?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 5*
4. Have you had this uncomfortable fullness after meals 6 months or longer?	☐ No ☐ Yes	
5. In the last 3 months, how often were you unable to finish a regular size meal?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 7*
6. Have you had this inability to finish regular size meals 6 months or longer?	☐ No ☐ Yes	
7. In the last 3 months, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip remaining questions*
8. Have you had this pain or burning 6 months or longer?	☐ No ☐ Yes	
9. Did this pain or burning occur and then completely disappear during the same day?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	

10. Usually, how severe was the pain or burning in the middle of your abdomen, above your belly button?	☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe	
11. Was this pain or burning relieved by taking antacids?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
12. Did this pain or burning usually get better or stop after a bowel movement or passing gas?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
13. How often was this pain or discomfort relieved by moving or changing positions?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
14. In the last 6 months, how often did you have steady pain in the middle or right side of your upper abdomen?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip remaining questions*
15. Did this pain last 30 minutes or longer?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
16. Did this pain build up to a steady, severe level?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
17. Did this pain go away completely between episodes?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
18. Did this pain stop you from your usual activities, or cause you to see a doctor urgently or go to the emergency department?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	

B1. Functional Dyspepsia

Diagnostic criteria*

Must include:

1. One or more of:
   a. Bothersome postprandial fullness
      Uncomfortably full after regular sized meal, more than 1 day/week (question 3>4)
      Onset more than 6 months ago (question 4=1)
   b. Early satiation
      Unable to finish regular sized meal, more than 1 day/week (question 5 >4)
      Onset more than 6 months ago. Yes. (question 6=1)
   c. Epigastric pain
      Pain or burning in middle of abdomen, at least 1 day/week (question 7>3)
      Onset more than 6 months ago. Yes. (question 8=1)
   d. Epigastric burning
      (This criterion is incorporated in the same question as epigastric pain)

AND

1. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms
   No question.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
  Yes. ***(question 8=1)***

B1a: Postprandial Distress Syndrome (PDS)

Diagnostic criteria*

Must include all of the following:

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
   Uncomfortably full after regular sized meal, more than 1 day/week (question 3>4)
2. Early satiation that prevents finishing a regular meal, at least several times per week
   Unable to finish regular sized meal more than 1 day/week (question 5>4)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
  Requires a "Yes" to both. (question 4=1) & (question 6=1)

B1b: Epigastric Pain Syndrome (EPS)

Diagnostic criteria*

Must include all of the following:

1. Pain or burning localized to the epigastrium, of at least moderate severity at least once per week
   Pain or burning in middle of abdomen, at least 1 day/week (question 7>3)
   Pain is at least moderate severity (question 10>2)
2. The pain is intermittent
   Pain or burning often disappears completely in the same day (question 9>1)
3. Not generalized or localized to other abdominal or chest regions

3

Chest pain occurs once a month or less often (question 1 <3)

Heartburn occurs once a month or less often (question 2 <3)

4. Not relieved by defecation or passage of flatus

   Never or rarely gets better after defecation (question 12=0)

5. Not fulfilling criteria for biliary pain
6. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

   Yes. (question 8 =1)

E. Functional Gallbladder and Sphincter of Oddi Disorders (for exclusion)

Diagnostic criteria*

Must include episodes of pain located in the epigastrium and/or right upper quadrant

Steady pain which may occur less than once per month (question 14>0)

AND all of the following:

1. Episodes lasting 30 minutes or longer

   At least often (question 15>1)

2. Recurrent symptoms occurring at different intervals (not daily)

   At least often (question 17>1)

3. The pain builds up to a steady level

   At least often (question 16>1)

4. The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit

   At least often (question 18>1)

5. The pain is not relieved by bowel movements

   Never or rarely. (question 12=0)

6. The pain is not relieved by postural change

   Never or rarely. (question 13=0)

7. The pain is not relieved by antacids

   Never or rarely. (question 11=0)

8. Exclusion of other structural disease that would explain the symptoms.

   No question.

Functional Bowel Disorders		
IBS 1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	(0) Never (1) Less than one day a month (2) One day a month (3) Two to three days a month (4) One day a week (5) More than one day a week (6) Every day	*Skip to question 9*
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	(0) No (1) Yes (2) Does not apply because I have had the change in life (menopause) or I am a male	
3. Have you had this discomfort or pain 6 months or longer?	(0) No (1) Yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
5. When this discomfort or pain started, did you have more frequent bowel movements?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
8. When this discomfort or pain started, how often did you have harder stools?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
9. In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	
10. In the last 3 months, how often did you have hard or lumpy stools?	(0) Never or rarely (1) Sometimes (2) Often (3) Most of the time (4) Always	Alternative scale: (0) Never or rarely (1) About 25% of the time (2) About 50% of the time (3) About 75% of the time (4) Always, 100% of the time

11. In the last 3 months, how often did you strain during bowel movements?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
12. In the last 3 months, how often did you have a feeling of incomplete emptying after bowel movements?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
13. In the last 3 months, how often did you have a sensation that the stool could not be passed, (i.e., blocked), when having a bowel movement?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
14. In the last 3 months, how often did you press on or around your bottom or remove stool in order to complete a bowel movement?	☐ Never or rarely ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	
15. Did any of the symptoms of constipation listed in questions 9-14 above begin more than 6 months ago?	☐ No ☐ Yes	
16. In the last 3 months, how often did you have loose, mushy or watery stools?	☐ Never or rarely → *Skip to question 19* ☐ Sometimes ☐ Often ☐ Most of the time ☐ Always	Alternative scale: ☐ Never or rarely ☐ About 25% of the time ☐ About 50% of the time ☐ About 75% of the time ☐ Always, 100% of the time
17. In the last 3 months, were at least three fourths (3/4) of your stools loose, mushy or watery?	☐ No ☐ Yes	
18. Did you begin having frequent loose, mushy, or watery stools more than 6 months ago?	☐ No ☐ Yes	
19. In the last 3 months, how often did you have bloating or distension?	☐ Never → ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip remaining question*
20. Did your symptoms of bloating or distention begin more than 6 months ago?	☐ No ☐ Yes	

21. In the last 3 months, how often did you feel uncomfortably full after a regular-sized meal?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 23*
22. Have you had this uncomfortable fullness after meals 6 months or longer?	☐ No ☐ Yes	
23. In the last 3 months, how often were you unable to finish a regular size meal?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip to question 25*
24. Have you had this inability to finish regular size meals 6 months or longer?	☐ No ☐ Yes	
25. In the last 3 months, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?	☐ Never ☐ Less than one day a month ☐ One day a month ☐ Two to three days a month ☐ One day a week ☐ More than one day a week ☐ Every day	*Skip remaining question*
26. Have you had this pain or burning 6 months or longer?	☐ No ☐ Yes	

C. Functional Bowel Disorders

C1. Irritable Bowel Syndrome

Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days/month in last 3 months associated with two or more of criteria #1 - #3 below:

Pain or discomfort at least 2-3 days/month (question 1>2)

For women, does pain occur only during menstrual bleeding? (question 2=0 or 2)

Improvement with defecation

Pain or discomfort gets better after BM at least sometimes (question 4>0)

Onset associated with a change in frequency of stool

Onset of pain or discomfort associated with more stools at least sometimes (question 5>0), OR

Onset of pain or discomfort associated with fewer stools at least sometimes (question 6>0)

Onset associated with a change in form (appearance) of stool

Onset of pain or discomfort associated with looser stools at least sometimes (question 7>0), OR

Onset of pain or discomfort associated wit harder stools at least sometimes (question 8>0)

3

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 3=1)

**"*Discomfort" means an uncomfortable sensation not described as pain.*

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week is recommended for subject eligibility.

Pain or discomfort more than one day per week (question 1>4)

Criteria for IBS-C

question 10>0 and question 16=0.

Criteria for IBS-D

question 10=0 and question 16>0.

Criteria for IBS-M

question 10>0 and question 16>0.

Criteria for IBS-U

question 10=0 and question 16=0.

C2. Functional Bloating

Diagnostic criteria*

Must include all of the following:

Recurrent feeling of bloating or visible distension at least 3 days/month in 3 months

Bloating or distention at least 2-3 days/month (question 19>2)

There are insufficient criteria for a diagnosis of functional dyspepsia.

Insufficient criteria for functional dyspepsia

[(question 13<5) OR (question 14=0)] , AND

[(question 15<5) OR (question 16=0)], AND

[(question 17<5) OR (question 18=0)]

There are insufficient criteria for a diagnosis of irritable bowel syndrome or functional constipation.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 19=1)

C3. Functional Constipation

Diagnostic criteria*

Must include two or more of the following:

Straining during at least 25% of defecations

At least often. (question 11>1)

b) Lumpy or hard stools at least 25% of defecations

At least often. (question 10>1)

c) Sensation of incomplete evacuation at least 25% of defecations

At least sometimes. (question 12>0)

d) Sensation of anorectal obstruction/blockage at least 25% of defecations

At least sometimes. (question 13>0)

4

e) Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

At least sometimes. (question 14>0)

f) Fewer than three defecations per week

At least often. (question 9>1)

Loose stools are rarely present without the use of laxatives.

Loose stools occur never or rarely (question 7=0), &

Insufficient criteria for IBS

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 15=1)

C4. Functional Diarrhea

Diagnostic Criterion*

Loose (mushy) or watery stools without pain occurring at least 75% of stools *AND*

Watery stools at least ¾ of time (question 17=1)

Pain or discomfort never occurs (question 1=0)

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 18=1)

Constipation Module		
1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	⓪ Never → *Skip to question 9* ① Less than one day a month ② One day a month ③ Two to three days a month ④ One day a week ⑤ More than one day a week ⑥ Every day	
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	⓪ No ① Yes ② Does not apply because I have had the change in life (menopause) or I am a male	
3. Have you had this discomfort or pain 6 months or longer?	⓪ No ① Yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
5. When this discomfort or pain started, did you have more frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
8. When this discomfort or pain started, how often did you have harder stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
9. In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
10. In the last 3 months, how often did you have hard or lumpy stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	

11. In the last 3 months, how often did you strain during bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
12. In the last 3 months, how often did you have a feeling of incomplete emptying after bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
13. In the last 3 months, how often did you have a sensation that the stool could not be passed, (i.e., blocked), when having a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
14. In the last 3 months, how often did you press on or around your bottom or remove stool in order to complete a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
15. In the last 3 months, how often did you have difficulty relaxing or letting go to allow the stool to come out during a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	
16. Did any of the symptoms of constipation listed in questions 9-15 above begin more than 6 months ago?	⓪ No ① Yes	
17. In the last 3 months, how often did you have loose, mushy or watery stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always	

Appendix G: VISUAL ANALOG SCALES FOR ASSESSING SYMPTOMS OF GASTROPARESIS IN REAL TIME

When you are told, please draw a vertical line through each of the lines below to rate how severe each symptom is at this moment in time.

Nausea

None Severe

Stomach Fullness

None Severe

Hunger

Very Hungry None

Bloating

None Severe

Belly Visibly Larger

None Severe

Upper Abdominal Pain (Above the Belly Button)

None Severe

Upper Abdominal Discomfort (Above the Belly Button)

None Severe

Retching (Dry Heaves) in the Past Hour

None _____ Once _____ Multiple times _____

Vomiting in the Past Hour

None _____ Once _____ Multiple times _____

Appendix H: THE BRISTOL STOOL FORM SCALE

Date and time of bowel movement:_____

Please describe your bowel movement (stool) as:
(Check the most appropriate answer for the form of your stool)

___Type 1: Separate hard lumps, like nuts (hard to pass).

___Type 2: Sausage-shaped but lumpy.

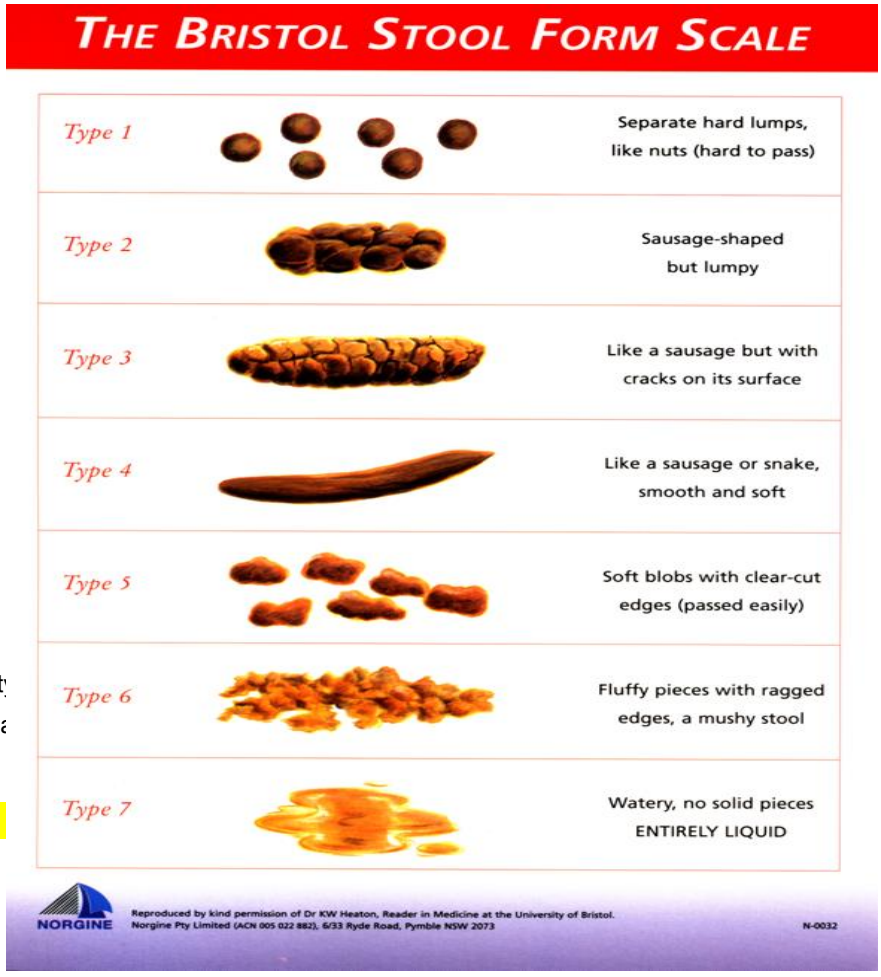
___Type 3: Like a sausage or snake but with cracks on its surface.

___Type 4: Like a sausage or snake - smooth and soft.

___Type 5: Soft blobs with clear-cut edges (easy to pass).

___Type 6: Fluffy pieces with ragged edges, a mushy stool.

___Type 7: Watery, no solid pieces.



Appendix I: Sample of Economic Analysis survey

Patient Information	Age		Gender	M / F	Race		Diabetic History	Y/N	
Prior GI Medical History	GI Surgery(ies)								
	Hysterectomies								
Initial patient management plan	Category of Motility Drug Use	Prokinetic	ASP per						
		Antiemetic	ASP per						
		Neuromodulator	ASP per						
		PPI	ASP per						
		Laxative	ASP per						
	Category of Non-Motility Drug Use		ASP per						
			ASP per						
			ASP per						
		Other	ASP per						
	Dietary plan		Cost						
Emergency room visit for Nausua/Vomiting	E/M Level		Procedure code		Avg. cost per				
Testing Modality	Scintigraphy	Time to test		Procedure code		Cost per		# of tests	
	SmartPill	Time to test		Procedure code		Cost per		# of tests	

Additional Dx	AD Manometry		Procedure code		APC		Cost per		
	SBFT		Procedure code		APC		Cost per		
	ROM		Procedure code		APC		Cost per		
	ARM		Procedure code		APC		Cost per		
	CT scan		Procedure code		APC		Cost per		
	MRI		Procedure code		APC		Cost per		
	Ultrasound		Procedure code		APC		Cost per		
	hydrogen breath test		Procedure code		APC		Cost per		
	C13 breath test		Procedure code		Cost per				
	Other		Procedure code		APC		Cost per		
	Other		Procedure code		APC		Cost per		

Physician Services	Service		Procedure code		APC		Avg. payment		
	Service		Procedure code		APC		Avg. payment		
	Service		Procedure code		APC		Avg. payment		
	Service		Procedure code		APC		Avg. payment		
	Service		Procedure code		APC		Avg. payment		
	Service		Procedure code		APC		Avg. payment		
Subsequent patient management plan	Category of Motility Drug Use	Prokinetic	ASP per						
		Antiemetic	ASP per						
		Neuromodulator	ASP per						
		PPI	ASP per						
		Laxative	ASP per						
	Category of Non-Motility Drug Use		ASP per						
			ASP per						
			ASP per						
		Other	ASP per						
	Dietary change		Cost						
	Surgery change	G tube changed to J tube	Y / N	Procedure code	Cost				

Appendix J: CLINICAL STUDY SITES

Investigator	Institution	Contact details
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REV.#	DESCRIPTION	DATE

1	New Issue	according to DMS data
2	Omitting GSRS survey, updating sites lists and CRO role	according to DMS data
3	a. Omit GES scans results provided to sponsor within 3 days of procedure. GES results will be provided to sponsor in a timely manner b. Allow per protocol performance of site standard of care Scintigraphy scan c. Allow per protocol of visit #3 performance by phone, sending receiver by FedEx d. EGD inclusion criteria to be extended to 3 years prior to enrollment e. Add primary end point interim analysis after enrollment of 150 patients f. Sample size increase to 275 subjects in order to compensate for 1 interim analysis g. Omit SF-36 survey- as per admin change #1 h. Omit ROME III modules filled by the subjects on visits 2, 5 and 6 – as per admin change #1 i. Omit Screening visit patient management plan- as per admin change #1 j. Correct Ensure meal volume to 240ml (1 can)- as per admin change #2 k. Correct Amount of radiolabeled substance (99mTc-sulfur colloid) to be mixed within the eggbeaters meal to be Between 0.5 and 1 mCi 99mTc-sulfur colloid marker- as per admin change #2	according to DMS data