Gastroparesis

Clinical Research Consortium

(GpCRC)

GpR 2: Continuation of the NIDDK Gastroparesis Registry for the Characterization and Clinical Course of Gastroparesis Patients

Protocol

Confidential

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Design synopsis

Objectives

- To expand a registry of patients for the study of the epidemiology, etiology, and degree of morbidity associated with gastroparesis. The Gastroparesis Registry 2 (GpR 2) will enroll new patients and patients from the initial NIDDK Gastroparesis Clinical Research Consortium Gastroparesis Registry (GpR) of gastroparesis patients which was initiated in February 2007 and completed in March 2011.
- To continue to follow and expand the data collections of a well-characterized cohort to further define the natural history and clinical course of gastroparesis.
- To provide a reliable source for recruitment of well-characterized patients with gastroparesis for therapeutic clinical trials, pathophysiological, molecular, histopathologic, or other ancillary studies. These subsequent clinical trials or ancillary studies will be conducted under separate study protocols with separate consent processes.

Population

- Diabetic, idiopathic and post-Nissen fundoplication gastroparesis patients with delayed gastric emptying
- Patients with normal gastric emptying, but with symptoms of gastroparesis

Inclusion criteria

- Symptoms of gastroparesis of at least 12 weeks duration with varying degrees of nausea, vomiting, early satiety, postprandial fullness, and/or abdominal pain
- An etiology of either diabetic, idiopathic, or post-Nissen fundoplication gastroparesis
- Gastric emptying scintigraphy of solids and liquids using the 4 hour Egg Beaters® protocol within the last 6 months with either:
    - Abnormal gastric emptying rate defined as an abnormal 2 hour (>60% retention) and/or 4 hour (>10% retention) result based on a 4-hour scintigraphic low fat Egg Beaters® gastric emptying study performed at a GpCRC clinical center. (This group will comprise ~80% of patients in the registry.)
    - Patients with a normal gastric emptying rate, but who have symptoms of gastroparesis. (This group will comprise ~20% of patients in the registry.)
- Age at least 18 years at initial screening visit

Exclusion criteria:

- Inability to comply with or complete the gastric emptying test by scintigraphy (including allergy to eggs)
- Presence of other conditions that could explain the patient's symptoms:
    - Pyloric or intestinal obstruction: by EGD, UGI, or Abdominal CT
    - Active inflammatory bowel disease
    - Known eosinophilic gastroenteritis
    - Primary neurological conditions that can cause nausea and vomiting such as increased intracranial pressure, space occupying or inflammatory/infectious lesions
    - Advanced liver disease
    - Chronic renal failure (serum creatinine >3 mg/dL) and/or on hemodialysis or peritoneal dialysis
    - Acute liver failure
    - Advanced liver disease (Child's B or C; a Child-Pugh-Turcotte (CPT) score of ≥7)
    - Acute renal failure

- Total or subtotal (near complete) gastric resection, esophagogastrostomy, gastrojejunostomy, or gastric bypass. **Note:** patients with prior Nissen fundoplication will be eligible for enrollment.
- Any other condition, which in the opinion of the investigator, could explain the symptoms or interfere with study requirements
- Inability to obtain informed consent

Recruitment targets: A total of 500 patients are to be enrolled in the Gastroparesis Registry 2 (GpR 2): 270 new patients and 230 patients continuing from the first Gastroparesis Registry

Recruitment period: 30 months

Follow-up period: 48-240 weeks (1-5 years); up to 5 years follow-up from the date of enrollment

Screening and Enrollment:
- Enrollment must occur within 16 weeks of informed consent and registration
- Follow-up visits will occur at 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 weeks

Data Collection:
- Baseline data collection includes demographic, socioeconomic characteristics and all measures listed below
- Follow-up data collection will include baseline measures and a repeat of certain procedures and laboratory tests as outlined in the data collection schedule (section 11.2)

Measures: Baseline (b) and Follow-up (f)
- Scintigraphic gastric emptying test at **(b)** and 48 weeks **(f)** (percent retention at 1, 2 and 4 hours)
- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
- Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
- Rome III Diagnostic Questionnaire for Adult Functional GI Disorders
- Health related quality of life (SF-36v2)
- Brief pain inventory (BPI)
- EGG and water load test
- Beck Depression Inventory (BDI-II)
- State Trait Anxiety Inventory (STAI)
- Patient Health Questionnaire (PHQ-15)
- Body mass index
- HbA1c and glucose levels
- Neuropathy Index using Neuropathy Total Symptom Score-6 (NTSS-6)
- Block 2005 Food Frequency Questionnaire
- Block Energy Expenditure Survey
- Nausea Profile and Vomiting questionnaire
- GpCRC abdominal pain questionnaire
- Treatment histories for gastroparesis
- Morbidity measures related to gastroparesis including mortality
- Electrogastrography (EGG) with caloric meal and wireless motility capsule (SmartPill®) (**Baseline only**)

Sample size considerations

- Sample size for GpR 2: 500 patients
- For each publication or ancillary study proposed to the Steering Committee the following sample size considerations must be addressed to ensure that the sample size results in an adequately powered analysis to address the primary aim of the proposal:

  Statement of the hypothesis to be addressed with references to the Protocol,
  Specification of primary outcome measure for the hypothesis,
  Specification of Type I error <0.05 and power >0.80 in sample size determination,
  Specification of primary comparison groups and outcome measures,
  Specification of minimum clinically meaningful effect size for the primary outcome,
  Specification of inclusion/exclusion criteria needed to define the subgroup of Registry patients needed for the hypothesis,
  Specification of methods for handling missing data,
  Specification of adjustments for multiplicity,
  Specification of the method of statistical analysis for primary and secondary objectives

1. Background and rationale

1.1. Historical background

Gastroparesis is a chronic symptomatic disorder associated with delayed gastric emptying. Gastroparesis predominantly affects young women (females outnumber males by a ratio of 4:1, the average age is 34).[1] The symptomatic profile of gastroparesis includes nausea (90% of patients), vomiting (>80%), bloating (75%), early satiety (60%), and abdominal pain (~50%). Symptoms in individual patients can vary in both the combination of symptoms and their severity.[1] Because of its chronic and often intractable nature, the disorder has a tremendous impact on both patients and society. Gastroparesis remains difficult to treat, in large part, because of the lack of knowledge of the underlying pathophysiology. Several factors, in particular, have impeded the progress in this field including the paucity of patients seen by any one center, the absence of uniform diagnostic criteria, and the lack of generally available and reliable methods for physiological testing. Given the complexity of the problem, and the profound degree of morbidity associated with this disorder, an important need exists to study patients in a systematic manner. Such studies can best be achieved by recruiting patients and collecting data from multiple centers as part of a network of investigators focused on this disorder. In recognition of this fact, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Gastroparesis Clinical Research Consortium in 2006 and determined its continuation for another 5 years addresses unmet needs in gastroenterology.

1.2. Gastroparesis Clinical Research Consortium

The Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of clinical centers, the Histology Reading Center, and the Scientific Data Research Center (SDRC). The individual clinical centers participate with one another in multicenter research studies and in collaboration with the SDRC in all aspects of the GpCRC. The SDRC supports the development of the study protocol, consent documents, and data collection forms, provides statistical expertise including data analysis in support of manuscript preparation, and overall study coordination and quality assurance. The SDRC also collaborates with the NIDDK Biosample Repository (plasma, serum) and the Genetics Repository (DNA) for specimen banking.

A Steering Committee (SC) comprised of the principal investigators from each clinical center in the Consortium, the principal investigators of the SDRC, and the NIDDK Project Scientist is the main governing body of the GpCRC. The Steering Committee has primary responsibility for the general organization of the GpCRC and for facilitating the development of a standardized nomenclature, diagnostic criteria, and the necessary components of the study database of patients with gastroparesis. The Steering Committee is also responsible for finalizing study protocols, supervising subject recruitment, monitoring study conduct, and reporting study results.

The NIDDK-appointed Data and Safety Monitoring Board (DSMB) members review GpCRC main study protocols, performance, data quality, and assess safety of participants. The SDRC with guidance from the NIDDK leadership coordinates the activities of the DSMB and the SC.

1.3. Mission of the GpCRC and overall objectives

The mission of the GpCRC is to improve understanding of the pathogenesis and natural history of gastroparesis of all etiologies and to advance the diagnosis and therapies of patients affected. The overall objectives of the GpCRC are to conduct multicenter observational studies and to conduct randomized, controlled treatment trials on well-characterized patients with gastroparesis.

1.4. Gastroparesis Registry

The GpCRC designed and implemented the initial Gastroparesis Registry (GpR) as an observational study to clarify the epidemiology, natural history, clinical course, and other outcomes

of gastroparesis. The Gastroparesis Registry consisted of patients who met specific criteria of gastroparesis recruited from the seven GpCRC clinical centers. The Gastroparesis Registry collected data on the epidemiology, etiology, and impact of gastroparesis. A well-characterized cohort was followed to examine the natural history and clinical course of gastroparesis. Patients were evaluated and treated according to the standards of care for this disorder, formulated by the American Gastroenterological Association and the American Neurogastroenterology and Motility Society. The Gastroparesis Registry Standard of Care was summarized in the Standard Operating Procedures (SOPs). The Gastroparesis Registry also served as a means to identify well-characterized patients for enrollment in subsequent clinical and translational research studies. Fasting plasma, serum, and DNA samples were collected and stored to address research questions from main GpCRC studies and for ancillary studies of etiology and pathogenesis of gastroparesis.

The initial Gastroparesis Registry began recruitment in February 2007, and a total of 587 patients were enrolled by the end of recruitment in March 2010. Patients were followed from 1 to 4 years. Because we collected data including demographic, physical, and socioeconomic characteristics, symptom onset, predominance and severity, gastric emptying metrics, nutritional status, medication use, quality of life measurements, psychometric evaluations and pain scores, as well as banking DNA, plasma, and serum samples in the NIDDK central repositories, the Registry was well positioned to answer many fundamental questions related to this condition.

Important findings are summarized below:

- *Idiopathic gastroparesis is a disorder that particularly affects young women, begins acutely in half of cases, and many patients are overweight. Idiopathic gastroparesis is a clinically diverse syndrome with variations in symptoms and other features related to gender, body mass, symptom onset, and, to a lesser degree, delayed gastric emptying.*[2]
- *Higher depression and anxiety scores are associated with gastroparesis severity on investigator- and patient-reported assessments. Psychological dysfunction does not vary by etiology or degree of gastric retention. Psychological features should be considered in managing gastroparesis.*[3]
- *Patients with nausea and vomiting with normal gastric emptying represent a significant medical problem and are, for the most part, indistinguishable from those with delayed emptying.*[4]
- *Many patients with gastroparesis consume a diet deficient in calories, carbohydrates, proteins, vitamins or minerals, despite being seen by doctors on a regular basis.*[5]
- *Bloating is an important symptom in gastroparesis: while it is associated with reduced nausea and vomiting, it can significantly impair quality of life.*[6]
- *Patients with idiopathic gastroparesis have more abdominal pain, early satiety and stomach fullness compared with patients with diabetic gastroparesis who have more vomiting and greater retention on gastric emptying.*[7]
- *Abdominal pain is a predominant symptom in a significant number of patients with gastroparesis and is associated more with female gender and idiopathic etiology, but not with gastric retention.*[8]
- *Despite chronic treatment at centers of expertise, the burden of gastroparesis remains high when patients are followed for over a year, despite mild improvements in several parameters. Further, the pattern of improvement is heterogeneous with bloating and abdominal pain remaining unchanged. These results emphasize the chronic nature of gastroparesis and the need for novel therapeutic approaches.*[9]

The Gastroparesis Registry 2 (GpR 2) is designed to expand upon the initial Gastroparesis

Registry for the study of the epidemiology, etiology, and degree of morbidity associated with gastroparesis. New patients will be enrolled in Gastroparesis Registry 2 in addition to allowing patients from the initial Registry to enroll and to continue follow-up visits.

Postsurgical gastroparesis is one of the primary causes of gastroparesis in addition to diabetic and idiopathic gastroparesis. Hence, enrollment into GpR 2 will be expanded to include patients with postsurgical gastroparesis developing after Nissen fundoplication, which is a procedure performed for gastroesophageal reflux disease. Post-Nissen fundoplication gastroparesis is being seen more frequently and represents an important form of gastroparesis with an increasing patient care burden. In post-Nissen fundoplication gastroparesis, vagal nerve dysfunction occurring during the surgical procedure probably accounts for the gastroparesis. Unlike other forms of postsurgical gastroparesis, patients with this disorder have an intact stomach similar to diabetic and idiopathic gastroparetics.

The gastric emptying scintigraphy test will be enhanced in the GpR 2 to measure emptying of solids and liquids. Regional gastric emptying of solids from the proximal and distal stomach will be assessed. We will attempt to capture the patient's gastroparesis symptoms at the time of the gastric emptying test (in the initial GpR, there could be an interval of up to 6 months between the symptom assessment and the gastric emptying scintigraphy test). The medications the patient is taking at the time of the gastric emptying test will be captured. For diabetic patients, the fasting glucose at the time of the gastric emptying test will also be captured. Additional questionnaires will capture information on diabetic patients and any related diabetic complications such as neuropathy, nephropathy, and retinopathy. New questionnaires will capture the presence of somatization and other disorders. Other questionnaires will be refined. Much was learned about the nutrition in gastroparesis; however, the data from GpR had some deficiencies related to quantification of weight loss and weight gain. Hence, in GpR 2, the full Block 2005 Food Frequency Questionnaire will be used and weight history information will be collected. Some of the general questionnaires will be restricted to GI symptoms. For instance, the McGill pain inventory was meant to capture information about abdominal pain. However, in viewing the results, some patients were using this to describe their fibromyalgia pain from extra-abdominal sources. In GpR 2, the follow-up visits will occur every 24 weeks, rather than every 16 weeks. The pathophysiology of the patients will be characterized by having the patients undergo additional tests to better understand their condition: wireless motility capsule to assess whole gut transit, autonomic function testing, electrogastrography, and water load satiety testing. Gastric emptying will be reassessed at 48 week visit to assess the clinical course of gastroparesis patients. Thus, the Gastroparesis Registry 2 will characterize patients with diabetic, post-Nissen fundoplication, and idiopathic gastroparesis and compare patients to similar types of patients with normal gastric emptying.

We plan to enroll and follow patients in the GpR 2 for five years or longer, and to follow initial GpR study patients for 9 years or longer. In addition, refinements to existing questionnaires and pathophysiologic measures, as well as preparation of new data collection forms will be implemented. This will allow us to address questions related to the pathogenesis, severity grading, complications, treatment responses, and clinical course in patients with gastroparesis. These questions include, but will not be limited to the following: What are the long term clinical outcomes of patients with gastroparesis or related conditions? Does the clinical course of patients with normal gastric emptying differ from those with delayed emptying? To what degree, do pathology findings correlate with symptoms? What is the relationship between overweight/obesity and gastroparesis?

2. Scientific background

Gastroparesis is a disorder of gastric neuromuscular sensory and motor function that affects patients (most of whom are women). Inadequate understanding about the pathogenesis of this condition, coupled with a general lack of awareness of the disease amongst most clinicians has resulted in a haphazard and often ineffective approach to treatment. The traditional concept of gastroparesis as a disorder of delayed gastric emptying has dominated physician thinking for decades and has influenced management approaches. However, as discussed below, the relationship between gastric emptying and symptoms is a very loose one and a rigid adherence to this definition may result in the dismissal of many patients with genuine illness. Prokinetic agents are frequently ineffective as sole therapeutic agents. Preoccupation with gastric emptying has distracted attention away from symptoms such as nausea and pain, and diverted resources that could have led to the development of effective therapies for them. On the other hand, documentation of delays in gastric emptying may be useful to distinguish patients with gastroparesis from individuals with normal emptying rates who have similar symptoms and might be considered to have functional dyspepsia or functional vomiting. It is likely that there is significant overlap not only symptomatically, but also in terms of underlying pathophysiological changes in gastric function in the different clinical conditions.[10]

2.1. Clinical symptoms

Although nausea and vomiting are the most well recognized and frequent symptoms of gastroparesis (Table 1), epigastric pain can be the most challenging and resource-consuming issue to address in selected individuals. In the more severe cases, the pain of gastroparesis may result in narcotic dependence.

Table 1: Characteristics of 146 patients with gastroparesis at tertiary motility centers[1]

Gender:	Female	82%
	Male	18%
Age at onset of symptoms:	34 years	
Symptoms:	Nausea	92%
	Vomiting	84%
	Bloating	75 %
	Early Satiety	60%
	Abdominal pain	46%

It is clear that the chronic nausea, abdominal pain, and an inability to enjoy even simple foods impose a burden of disease on its sufferers. This is reflected in the reduced quality of life seen in patients with gastroparesis.[11]

2.2. Epidemiology and natural history

There is a paucity of data regarding prevalence and incidence of gastroparesis in the community. It has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition.[12] Recent population studies from Olmsted County in Minnesota suggests the prevalence to be lower.[13] However, trends for gastroparesis-related hospitalizations in the United States between 1995 and 2004 suggest an increase in hospitalizations.[14] Two recent papers demonstrate the impact of gastroparesis on morbidity, increased hospitalizations, emergency department visits, and in one study, increased mortality.[13,15] These new data on incidence, natural history, co-morbidity, and impact of diabetic gastroparesis in patients in the United States have increased awareness of gastroparesis.

Diabetes mellitus is the most common systemic disease associated with gastroparesis. Published data suggest that gastroparesis can develop in 20-55% of patients with type 1 diabetes and up to 30% of patients with type 2 diabetes; however the incidence and prevalence may be lower in the general community of diabetics who do not seek specialized care.[16,17]

A similar number of patients present with gastroparesis of an idiopathic nature. Gastroparesis is seen in up to 34% of patients with functional dyspepsia, although the degree of gastroparesis is usually milder than that seen in diabetics.[18] The majority of gastroparetics, whether of the diabetic or idiopathic type, are women (up to 80% in some series). Patients are typically young to middle aged.

Postsurgical gastroparesis (PSG), although comprising a minority of the patients, remains an important cause of gastroparesis. PSG is often a consequence of vagotomy or vagal nerve injury during gastrointestinal surgery. Classically, operations for peptic ulcer disease such as vagotomy with or without hemigastrectomy have been those resulting in gastroparesis. However, surgery for ulcer disease has decreased over the last decade because of effective treatments with proton pump inhibitors and therapy against *Helicobacter pylori* for ulcer disease. Other surgeries such as Nissen fundoplication for GERD have increased. Thus, the surgeries causing PSG may also be changing as the types of gastric surgeries evolve.

The natural history of gastroparesis is poorly understood and, even in diabetics, symptoms may fluctuate considerably. Many patients report relatively symptom-free intervals of varying durations. In others, a progressively downhill course is observed, requiring interventional procedures to restore nutritional intake and provide palliation. A subset of the idiopathic variety may present with abrupt onset of symptoms, sometimes in association with acute gastroenteritis or other non-specific illness, and it is presumed that this may represent a post-viral syndrome. The prognosis in such cases has been reported to be better than other subtypes with gradual return to normal over several years in a significant proportion of patients.[19] Many therapies for gastroparesis relieve symptoms only in subsets of patients or are associated with significant side effects.

The severity of symptoms also varies widely, but, because of the significant referral bias present in the reported literature, the true nature of the clinical spectrum is not known. Recent investigations have focused on the quantification of disease severity both for research purposes and to assist in the delineation of which patients are likely to benefit from different treatment modalities of gastroparesis. A symptom questionnaire, the Gastroparesis Cardinal Symptom Index (GCSI), has been developed and validated in university-based clinical practices for quantifying symptoms in gastroparesis.[11,20] The GCSI is based on three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating) and is part of the longer Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM).

A simple clinical approach to classify severity of gastroparesis is as follows:

Grade 1. Mild Gastric Neuromuscular Dysfunction
Symptoms relatively easily controlled
Able to maintain weight and nutrition on a regular diet

Grade 2. Compensated Gastric Neuromuscular Dysfunction
Moderate symptoms with partial control
Able to maintain nutrition with dietary and lifestyle adjustments

Grade 3. Chronic Gastric Failure
Refractory symptoms
Inability to maintain nutrition via oral route

2.3. Pathogenesis and pathophysiology

The intramural structures that are potentially affected in gastroparesis are diverse and in close proximity to each other, representing an environment that is quite unlike any other in the body outside the gastrointestinal tract in its complexity. These include (1) enteric nervous system neurons, glia and supporting cellular elements; (2) associated extrinsic vagal and spinal nerves; (3) interstitial cells of Cajal (ICC); and (4) smooth muscle. Our state of knowledge does not as yet permit us to identify which one of these elements, if any, represents the primary or predominant site of disease.

Diabetes results in fundamental and wide-ranging changes in the internal and external metabolic milieu of virtually all cell and tissue types in the body. Thus, the pathogenesis of diabetic gastroparesis is likely to be multifactorial in origin. In this regard, there is suggestive evidence for changes in both form and function affecting a wide spectrum of gastric cellular components in experimental diabetes in rodents including the vagus nerve, intrinsic nerves of the stomach, ICCs, and gastric smooth muscle. However, knowledge about the relative importance of the various dysfunctional elements and the relative influences of metabolic or immunologic alterations on each component is incomplete.

Much of the clinical literature has assumed that the major defect in diabetic gastroparesis reflects vagal dysfunction.[16] However, there is limited correlation between gastric and cardiovascular vagal function (either parasympathetic or sympathetic) in diabetics. Metabolic and immunologic factors may contribute to the symptom presentations and motor dysfunction of diabetic gastroparesis. In both healthy participants and diabetics with gastroparesis, acute hyperglycemia by itself can elicit both symptoms (nausea) and physiological changes in gastric function (there is a dose-dependent relationship between the rate of gastric emptying and the blood glucose concentration).[21-28] The higher prevalence of gastroparesis in patients with cardiovascular autonomic neuropathy may be a reflection of the long-standing nature of the disease in these patients.[29] Pathological findings in humans have also been mixed. Guy et al, and colleagues reported electron microscopic evidence of severe reduction in the density of unmyelinated axons in the vagus in one of two cases with severe diabetic gastroparesis;[30] a single report also showed loss of myelinated axons in the cervical vagus.[31] However, Yoshida and co-workers found no abnormalities in the abdominal vagus on light microscopy in five diabetics (two with gastroparesis).[32]

In recent years, attention has shifted to defining damage to intrinsic elements in the gastric wall (enteric neurons, ICC, and muscle) in gastroparesis. However, limited investigations reveal no consistent histopathologic deficit. Myenteric plexus degeneration was noted in a single case report in the French literature[33] and changes in axonal processes but not cell bodies were reported in the

esophagus of 18 out of 20 diabetic patients.[31] A study of four women with refractory diabetic gastroparesis who had their stomachs removed showed no evidence of significant pathology in either the intrinsic nerves or the vagus; by contrast, major degeneration, atrophy, and collagenization was noted in the muscle, suggesting a predominant myopathic effect.[34] A larger study of 18 nondiabetic controls and 16 patients with long-standing diabetes (five of whom had gastroparesis), using conventional histology and Smith's silver technique, found no abnormalities in either smooth muscle or the numbers or appearance of neurons or axons in the myenteric plexus of the stomach of diabetics, with or without gastroparesis.[32]

A recently published study from our consortium using full thickness biopsies has provided further insight into the pathology. In this study on 40 patients with gastroparesis (half of which were diabetic and the other half idiopathic) cellular abnormalities were found in the majority of patients with gastroparesis. The most common defects were loss of ICC (50%) with remaining ICC showing injury, an abnormal immune infiltrate containing macrophages (57%) and decreased nerve fibers (35%). On light microscopy, no significant differences were found between diabetic and idiopathic gastroparesis with the exception of nNOS expression which was decreased in more idiopathic gastroparetics (40%) compared to diabetic (20%) patients. On electron microscopy, a markedly increased connective tissue stroma was present in both disorders. These findings suggest that examination of tissue can lead to valuable insights into the pathophysiology of these disorders and offers hope that new therapeutic targets can be found.[35]

In a significant subset of gastroparesis patients, no cause is found, and the condition is deemed to be idiopathic in nature. Idiopathic gastroparesis is even less well understood than the diabetic variety. Clinical experience suggests that a subset of patients may develop gastric dysfunction after an acute viral illness. In a study of 11 children, 8 tested positive for rotavirus, and all had complete recovery within 6 to 24 months.[36] There have been case reports of patients developing gastroparesis after vaccination (Hepatitis B, anthrax, tetanus) and after Lyme disease infection suggesting an immune related etiology.[37] However, demonstration of inflammation in the gastric wall is rare. In one case report, a young male who developed acute symptoms of gastroparesis was evaluated by full thickness gastric wall biopsy. Histopathology demonstrated an inflammatory infiltrate comprised of T lymphocytes (CD4+ and CD8+) and a marked decrease of substance P/tachykinin immunoreactive staining in nerve fibers and myenteric neurons.[38] This patient responded to steroid therapy supporting the causality of inflammation in selected cases of idiopathic gastroparesis. In another report, full thickness gastric biopsy from a patient with idiopathic gastroparesis demonstrated markedly reduced numbers of myenteric neurons and ICC, confirmed by staining of protein gene product 9.5 (PGP 9.5) and C-kit respectively, with minimal inflammatory changes in the smooth muscle and minimal fibrosis of the submucsa,[39] suggesting that degeneration of neurons and/or ICC play a principal role in other cases of idiopathic gastroparesis.

In addition to delays in gastric emptying, a variety of other pathophysiological changes in gastrointestinal function have been identified in subsets of patients with gastroparesis. Many patients can have gastric dysrhythmias, possibly accounting for their symptoms. Gastric dysrhythmias can be assessed by cutaneous electrogastrography. Interestingly, there is a subset of gastroparesis patients who also have delayed colonic transit, suggesting in some patients a diffuse GI motility disorder. In diabetic patients with gastroparesis, there are often other abnormalities such as peripheral neuropathy, nephropathy, and retinopathy. In addition, autonomic neuropathy can be present in diabetic patients; it is not known if autonomic neuropathy plays a role in idiopathic gastroparesis. However at this time, there is little scientific evidence to suggest that these other factors represent key therapeutic targets for control of gastroparesis symptoms.[16]

Potential therapeutic targets: pathophysiological changes in gastroparesis

- Delayed emptying of solids and liquids
- Accelerated emptying of liquids
- Gastric hypersensitivity
- Impaired accommodation and fundal hypocontractility
- Antral hypomotility
- Pylorospasm
- Antropyloroduodenal uncoordination
- Gastric dysrhythmias
- Small intestinal transit abnormalities
- Colonic transit abnormalities
- Autonomic neuropathy
- Hypercoagulation and/or vascular disease

2.4. Diagnostic tests

By definition, gastroparesis is characterized by a delay in gastric emptying, although as noted above, this is fraught with controversy. Most individuals suspected to have gastroparesis require upper gastrointestinal endoscopy or a radiographic upper gastrointestinal series to exclude mechanical obstruction or ulcer disease.

Although barium meals can identify delayed gastric transit, scintigraphic demonstration of delayed emptying of a solid meal is considered the gold standard for the diagnosis of gastroparesis. Measurement of gastric emptying of solids is thought to be more sensitive for detection of gastroparesis because liquid emptying may remain normal even in patients with advanced disease or may even be accelerated in early diabetes or in patients with dumping syndrome after surgery. For solid-phase testing, most centers use a technetium 99m sulfur colloid-labeled egg sandwich as a test meal. More recently, a meal using Egg Beaters® egg whites (ConAgra Foods, Inc, Downers, IL) with standard imaging at 0, 1, 2, and 4 hours postprandially has been proposed to provide a degree of standardization between different centers.[40] There may be significant day-to-day variability (up to 20%) in rates of gastric emptying.[41] The simplest approach for interpreting a gastric emptying study is to report the percent retention at defined times after meal ingestion (usually 2 and 4 hours). The half emptying time also may be calculated; however, extrapolation of the emptying curve from an individual who did not empty 50% of the ingested meal during the actual imaging time may provide an inaccurate determination of the half emptying time.[42]

Besides gastric emptying scintigraphy, other tests used to assess gastric emptying are the wireless motility capsule and the gastric emptying breath tests. Breath testing uses ^{13}C labeled food substance where the rate limiting stop in the pulmonary excretion of ^{13}C is gastric emptying.[43] Patients need normal small intestinal absorption, liver metabolism, and pulmonary excretion. The wireless motility capsule is a non-digestible capsule that empties with the phase III migrating motor complex. This wireless motility capsule measures gastric emptying along with small bowel transit time and colonic transit time.[44]

Gastric dysrhythmias are commonly found in patients with gastroparesis as determined by electrogastrography (EGG). Acute hyperglycemic events also elicit gastric dysrhythmias (predominantly tachygastrias), which resolve once euglycemia is achieved.[28] However, a normal EGG does not correlate with normal gastric emptying and its relation to symptoms is unclear.[42]

2.5. Treatment

Consensus guidelines for the treatment of gastroparesis have been published.[12] The general principles for treating symptomatic gastroparesis are to: (i) correct and prevent fluid, electrolyte, and nutritional deficiencies; (ii) reduce symptoms; and (iii) identify and rectify the underlying cause of gastroparesis, if possible. Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity, and antiemetic drug therapy.

Table 2: Anti-nausea medications for treatment of gastroparesis[12]

Class of agent	Examples
Dopamine D_2-receptor antagonists With prokinetic activity Without prokinetic activity	 Metoclopramide, domperidone Prochlorperazine, trimethobenzamide
Serotonin 5-HT_3-receptor antagonists	Ondansetron, granisetron, dolasetron, tropisetron
Tricyclic antidepressants	Desipramine, nortriptyline, amitriptyline
Muscarinic M_1-receptor antagonists	Scopolamine, hyoscyamine
Histamine H1-receptor antagonists	Dimenhydrinate, meclizine, promethazine
Cannabinoids	Tetrahydrocannabinol
Benzodiazepines	Lorazepam
Neurokinin NK_1-receptor antagonists	Aprepitant

The H_1, D_2 and M_1 receptor antagonists have overlap. The classification reflects the predominant activity.

In most cases, rigorous investigations have not assessed therapeutic responses as a function of symptom severity, but a number of basic recommendations can be made. Dietary modifications should be tried for patients with mild symptoms (Grade 1). When possible, patients should avoid the use of medications that delay gastric emptying. If needed, low doses of antiemetic or prokinetic medications can be taken on an as needed basis. Diabetic patients should strive for optimal glycemic control to minimize effects of hyperglycemia on gastric function. For individuals with grade 2 compensated gastroparesis, treatment recommendations commonly involve a combination of antiemetic (Table 2) and prokinetic medications (Table 3) given at regularly scheduled intervals to relieve more chronic symptoms of nausea, vomiting, fullness, and bloating.

Antiemetic and prokinetic agents frequently have no effect on the pain and discomfort that may be associated with gastroparesis. In these patients, measures which are directed to pain control but which do not exacerbate the other manifestations of gastroparesis must be designed.

For patients with grade 3 severe gastroparesis, more aggressive treatments including hospitalization for intravenous hydration, insulin administration, and intravenous administration of antiemetic and prokinetic agents are considered (Tables 2 and 3).

Table 3: Prokinetic medications for treatment of gastroparesis[12]

Class of agent	Presently available	Available under special circumstances	Under study
Dopamine D_2-receptor antagonists	Metoclopramide	Domperidone*	Itopride
Motilin receptor agonists	Erythromycin, azithromycin		Mitemcinal
Ghrelin receptor agonists			TZP-101 TZP-102
5-HT_4-receptor agonists		Tegaserod† Cisapride†	Renzapride, mosapride
Muscarinic receptor agonists	Bethanechol		
Acetylcholinesterase inhibitors	Physostigmine, neostigmine		Actinomide

*Via FDA IND and IRB approval.
†Under strict FDA IND protocol approved by pharmaceutical company and IRB.
FDA, Food and Drug Administration; IND, investigational new drug; IRB, Institutional Review Board;

2.6. Management of refractory gastroparesis

Chronic care of individuals with severe refractory symptoms may include enteral or parenteral nutritional support with endoscopic and/or surgical intervention (Table 4). Patients require full nutritional evaluation to determine their status.

Table 4: Criteria for initiation of enteral nutritional supplementation[12]

Severe weight loss, unintentional weight loss >5-10% of usual body weight over 3-6 months
Repeated hospitalizations for refractory gastroparesis requiring intravenous hydration and/or medication
Inability to meet weight goals set by doctor, dietician, and patient
Patient would benefit from gastric decompression
Patient would benefit from a way to absorb medications every day to gain therapeutic levels
Patient has maintained body weight, but experiences significant clinical manifestations such as:
- Diabetic ketoacidosis
- Cyclic nausea and vomiting
- Overall poor quality of life due to gastroparesis symptoms

Modified from the University of Virginia Health System Nutrition Support Traineeship Syllabus.

Two therapeutic options have been introduced for patients who do not respond to standard pharmacological measures. *Botulinum* toxin injection into the pylorus is postulated to reduce outflow obstruction due to presumed non-relaxation of the pyloric sphincter. Initial pilot studies have shown promising improvement in symptoms as well as objective measures of gastric emptying and pyloric pressure. However, controlled trials have not supported its use, although these have been performed in small numbers of patients. It is not clear what role this treatment will play in the global approach to patients with gastroparesis. Gastric electrical stimulation has been reported in two small controlled studies and several case series to reduce nausea and vomiting in patients with refractory diabetic,

idiopathic, and postsurgical gastroparesis.[16] Currently, there is one approved device (Enterra, Medtronic, Inc.) for gastric stimulation. With this device, stimulating wires are sutured into the gastric muscle along the greater curvature during laparoscopy or laparotomy. These leads are attached to an implanted pulse generator which is positioned in a subcutaneous pouch on the abdominal wall. Improvements in symptoms are not consistently associated with acceleration of gastric emptying, consistent with a predominantly neuromodulatory mechanism of action. At the present time, gastric electrical stimulation therapy is approved for humanitarian use only and requires approval from each institution's Institutional Review Board (IRB). The device is expensive and third party reimbursements continue to be a problem. The overall response rate is probably less than 70%, with most patients continuing to be somewhat symptomatic.

3. Objectives and hypotheses

Detailed epidemiological, clinical, physiological, and patient outcome data will be collected in the GpR 2, with the long-term goal of phenotyping patients to classify them into pathophysiologically defined subsets. This classification will facilitate the search for etiopathogenesis such as genomic analysis and examination of viral signatures, and will enhance the ability to define and conduct large clinical trials, ultimately leading to the development of more rational and effective therapeutic approaches for gastroparesis. In addition to these major clinical advances, the phenotypic classifications will also provide a strong foundation for experimental research and the development of relevant animal models.

The specific objectives of the Gastroparesis Registry 2 (GpR 2) are:

- To continue and expand upon the first NIDDK Gastroparesis Clinical Research Consortium Gastroparesis Registry (GpR) of gastroparesis patients that was initiated in February 2007 and completed in March 2011.
- To continue to follow and expand the data collections of a well-characterized cohort to further define the natural history and clinical course of gastroparesis.
- To provide a source for recruitment of well-characterized patients with gastroparesis for therapeutic clinical trials, pathophysiological, molecular, histopathologic, or other studies. These subsequent clinical trials or other ancillary studies will each be conducted under separate study protocols with separate consent processes.

Secondary Objectives

- To determine whether gastric emptying of liquids augments the solid gastric emptying test in identifying patients with delayed gastric emptying.
- To determine whether symptoms are better correlated with gastric emptying of solids or liquids.
- To determine whether delayed gastric emptying of liquids is associated with more severe gastroparesis, both in terms of gastric emptying and symptoms.
- To determine whether regional gastric emptying assessment with analysis of proximal and distal gastric function augments the conventional solid gastric emptying test in identifying patients with gastroparetic symptoms.
- To relate dyspeptic symptoms of gastroparesis with proximal, distal, and total gastric retention on GES.
- To determine the incidence of upper GI symptoms and gastric dysrhythmias in the electrogastrogram (EGG) signal (e.g. overall patterns, percentage distribution of EGG power and power ratios in the normal 3 cycles per minute, bradygastria and tachygastria ranges) after ingestion of the standard solid meal (SmartBar®).
- To relate the EGG results with wireless motility capsule (SmartPill®) results including rates of gastric emptying of the standard solid meal, intragastric pH, and antral contractions (motility indices) and upper GI symptoms.
- To compare EGG results and upper GI symptom results evoked by the water load satiety test and by the standard solid meal test; and
- To relate EGG results induced by the water load test and the volume of water ingested with gastric emptying test results (e.g., regional emptying rates, liquid vs. solid meal emptying rates) to determine if gastric myoelectrical patterns may predict delays in emptying or symptoms.

3.1. Primary and secondary hypotheses

The major broad hypotheses that will be tested using the GpR 2 as a primary tool are as follows:

3.1.1. Symptoms of gastroparesis, quality of life

- Nausea without vomiting, or abdominal pain, is associated with decreased quality of life in patients with gastroparesis.
- Severe abdominal pain is infrequently the predominant symptom in patients with gastroparesis.
- Somatization indices are no different in patients with nausea and vomiting and normal gastric emptying as compared with patients with delayed emptying.
- Headaches, particularly migraine headaches, are present in many patients with gastroparesis and are associated with functional disorders including fibromyalgia and irritable bowel syndrome.
- Nutrition deficiencies are present in many patients with gastroparesis and relate to both symptoms and delay in gastric emptying. In particular, vitamin D deficiency correlates with poor gastric emptying.
- Pre-morbid obesity precedes gastroparesis in many patients.
- Weight gain after gastroparesis is associated with a worse prognosis than no change in weight.
- The reduced quality of life in patients with symptoms of gastroparesis is related to symptoms, etiology of gastroparesis, co-morbid disorders, gastric emptying delay, sex, age, and Rome III diagnosis.
- Ethnic and racial characteristics impact on the severity of symptoms, health-related quality of life, and gastric emptying in patients with gastroparesis.

3.1.2. Etiology of gastroparesis

- Patients with type 1 diabetes mellitus and type 2 diabetes mellitus will have different upper GI symptoms and different rates of gastric emptying depending on their HbA1c (greater than 8.5%, 7.5 to 8.5% and 6.5 to 7.49%).
- A heritable component of gastroparesis is detectable in some patients.
- Clinical presentation, natural history, and response to treatment in patients with postsurgical gastroparesis (PSG) are different than idiopathic and diabetic gastroparesis.
- Cholecystectomy influences the symptom presentation of patients with gastroparesis.
- The clinical course of idiopathic gastroparesis patients with positive autoimmune markers will differ from patients without the autoimmune markers.
- Symptom resolution in post-viral gastroparesis relates to improved gastric emptying.
- Symptoms in post Nissen fundoplication gastroparesis show improvement over the first two post-operative years that does not relate to improved vagal function (i.e., non-vagal pathways are recruited).

3.1.3. Treatments

- Specific medications such as domperidone or marinol are associated with improvement in symptoms.
- Complementary and alternative medicines (CAM) are used by many patients with gastroparesis.

3.1.4. Clinical course of gastroparesis

- The clinical course of gastroparesis varies by diagnostic categories such as diabetic, idiopathic, and post-surgical: (1) Diabetic gastroparesis will be related to the clinical course of a patient's diabetes mellitus and autonomic nervous system (ANS) neuropathy; (2) Post-infectious idiopathic gastroparesis will be different from other types of idiopathic gastroparesis.

- The delay in gastric emptying predicts the clinical course of patients with gastroparesis.
- Most patients with gastroparesis have a disease course with episodes of exacerbations.
- A subset of patients with gastroparesis has evidence of an inflammatory process. These patients have a slow downhill course.
- A grading system (mild, compensated, chronic failure) for gastroparesis can be developed that predicts the subsequent clinical course of patients.
- Control of gastroparetic symptoms in diabetes (as opposed to improved emptying) leads to better glycemic control (decreased hemoglobin A1c).
- The predominant symptom in gastroparesis impacts on the clinical course of gastroparesis.
- Patients with gastroparesis have a higher mortality rate than the general population.
- The survival outcomes of gastroparesis will vary by diagnostic categories such as diabetic, idiopathic, and post-surgical. Diabetic gastroparesis patients may have a shorter survival compared to other diagnostic categories.

3.2. Hypotheses related to test findings

3.2.1. Gastric emptying of solids and liquids

Patients will undergo a gastric emptying scintigraphy test that simultaneously measures gastric emptying of solids and liquids for their clinical evaluation.

- Delayed gastric emptying is linked to greater impairment in quality of life, increased economic cost, increased healthcare utilization, and worse clinical outcomes.
- Profound delays in solid food gastric emptying (e.g. less than 10% emptied at 2 hours or less than 25% emptied at 4 hours) relate to symptoms, whereas mild delays (e.g. 25- 50% emptied at 2 hours or 50-90% emptied at 4 hours) have little correlation with symptoms.
- Patients with nausea and vomiting and normal gastric emptying can be distinguished from slow emptiers based on clinical history.
- Gastric emptying improves over time in a subset of patients with gastroparesis. Conversely, patients with symptoms but normal gastric emptying at presentation may manifest delayed emptying if retested within a year.
- Gastric emptying can be variable on repeat testing in patients with gastroparesis symptoms. Specifically, some patients with normal gastric emptying initially but with symptoms of gastroparesis may develop delayed gastric emptying on repeat testing. On the other hand, patients with delayed gastric emptying will continue to have delayed gastric emptying.
- Gastric emptying of liquids identifies additional patients with gastroparesis who have normal gastric emptying of solids.
- Gastroparetic symptoms correlate better with gastric emptying of solids than to gastric emptying of liquids.
- Patients with delayed gastric emptying of both solids and liquids have more severe symptoms, and worse quality of life than patients with normal gastric emptying or isolated delay in either gastric emptying of solids or liquids.

3.2.2. Regional gastric emptying

Images from each gastric emptying scintigraphy test will be saved to assess emptying from the proximal and distal regions of the stomach.

- Regional gastric emptying with analysis of proximal and distal emptying improves the identification of gastric transit abnormalities over the conventional analysis of only total gastric emptying.
- Delayed gastric emptying from the proximal stomach is associated with early satiety and postprandial fullness. Delayed gastric emptying from the distal stomach is associated with symptoms of nausea and vomiting.

3.2.3. Wireless motility capsule

- Wireless motility capsule (WMC) studies will reveal a subset of patients with gastroparesis who also have subtle or overt dysmotility of the small and/or large intestine which will adversely impact prognosis.
- WMC methods detect delays in gastric emptying in higher percentages of patients with suspected gastroparesis versus 4 hour gastric retention on scintigraphy. ***Expectation:*** We anticipate WMC will show delays in 60% of patients with symptoms suggestive of gastroparesis vs. in 40% with gastric scintigraphy based on data from initial trial of WMC in patients with prior scintigraphic demonstration of gastroparesis.[45]
- Delays in small intestinal and/or colon transit are frequently observed in patients with symptoms suggestive of gastroparesis. ***Expectation:*** We anticipate WMC methods will detect delays in small intestinal transit in 20% and delays in colon transit in 50% of patients with suspected gastroparesis. Generalized transit delays in 2 or 3 regions (stomach, small intestine, colon) will be observed in 35% of patients with suspected gastroparesis based on data from prior published retrospective analysis of UMI and MGH databases.[46]
- Different symptom profiles correlate with distinct gastric and extragastric motor defects.
  Subhypotheses:
  a. Fullness and early satiety severity correlates with delays in gastric emptying. ***Expectations:*** Postprandial fullness/early satiety subscale scores on the Gastroparesis Cardinal Symptom Index (GCSI) show progressive increases from normal WMC gastric emptying (<5 hr) to mildly delayed WMC gastric emptying (5-12 hr) to severely delayed WMC gastric emptying.
  b. Bloating and distention severity correlates with delays in small intestinal and colonic transit. ***Expectations:*** Bloating/visible distention subscale scores on the GCSI are greater in those with small bowel (SB) transit > 6 hr versus those with SB transit < 6 hr. Bloating/visible distention subscale scores also show progressive increases from normal WMC colon transit (<59 hr) to moderately delayed WMC colon transit (59-100 hr) to severely delayed WMC colon transit (>100 hr).
  c. Upper abdominal pain and discomfort correlate with abnormalities in pressure profiles in the stomach or small intestine. ***Expectations****:* Upper abdominal pain/discomfort subscale scores on the GCSI are greater in those with gastric contractions >29 and motility indices (MI) >9.82 in the hour before gastric emptying vs. in those with lower values. Upper abdominal pain/discomfort subscale scores are greater in those with elevated SB contractions and MI vs. in those with lower values.
  d. Symptom onset after meal ingestion and duration will correlate with the region of motor impairment. ***Expectation****:* Postprandial fullness/early satiety and upper abdominal pain/discomfort scores on visual analog scale (VAS) testing will begin earlier and resolve quicker as they derive predominantly from gastric dysfunction, whereas bloating and distention will peak later and persist longer due to their genesis in the small intestine and/or colon.

3.2.4. Autonomic function testing

- Autonomic dysfunction is common among patients with gastroparesis, including those with idiopathic gastroparesis.
- Patients with increasing autonomic dysfunction have more severe symptoms and impairment in quality of life.
- Autonomic dysfunction is more common among patients with acute onset or post-infectious gastroparesis compared to patients with an insidious onset of gastroparesis.

- Patients with autonomic dysfunction have a more diffuse dysmotility compared to patients without autonomic dysfunction.
- Associated phenomena such as autonomic neuropathy or dysmotility of other gastrointestinal regions are important in determining the natural history and clinical outcomes in patients with gastroparesis.

3.2.5. Electrogastrography

- Ingestion of a standard solid meal evokes gastric dysrhythmias and upper GI symptoms that vary across a sub group of patients with gastroparesis.
- Upper GI symptoms and gastric dysrhythmias are evoked by the water load satiety test in the majority of patients with idiopathic and diabetic gastroparesis.
- Frequency of normal 3 cycles per minute (cpm) activity will vary across subgroups of patients, based on demographics, clinical and gastric pathophysiological characteristics compared with patients with gastric dysrhythmias.
- Selected characteristics of the EGG signal and volumes of water ingested correlate with gastric emptying rates and upper GI symptoms and may predict emptying abnormalities.
- Satiety meal testing at baseline correlates with baseline symptoms of severity as well as outcome after 1 or more years but not with gastric emptying.

4. Case definitions for Gastroparesis Registry 2

4.1. Overview

The traditional method of defining gastroparesis relies on demonstration of delayed gastric emptying in a symptomatic patient who does not have an obstruction or ulcer explaining their symptoms. The gastric emptying test does not always correlate with symptoms. Nevertheless, this definition based on delayed gastric emptying has the advantage of widespread acceptance and ready availability in the community and will provide a more uniform group of patients.

This study will enroll patients with gastroparesis and delayed gastric emptying. These patients can have either diabetic, idiopathic, or post-Nissen fundoplication gastroparesis. In addition, patients with symptoms similar to gastroparesis, but with normal gastric emptying will be enrolled as a reference group.

Overlap with other functional dyspepsia: The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety, and postprandial fullness. Abdominal discomfort and pain also are noted by many affected patients and represent challenging symptoms to treat. There is some overlap between gastroparesis and functional dyspepsia as both symptoms and gastric emptying test results may meet definitions for both in a subset of patients. As a consequence, some patients with mild abdominal pain, nausea, vomiting, and evidence of delayed emptying are considered to have functional dyspepsia by some clinicians and gastroparesis by others. Patients with marked delay in gastric emptying should be diagnosed with gastroparesis and not functional dyspepsia. In general, predominant abdominal pain with lesser degrees of nausea is more consistent with a diagnosis of functional dyspepsia, whereas predominant nausea and vomiting with lesser degrees of abdominal pain is more characteristic of gastroparesis. Under the new Rome III criteria, nausea is not a diagnostic criterion for functional dyspepsia and so for the purposes of the Gastroparesis Registry 2, any patient with nausea (regardless of the degree of other dyspeptic symptoms) who has delayed gastric emptying will be classified as gastroparesis.

4.2. Symptoms of gastroparesis

4.2.1. Gastroparesis with delayed emptying:

In the Gastroparesis Registry 2, the case definition for gastroparesis will require the following:

- Symptoms of nausea, vomiting, abdominal pain, bloating, and/or early satiety for at least 12 weeks (not necessarily contiguous)
- Scintigraphic evidence of delayed gastric emptying (using a standardized low fat Egg Beaters® meal defined as greater than 60% retention at 2 hours and/or greater than 10% retention at 4 hours
- Exclusion of other causes of symptoms such as mechanical obstruction, inflammatory, or other structural lesions of the GI tract or non-gastrointestinal causes

This case definition for gastroparesis will provide a uniform group of patients for study for the GpCRC. GpR 2 will enroll patients with gastroparesis and defined as above with the following diagnostic categories: Diabetic, Idiopathic, and Post-Nissen fundoplication

4.2.2. Symptomatic nausea and vomiting without delayed gastric emptying

Patients will qualify for enrollment in this category if they meet the criteria for gastroparesis defined for the protocol with the exception of a normal scintigraphic gastric emptying and no other

cause found. Many patients present with symptoms similar to those of gastroparesis but exhibit normal scintigraphic gastric emptying of a solid meal. Many of these individuals satisfy the Rome III definitions of chronic idiopathic nausea or functional vomiting.

4.3 Target composition

Patients will be recruited predominantly from outpatient clinics either in gastroenterology, diabetes, or primary care settings. Inpatients (patients in the hospital) with the diagnosis of gastroparesis will also be invited to participate.

In GpR 2, we will cap the number of the patients with symptomatic nausea and vomiting with normal gastric emptying (as described in section 4.2 above) to 20% of the total patients enrolled. In the GpR 2, patients with prior Nissen fundoplication will be eligible for enrollment and we will cap the patients with post-Nissen gastroparesis to 20% of the patients with delayed gastric emptying. Assuming the goal of 500 patients are entered into GpR 2 and assuming similar types of enrollment as in the first registry this will result in the following types of patients: 200 idiopathic gastroparesis patients, 50 idiopathic patients with normal gastric emptying, 120 with diabetic gastroparesis, 30 diabetic patients with normal gastric emptying, 80 post-Nissen gastroparesis patients, and 20 post-Nissen patients with normal gastric emptying.

5. Eligibility criteria

5.1. Inclusion criteria

- Symptoms of gastroparesis of at least 12 weeks duration (do not have to be contiguous) with varying degrees of nausea, vomiting, early satiety, post-prandial fullness, and/or abdominal pain
- An etiology of either diabetic, idiopathic, or post-Nissen fundoplication gastroparesis
- Gastric emptying scintigraphy of solids and liquids test using 4 hours Egg Beaters® protocol within the last 6 months with either:
  - Abnormal gastric emptying rate defined as an abnormal 2 hour (>60% retention) and/or 4 hour (>10% retention) result based on a 4-hour scintigraphic low fat Egg Beaters® gastric emptying study performed at a GpCRC clinical center.
  - Patients with a normal gastric emptying rate but with symptoms of gastroparesis may be enrolled and classified as possible gastroparesis or gastroparesis-like with normal gastric emptying
- Age at least 18 years at initial screening visit

5.2. Exclusion criteria

- Inability to comply with or complete the gastric emptying scintigraphy test (including allergy to eggs)
- Presence of other conditions that could explain the patient's symptoms:
  - Pyloric or intestinal obstruction as determined by endoscopy, upper GI series or abdominal CT scan
  - Active inflammatory bowel disease
  - Known eosinophilic gastroenteritis
  - Primary neurological conditions that could cause nausea and/or vomiting such as increased intracranial pressure, space occupying or inflammatory/infectious lesions
  - Acute liver failure
  - Advanced liver disease (Child's B or C; a Child-Pugh-Turcotte (CPT) score of ≥7)
  - Acute renal failure
  - Chronic renal failure (serum creatinine >3 mg/dL) and/or on hemodialysis or peritoneal dialysis
- Total or subtotal (near complete) gastric resection, esophagogastrostomy, gastrojejunostomy, or gastric bypass. Note: patients with prior fundoplication will be eligible for enrollment.
- Any other plausible structural or metabolic cause
- Any other condition, which in the opinion of the investigator would interfere with study requirements
- Inability to obtain informed consent

Clinical centers must be certified by the Scientific Data Research Center to start enrollment in the Gastroparesis Registry 2. Prior to implementation of this protocol, the principal investigator must have the protocol and consent form approved by the Institutional Review Board for Human Research (IRB) at his/her institution. Once a candidate for GpR 2 has been identified, study related details will be carefully discussed with the patient including the follow-up visit schedule and procedures. The patient will be asked to read and sign the consent form that was approved by the IRB. There will be a separate consent for the collection, storage, and use of DNA for genetic research.

6. Schedule of visits and procedures

6.1. Overview

Patients will have a scintigraphic gastric emptying test of both solids and liquids for their clinical evaluation of gastroparesis. To rule out other disorders, patients must have had an upper endoscopy within 2 years prior to registration. Information will be collected during screening using 1) medical history and physical examination; 2) validated questionnaires; 3) laboratory studies; and 4) gastric emptying test. In addition, tests investigating the pathophysiology will include ingesting a wireless motility capsule to assess whole gut transit, autonomic function testing, electrogastrography to assess for gastric dysrhythmias, water load testing to assess for gastric accommodation. Plasma and serum samples will be saved on each patient. Patients will then be followed over time, being seen every 24 weeks, collecting information on 1) treatments being used, 2) change in medical condition; and 3) validated questionnaires assessing symptoms, abdominal pain, and quality of life. A follow-up gastric emptying test will be obtained at the 48 week visit. Plasma and serum samples will be collected from each patient on a yearly basis.

6.2. Patient selection, screening and enrollment visits

Many of the Gastroparesis Registry 2 (GpR 2) patients will likely come from the first Gastroparesis Registry, the current patient rosters of the GpCRC investigators, and new patients referred to them for evaluation and treatment of gastroparesis. Patients who are thought to be eligible will be invited to screen for enrollment in the GpR 2. Patients may be referred from physicians outside the Consortium and some patients may refer themselves to be included in the GpR 2. Patients considered by the clinical center investigator as likely to be eligible for enrollment in the GpR 2 may be consented and screened at a visit that is part of the ongoing clinical care of the patient. Tests may be ordered and billed to insurance to appropriately complete the evaluation of the disease and general medical condition according to reasonable standard of care.

Consent for screening and HIPAA authorization to disclose protected health information with the GpR 2 must be obtained from the patient prior to initiating data collection for the GpR 2; this consent and authorization must be obtained at the start of the initial screening visit. At the initial screening visit, the details of GpR 2 participation will be introduced. If the patient consents and is judged to have definite or possible gastroparesis, then he/she may enter the formal screening phase. Screening will include both prospective and retrospective data collection. Prospective data collection will be carried out by completion of forms and questionnaires by patients and by performance of various laboratory tests and clinical procedures on patients. Retrospective data collection will be carried out by review of the patient's medical chart and abstraction of various data elements. Abstracted data may include laboratory and radiology test results within defined time windows. The screening visits may occur on separate calendar days and may take place over several visits occurring over a period of up to 16 weeks after registering the patient for study screening.

The maximum follow-up on a patient enrolled into the GpR 2 will be approximately 5 years. Data will be collected during screening visits to establish baseline values, and then every 24 weeks after enrollment. If the patient returns in the interim for exacerbation of gastroparesis symptoms, an interim visit will be keyed in the database to reflect the exacerbation of symptoms. Appendix 11.2 summarizes the data collection schedule for screening, enrollment, and follow-up visits.

The purpose of the screening visits is to collect data needed to determine eligibility and establish baseline values. Activities at screening visits include:

- Reviewing and signing the Gastroparesis Registry 2 informed consent
- Reviewing and signing the Gastroparesis Registry 2 HIPAA authorization form
- Assignment of GpCRC patient identification number (if patient is new to the GpCRC)
- Detailed medical/medication history
- Physical examination including vital signs, height, weight, and anthropometric measurements
- Review status of laboratory tests, including those reflecting glycemic control
- Review status of gastrointestinal tests including endoscopy
- Review status of gastric emptying scintigraphy
- If needed, patient to sign medical records release to obtain prior reports
- Patient to provide location/contact information
- Obtain retrospective health history information/materials relevant to study eligibility
- Clinical center coordinator to register patient on clinic data system
- If needed, clinical center coordinator to request prior reports from health care provider
- Perform electrogastrogram (EGG) with caloric meal and wireless motility capsule test
- Perform autonomic function testing
- Perform EGG with water load test
- Questionnaires to be filled out by the patients
    - Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
    - Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
    - Health related quality of life (SF-36v2)
    - Beck Depression Inventory (BDI-II)
    - State Trait Anxiety Inventory (STAI)
    - Patient Health Questionnaire (PHQ-15)
    - Neuropathy Total Symptom Score (NTSS-6)
    - Rome III Diagnostic Questionnaire for Adult Functional GI Disorders
    - Brief Pain Inventory
    - Block 2005 Food Frequency Questionnaire
    - Block Energy Expenditure Survey
    - Nausea Profile and Vomiting questionnaire
    - GpCRC abdominal pain questionnaire

During the screening visits, the patient completes the questionnaires needed for enrollment in the Gastroparesis Registry 2 and has blood drawn for standard of care laboratory tests and specimen (plasma, serum, and DNA) banking. The patient must attend the screening visits after an overnight fast of at least 8 hours and will be instructed to bring a snack to be eaten after fasting blood is drawn. Review patient chart for standard of care baseline laboratory data required (see Appendix 11.3):

- Complete blood count (white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count)
- Comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, and liver panel including total protein albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase)
- Thyroid stimulating hormone (TSH)
- Erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hs-CRP), antinuclear antibody (ANA)
- Vitamin B12, 25-hydroxy vitamin D level
- Hemoglobin A1c
- Lipid panel (total cholesterol, LDL, HDL, triglycerides)

Tests must have been done within 16 weeks prior to registration, except ANA which may have been done in last year. Other procedures during screening visits include:

- Fasting blood collection for plasma and serum banking
- Blood collection for DNA banking (no fasting required)

Gastric emptying scintigraphy: To establish a diagnosis of definite gastroparesis (see section 4.1 for definition), the patient must have a 4 hour scintigraphic evaluation of gastric emptying of solids and liquids using a standardized low fat Egg Beaters® meal with an accompanying PAGI-SYM completed at a GpCRC center in last 6 months (schedule as needed) and available for review. Since the patients are symptomatic from a possible gastric motility disorder, the gastric emptying of solids and liquids scintigraphy test is being performed for the patients' clinical evaluation. The GpCRC investigator must confirm that the patient meets the criteria for definite gastroparesis. The gastric emptying scintigraphy may have been obtained within 6 months prior to registration. Medications that delay gastric emptying such as narcotic analgesics and medications that enhance gastric emptying such as prokinetics will be stopped 3 days prior to the gastric emptying test. Medications taken during the past week will be recorded. For diabetic patients, a fasting blood glucose level must be checked prior to the gastric emptying test to ensure it is less than 270 mg/dL. Patients will also complete the PAGI-SYM form immediately prior to the gastric emptying test.

The gastric emptying tests will be performed at the GpCRC clinical centers. The clinical centers will save each scintigraphy test and send the de-identified images to Dr. Alan Mauer at Temple University Nuclear Medicine for central analysis of regional gastric emptying.

Screening visit 2: Patients must discontinue use of proton pump inhibitors for 7 days, and stop histamine 2 antagonists, prokinetics, narcotics, anticholinergics, and cannabinoids for 3 days prior to this visit. If the patient normally takes insulin, they will be asked to take only half of their normal long-acting insulin. Record fasting glucose for diabetic patients; the blood glucose level must be checked to ensure it is less than 270 mg/dL to continue with the test. Patients will come to the center after fasting and will have a baseline electrogastrogram (EGG). Then they will eat a nutrient bar (SmartBar®) with water and swallow a wireless motility capsule (SmartPill®) with additional water, followed by a 90 minute EGG recording. Patients will continue to abstain from prokinetics, proton pump inhibitors, 'over the counter' laxatives, isotonic PEG electrolyte preparations (e.g. MiraLax), and prescription laxatives (e.g. lubiprostone) after ingesting the SmartPill® until they return for the follow-up visit in 4-7 days. These tests are described in detail in section 6.7.3. (All details of the EGG recording procedure, wireless motility capsule test, and specific questionnaires will be in the Standard Operating Procedures (SOP) manual.)

Screening visit 3 (4-7 days after visit 2): Record fasting glucose for diabetic patients; the blood glucose level must be checked to ensure it is less than 270 mg/dL to continue with the test. If the patient's blood glucose level is greater than 270 mg/dL, the EGG and water load test must be rescheduled for another day.

The study physician or coordinator will collect the SmartPill® receiver and download the data, and then the patient will undergo autonomic function testing to evaluate heart rate variability (see section 6.7.4.). Next the patient will have a 15 minute baseline electrogastrogram (EGG) and then complete a water load test, followed by a 30 minute EGG recording (this test is described in section 6.7.5). Patients will have blood drawn for DNA and serum/plasma banking as the last procedure for the visit.

Enrollment: The GpR 2 data system will include software to check patient eligibility based on keyed

data forms. The eligibility check task may be run at any time, and there is no limit on the number of times it may be run. The output from the task will list the eligibility checks that the patient has failed and a summary finding that the patient is eligible or ineligible for enrollment into the study. Thus staff can use this task to identify the items that still need to be completed, keyed, or verified after data from screening visits are keyed. The date of enrollment is the time zero for reckoning all follow-up visits (i.e., all follow-up visits are scheduled at specific times measured from the date of enrollment). On the day of enrollment the data system will generate a visit windows schedule for the patient; this schedule will indicate the ideal date for each follow-up visit, as well as the time window around the ideal date during which the follow-up visit may be done and the data collected at the visit may be used in the study.

Note: Some patients may not be able complete all the study procedures. For instance, some may not have the liquid phase gastric emptying scintigraphy performed due to center specific logistical issues or some may not be able to swallow the SmartPill® or some may not complete EGG with SmartBar or water load testing. These patients may still be enrolled.

6.3. Follow-up visits

Gastroparesis Registry 2 follow-up visits will be scheduled every 24 weeks after enrollment. Participants will return for follow-up visits at 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 weeks after enrollment. Each visit will have an interval of time (follow-up visit window) surrounding the ideal target date for the visit during which the study procedures may be completed and the data may be keyed in the study database. The ideal target date for a follow-up visit is the exact anniversary (24, 48, 72, 96, 120, 144, 168, 192, 216, 240 weeks) from enrollment. Visit windows will be constructed to be contiguous, so that at any point in time, a follow-up visit window is open. The specific procedures to be completed at each of the follow-up visits are detailed in the Data Collection Schedule in the Appendix (section 11.2).

Weeks 24, 72, 120, 168 and 216 visits

Follow-up medical history (medication changes/additions, symptom exacerbations or interventions, surgeries, hospital admissions, new diagnoses of co-morbidities, complications of interventions such as infections), and physical examination including weight, height, and waist/hip circumference, blood pressure, heart rate, respiratory rate and body temperature. Blood will be drawn to obtain HbA1c values for patients with diabetes. Participants will complete the following questionnaires:

- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
- Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
- Beck Depression Inventory (BDI-II)
- State Trait Anxiety Inventory (STAI)
- Neuropathy Total Symptom Score (NTSS-6)
- Nausea Profile and Vomiting questionnaire
- Patient Health Questionnaire (PHQ-15)

Week 48 visits (2 separate days)

The week 48 follow-up visits require 2 separate days of testing and participants will come fasting for each day of testing. Medications that delay gastric emptying such as narcotic analgesics and medications that enhance gastric emptying such as prokinetics will be stopped for 3 days prior to the visits. A follow-up medical history (medication changes/additions, symptom exacerbations or interventions, surgeries, hospital admissions, new diagnoses of co-morbidities, complications of

interventions such as infections, documentation of any additional GI tests performed as part of standard of care), and physical examination, including weight, height, and waist/hip circumference, blood pressure, heart rate, respiratory rate and body temperature will be performed.

Participants will have a repeat 4 hour gastric emptying scintigraphy test of solids only using the Egg Beaters® with toast and jam will be performed. Medications taken during the past week will be recorded. For diabetic patients, a fasting blood glucose level must be checked within the hour prior to the gastric emptying test to ensure it is less than 270 mg/dL. Patients will also complete the PAGI-SYM questionnaire immediately prior to the gastric emptying test.

On a second day, the autonomic function testing and a repeat EGG with water load test will be performed. On the morning of the EGG and water load satiety test, the patient will arrive fasting. Patients may take their usual medications with a small amount of water (up to 4 oz) up to two hours prior to the study, but should refrain from coffee, tea, or juice. After arriving to the clinic, the patient's blood glucose level must be checked to ensure it is less than 270 mg/dL. If the patient's blood glucose level is greater than 270 mg/dL the EGG and water load satiety test must be rescheduled for another day.

Draw 10 mL of blood for serum banking and 10 mL of blood for plasma banking at the NIDDK Biosample Repository. Blood will be drawn to obtain HbA1c values for patients with diabetes. Participants will complete the following additional questionnaires:

- Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
- Beck Depression Inventory (BDI-II)
- State Trait Anxiety Inventory (STAI)
- Neuropathy Total Symptom Score (NTSS-6)
- Block 2005 Food Frequency Questionnaire
- Block Energy Expenditure Survey
- Rome III Diagnostic Questionnaire for Adult Functional GI Disorders
- Health related quality of life (SF-36v2)
- Patient Health Questionnaire (PHQ-15)
- Nausea Profile and Vomiting questionnaire
- Brief Pain Inventory
- GpCRC abdominal pain questionnaire

Weeks 96, 144, 192, and 240 visits

Follow-up medical history (medication changes/additions, symptom exacerbations or interventions, surgeries, hospital admissions, new diagnoses of co-morbidities, complications of interventions such as infections), and physical examination including weight, height, and waist/hip circumference, blood pressure, heart rate, respiratory rate and body temperature. Draw 10 mL of blood for serum banking and 10 mL of blood for plasma banking at the NIDDK Biosample Repository. Blood will be drawn to obtain HbA1c values for patients with diabetes. Participants will complete the following questionnaires:

- PAGI-SYM, PAGI-QoL
- Beck Depression Inventory (BDI-II)
- State Trait Anxiety Inventory (STAI)
- Rome III functional GI disorders questionnaire
- Health related quality of life (SF-36v2)

- Patient Health Questionnaire (PHQ-15)
- Block Energy Expenditure Survey
- Block 2005 Food Frequency Questionnaire
- Nausea Profile and vomiting questionnaire
- Brief Pain Inventory
- GpCRC abdominal pain questionnaire

Interim visits

Separate entries will be made in the Gastroparesis Registry 2 data system for symptom flares requiring medical intervention. In addition, information will be obtained each time a new medicine for gastroparesis symptoms is started and the response to this treatment.

6.4. Data form contents

The Gastroparesis Registry 2 data collection forms will capture the following:

- Demographics
- Onset and duration of symptoms
- Nature and severity of symptoms
- Characteristics of nausea and vomiting
- Prior gastrointestinal and gynecologic surgeries and the dates of these surgeries
- Characteristics of weight prior to and since onset of gastroparesis symptoms
- Other GI symptoms particularly chronic pancreatitis
- Presence of diabetes (including gestational diabetes)
- If diabetic, onset, type, glycemic control, other system involvement (eye, kidney, heart, peripheral and autonomic neuropathy)
- Presence of "overlap" symptoms
- Results from upper GI endoscopy performed within 2 years prior to registration
- Results from gastric emptying test including PAGI-SYM and fasting glucose on day of gastric emptying test for diabetic patients performed at a GpCRC clinical center within 6 months prior to registration
- Other medical problems particularly any history of connective tissue disorder
- Family history of GI or related illness
- Past medical/surgical events and illness history, including coronary artery disease or stroke

Baseline medication history: The GpR 2 data forms will capture all prescription medications taken within 6 months prior to registration. These will include medications taken for the treatment of gastroparesis, pain (visceral or somatic) and many others. GpR 2 data forms will also include information on use of alternative therapies, antioxidants, vitamins, and/or other dietary supplements. Any known medication allergies will be documented.

Follow-up medical history: Follow-up health history will include data on symptom severity; nutritional changes, medication changes or additions; key events or interventions; surgeries; hospital admissions; new diagnoses of co-morbidities; complications of diabetes such as retinopathy, neuropathy, nephropathy; and cardiovascular events.

6.5. Laboratory Tests

All laboratory test results may be obtained as archival material from the patient's chart or should be collected as part of the standard of care during screening. Maximum acceptable intervals between the date of collection of laboratory results and GpR 2 registration (date of initial screening visit) will be specified on the data collection form. The blood collection date of the laboratory tests must be

recorded on the data form. The etiologic tests: anti-nuclear antibody (ANA), high sensitivity C-reactive protein (hs-CRP), sedimentation rate (ESR); complete blood count (white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count); comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, and liver panel including total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase); thyroid stimulating hormone (TSH); vitamin B12, 25-hydroxy vitamin D level, lipid profile (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides) and hemoglobin A1c are required once as part of screening. **HbA1c will be required at each follow-up visit for diabetic participants.**

6.6. Plasma, serum, and DNA for banking

Fasting blood collection for plasma and serum banking will be banked in the NIDDK Biosample Repository. Blood will be collected at the screening/enrollment visit and yearly thereafter on all patients enrolled in the Gastroparesis Registry 2. Blood collection for DNA extraction and banking will be performed during screening. The banked samples will be used for specific Gastroparesis Registry 2 research questions and other GpCRC ancillary studies. Standardized methods for plasma, serum, and DNA processing that allow for maximal preservation of banked specimens and storage in designated -70 degrees C freezers will be applied across all clinical centers and at the NIDDK central repositories (see GpR 2 Standard Operating Procedures (SOP) I: Clinical Center Operations).

6.7. Specific tests

6.7.1. Gastric emptying of solids and liquids

The gastric emptying test for enrollment into GpR 2 will be a combined simultaneous gastric emptying of solids and liquids using the Egg Beaters® meal protocol.[40,47] Liquid egg white will be labeled with Tc-99m and water labeled with Indium-111. The liquid emptying is measured in the presence of the solid meal. An allergy to eggs is a contraindication to this test.

Patients are instructed to stop medications that could affect gastrointestinal motility for the 3 days prior to the gastric emptying scintigraphy and to come for the test in the morning after fasting overnight with nothing to eat after midnight, (an 8 hour fast). The patient fills out the PAGI-SYM questionnaire assessing symptoms over the past 2 weeks. Diabetic patients must have a fasting blood glucose level checked within the hour prior to consumption of the meal.

Gastric emptying scintigraphy is performed using a standard low-fat, Egg Beaters® (egg white) meal to measure solid emptying. The Egg Beaters® are radiolabeled with 0.5 -1 microcurie technetium-99m sulfur colloid and served with two pieces of white bread and strawberry jam.[40,48] The meal has a caloric value of 255 kcal (nutritional composition: 72% carbohydrate, 24% protein, 2% fat, and 2% fiber). The participant is instructed to ingest the meal within 10 minutes. Each participant then drinks 120 mL of water containing 125 microcurie (4.6 MBq) of Indium 111-DTPA (diethylene triamine pentacetic acid) for the measurement of liquid gastric emptying and small bowel and/or colon transit.[47]

For quality control, the staff technologist records how long it takes the participant to consume the meal and how much they consume. The patient should ingest the whole meal. If the patient cannot eat the entire meal, at least 50% of each component should be consumed for the test. If the patient vomits part of the meal at any time during the test, this should be indicated on the report. Clinically the study is non-diagnostic for gastroparesis if normal and only a small portion is eaten. If gastric emptying is delayed for a small meal ingested it can, however, indicate delayed gastric emptying.

Combined technetium-99m and Indium-111 imaging begins immediately after consumption of the liquid and is repeated at 30 min, 1 hour, 2 hours, 3 hours, and 4 hours to record gastric emptying of liquids and solids. If small bowel transit is to be obtained, then In-111 imaging is also performed at 5 and 6 hours after meal ingestion.[47,49] Between all image sets, the participants are permitted normal quiet activity (e.g., reading, watching television and/or videos) in the standing or sitting position.

Note: If gastric emptying of liquids is performed on a separate day than gastric emptying of solids, the patient consumes an unlabeled Egg Beaters® meal (Egg Beaters®, bread, jam) with the radiolabelled water.

Analysis of the gastric emptying data is performed. Images are recalled from a computer disc and analyzed to determine gastric counts. Regions of interest (ROIs) are manually drawn around the total stomach at each time interval. A geometric mean of the anterior and posterior values is used to correct for depth changes (geometric mean counts = square root [anterior counts ×posterior counts]) and counts are corrected for radioisotope decay.

Normal values for gastric emptying scintigraphy and small bowel transit have been established in earlier studies using healthy volunteers. Gastric retention of Tc-99m > 60% at 2 hours and/or > 10% at 4 hours was considered evidence of delayed gastric emptying of solids.[40,48] Rapid gastric emptying of solids was defined as < 35% retention of Tc-99m at 1 hour. Delayed gastric emptying of liquids in the presence of solids is greater than 50% retention of In-111 at 1 hour emptying, a value representing the mean plus 2 standard deviations of values derived from 20 normal subjects from prior studies using a similar solid and liquid meal.[47,49]

6.7.2. Regional gastric emptying

The gastric emptying tests will be performed at the local centers and the images saved. The centers will need to de-identify the patient information using available software and send the images in DICOM format to Temple University Nuclear Medicine for regional gastric emptying scintigraphy analysis. (Details will be in the GpR 2 Standard Operating Procedures (SOP) I: Clinical Center Operations manual.)

Analysis: Gastric emptying scintigraphies using the standardized meal with 4 hour imaging will be analyzed for proximal, distal, and total gastric retention in patients undergoing GES for clinical evaluation. Regional gastric emptying of the proximal and distal stomach will be analyzed by drawing regions representing the proximal and distal portions of the stomach. Proximal gastric retention will be expressed as the percent of radioactivity in the proximal stomach calculated by dividing the corrected counts in the proximal stomach at each time period by the total counts in the total stomach at time 0. Distal gastric retention in the distal stomach will be expressed as the percent of radioactivity in the distal stomach calculated by dividing the radioactivity count in the distal stomach at each time period by the count in the total stomach at time zero. We will look at the regional emptying curves: % in that region at specific times, and time to maximum in distal stomach, and slope of emptying in each region.

6.7.3. Wireless motility capsule and EGG

A wireless motility capsule, SmartPill® measures gastric emptying, small bowel transit time (SBTT), and colon transit time (CTT) and is approved for the evaluation of presumed gastroparesis and slow transit constipation. The SmartPill® has pH, pressure, and temperature sensors to quantify gastric, small bowel, and colon transit and contractility. SmartPill® showed good correlation with gastric scintigraphy (R=0.73) in 87 controls and 61 patients with prior gastroparesis diagnoses.

SmartPill® sensitivities and specificities (65% and 87%) were comparable or superior to 4 hour scintigraphy (44% and 93%) and supported equivalency of SmartPill® with scintigraphy methods advocated by consensus guidelines.[45] In constipated patients, SmartPill® colon transits showed good correlations with radioopaque marker studies.[50,51] In retrospective analyses, SmartPill® testing gave many new diagnoses in 86 patients with symptoms in the upper or lower gut including detecting slow transit constipation or small bowel dysmotility in patients thought to have only gastroparesis.[46] This emphasizes the effectiveness of SmartPill® to characterize regional and generalized motor disorders in one test.

Test procedure criteria: Patients must be able to stop proton pump inhibitors for 7 days, and stop histamine 2 antagonists, prokinetics, narcotics, anticholinergics, and cannabinoids for 3 days. The SmartPill® is contraindicated in patients with bezoars (retained liquid or poorly organized solids are permitted), dysphagia, prior gut lumen surgery (prior Nissen fundoplication is permitted), known strictures, prior inflammatory bowel disease, prior diverticulitis, chronic frequent NSAID use, and cardiac medical devices (gastric stimulators, insulin pumps, continuous glucose monitors are permitted).

Patient preparation required for the SmartPill® with EGG test

1) Patient will stop proton pump inhibitors for 7 days prior to visit 2;
2) Patient will stop histamine 2 antagonists, prokinetics, narcotics, anticholinergics, constipation medications (over the counter laxatives, isotonic polyethylene glycol (PEG) electrolyte preparations (e.g. MiraLax), and prescription laxatives (e.g. lubiprostone), and cannabinoids for 3 days prior to the visit; and
3) Patients will continue to abstain from prokinetics, proton pump inhibitors, and 'over the counter' laxatives, isotonic PEG electrolyte preparations (e.g. MiraLax), and prescription laxatives (e.g. lubiprostone) after ingesting the SmartPill® until they return for the follow-up visit in 4-7 days.
4) Patients will not swallow the SmartPill®, if they have a history of bezoars (retained liquid or poorly organized solids are permitted), significant dysphagia, prior gut lumen surgery (except fundoplication), known strictures, prior inflammatory bowel disease, and cardiac medical devices (gastric stimulators, insulin pumps, continuous glucose monitors are permitted).

Data to be Collected:

Survey Instruments: PAGI-SYM, Rome III questionnaire, and visual analog symptom (VAS) scales: Patients will be instructed to put a cross in 10 cm lines reflecting symptom severity of nausea, fullness, hunger, pain, discomfort, bloating, and distention. VAS data sheets will be completed before SmartPill® ingestion, and at 10, 20, 30, 60, and 90 minute time periods after ingestion of the SmartPill®.

Items needed for the test:

The SmartPill® data capture system and receiver, a SmartPill® capsule, a SmartBar®, a cup that has a 50mL measured mark for water during meal ingestion (at least 100mL of water is needed for the test), 3 EGG leads, a dedicated quiet area for the EGG recording, a reclining chair, a blanket, 3CPM EGG equipment and software, and a laptop or computer with the SmartPill® analytic software are required for this test.

Test protocol:

The Study Physician will complete the Baseline Medical History and Physical Examination, if not previously performed. On the day of the test, patients are instructed to come in the morning after

fasting overnight with nothing to eat after midnight - an 8 hour fast. Women of child-bearing potential will have urine pregnancy tests. Diabetics will have a finger stick testing of blood glucose and if >270 mg/dL, the study will be rescheduled. Prior to testing, participants will complete the PAGI-SYM questionnaire assessing symptoms over the past 2 weeks and the Rome III questionnaire. The SmartPill® will be activated and calibrated.

To streamline the number of visits for each patient, SmartPill® ingestion will be performed on the same day as EGG testing with the SmartBar® as the standard test meal. Baseline symptoms prior to EGG recording will be obtained using visual analog scales (VAS) for stomach fullness, hunger, nausea, bloating, and abdominal discomfort. The patient will recline in a chair at at 30-45 degree angle in a comfortable position. A fasting EGG will be performed for 15 minutes before SmartBar® ingestion.

After the baseline EGG recording is completed, the patient will begin the standard solid meal test by sitting up in the chair and ingesting one SmartBar® in a 10 minute period with 50 mL of room temperature water. It is expected that 100% of the bar will be ingested. The percentage of the SmartBar® that is consumed will be documented. After the SmartBar® is consumed; the SmartPill® will be ingested with another 50 ml of water and another visual analog scales symptoms sheet will be completed. The subject will then recline in the 30-45 degree position that they were in for the fasting baseline condition. The electrodes will be checked to verify that they are well adhered to the skin and the respiratory belt will be checked to verify it is snug before starting the EGG recording for the 90 minute postprandial period. Visual analog scales for stomach fullness, hunger, nausea, bloating, and abdominal discomfort will be completed at the 10, 20, 30, 60, and 90 minute time periods after ingestion of the SmartPill®. The patient may get out of the chair to stretch for 2 minutes at 30 and 60 minutes if necessary. At the 90 minute point the test is completed and the electrodes are removed. (Further details of the EGG recording and questionnaires will be in the SOP.)

Patients will be permitted to leave the study center after completion of the 90 minute EGG recording after SmartPill® ingestion. Study participants will leave with instructions to:

1) Remain fasting for 6 hours after SmartPill® ingestion; thereafter resume a normal diet; maintain a diary recording times of meal ingestion, bowel movements, and sleep; and keep the receiver in close proximity for 4-7 days. An event marker on the receiver will be depressed for diary entries.
2) Complete all remaining questionnaires for GpR 2: food questionnaire, nausea and vomiting questionnaire, neuropathy profile; abdominal pain questionnaire, state trait anxiety
3) Continue to abstain from prokinetics, proton pump inhibitors, and 'over the counter' laxatives, isotonic PEG electrolyte preparations (e.g. MiraLax), and prescription laxatives (e.g. lubiprostone) after ingesting the SmartPill® until they return for the follow-up visit
4) Return fasting for a follow-up visit 4-7 days after SmartPill® ingestion to return the receiver, questionnaires, and diaries for analysis.

SmartPill® expulsion will be queried and a second follow-up will be scheduled if needed. Standard protocols will be activated if SmartPill® retention is suspected after 14 days.

SmartPill® transit and contractile parameters collected

Gastric emptying will be calculated from time of ingestion to the time the capsule passes to the duodenum as defined by abrupt >2 pH unit increases from the lowest postprandial value to >4 that do not decrease to <4 for >10 minutes. Gastric emptying >5 hr is considered delayed. Ileocecal passage

is defined when >1 pH unit decreases occur >30 min after gastric emptying; such pH decreases are noted in >95% of cases. Small bowel transit will be calculated from times of duodenal to ileocecal passage. Small bowel transit >6 hours is considered delayed. Anal expulsion is determined by 0.045°F/second temperature decreases. Colon transit will be calculated from times of ileocecal passage to anal expulsion. Colon transit >59 hours is considered delayed. Two pressure parameters will be computer calculated (MotilitGI, GIMS Data Viewer, SmartPill Corp., Buffalo, NY). Numbers of contractions >25 mmHg will be standardized to activity per 15 min to compare gastric, small bowel, and colon recordings of different length. Summed contractility measures >25 mmHg per 15 minutes will be provided by motility indices calculated as log (mmHg x min). Numbers of gastric contractions <29 and motility indices <9.82 in the hour before gastric emptying are considered abnormal.

Symptom profiles in those with isolated delayed gastric, small bowel, and colon transit as well as with generalized transit delays in >2 gut regions, and normal transit throughout. Symptoms will be compared in those with increased vs. normal vs. decreased contractile parameters in the same subsets. These studies will provide detailed characterizations of diffuse and generalized gut transit and contractile abnormalities in patients presenting with symptoms of gastroparesis.

6.7.4. Autonomic function testing

Using the ANSAR ANX 3.0 system, the patient will undergo six challenges to evaluate sympathetic and parasympathetic function. The test consists of:

1) a five minute, resting, initial baseline,
2) a one minute parasympathetic challenge of paced, rhythmic, deep breathing,
3) a one minute (second) baseline – the Valsalva baseline,
4) a 1:35 minute Valsalva challenge, which consists of a series of five short Valsalvas (no more than 15 seconds in duration) with short rests in between each,
5) a two minute (third) baseline – the stand baseline, and
6) a five minute postural change (stand) challenge which consists of a rapid change in posture, followed by approximately five minutes of quiet upright posture.

The system records the patient's electrocardiogram (ECG) blood pressure (BP) and heart rate responses to evaluate sympathetic and parasympathetic function.

6.7.5. EGG and water load test protocol:

For each EGG and water load test, the clinical center needs to have a cup that has a 50 mL measured mark for water, 3 EGG leads, a dedicated quiet area for the EGG recording, a reclining chair, a blanket and the 3CPM EGG equipment and software.

Test protocol

On the morning of the EGG and water load satiety test, the patient will arrive fasting. Patients may take their usual medications with a small amount of water (up to 4 oz) up to two hours prior to the study, but should refrain from coffee, tea, or juice. After arriving to the clinic, the patient's blood glucose level must be checked to ensure it is less than 270 mg/dL. If the patient's blood glucose level is greater than 270 mg/dL the EGG and water load satiety test must be rescheduled for another day.

Baseline symptoms prior to EGG recording will be obtained using visual analog scales for stomach fullness, hunger, nausea, bloating, and abdominal discomfort. The subject will mark each symptom line with a vertical line to indicate how they currently feel in terms of that symptom. Once the EGG and respiratory signals are stable, the baseline EGG recording period can begin. Patients will undergo a 15 minute baseline EGG in a reclining chair with the subject positioned at a 30-45 degree tilt.

Patients will begin the Water Load Satiety Test. For this, participants will sit upright. During the test, participants will drink cool water for a 5 minute period until they feel "**completely full**." The total volume of water consumed will be recorded.

A continuous 30 minute EGG recording is then obtained. The patient's symptoms are recorded using VAS at 10, 20, and 30 minutes after ingestion of the water (at the end of the 0-10 minute, 11-20 minute, and the 21-30 minute post-satiety periods). The test is completed after the 30 minute recording period and the electrodes are removed. (Complete details will be contained in the SOP.)

6.7.6. Standardized questionnaires

Several standardized questionnaires will be administered at baseline (prior to enrollment) and during follow-up at specified intervals (see Appendix 11.2 for the data collection schedule). The purpose of the questionnaires is to obtain important information regarding gastroparesis symptoms, nutrition, pain, and health-related quality of life.

Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM).[52-54] The self-reported questionnaire is composed of 20 items and 6 subscales. The severity of each symptom item over a 2-week recall period is scored from 0 (none or absent) to 5 (very severe). The GCSI, a 9 symptom survey relevant to gastroparesis stratified in 3 subscales—nausea/vomiting, fullness/early satiety, and bloating, is contained in the PAGI-SYM. The GCSI correlates with patient severity ratings and is responsive to changes in overall symptoms. Two additonal items for constipation and diarrhea also will be recorded and scored and their main symptom will be determined.

Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL). A validated 30 item questionnaire to assess quality of life in patients with dyspepsia, GERD, or gastroparesis. Copyright© 2004 Johnson & Johnson.

Rome III Diagnostic Questionnaire for Adult Functional GI Disorders. The Rome Foundation has developed a 93 item diagnostic questionnaire to assist physicians, health care professionals and researchers in identifying individuals who have one or more functional gastrointestinal disorders (FGIDs). Rome III modules for (1) nausea, vomiting, and belching and (2) functional dyspepsia to assess upper symptoms and (3) functional bowel disorders to assess lower symptoms are validated surveys from the Rome Foundation to quantify symptoms and suggest functional disorders involving the upper or lower gut. Copyright© 2006 by Douglas A. Drossman, Enrico Corazziari, Michel Delvaux, Robin C. Spiller, Nicholas J. Talley, W. Grant Thompson, William E. Whitehead.

Beck Depression Inventory, Second Edition (BDI-II).[55] The BDI-II is a commonly used, reliable 21-item self-report measure designed to assess for depression.

State Trait Anxiety Inventory.[56] The STAI is a 40-item self-report measure designed to assess both situational and characterological anxiety. This measure provides two subscale scores (State and Trait) and has been shown to exhibit good reliability and internal consistency.

Patient Health Questionnaire (PHQ-15).[57] The PHQ-15 is a brief, self-administered questionnaire that may be useful in screening for somatization and in monitoring somatic symptom severity in clinical practice and research.

Brief Pain Inventory (BPI).[58] Developed in 1989 by Dr. Charles Cleeland for rapid assessment of the severity and impact of pain in cancer patients. The BPI has since been translated into more than two dozen languages, and is widely used in both research and clinical settings.

SF-36 Health Survey (SF-36).[59] The SF-36 is a 36-item, self-report measure designed to assess quality of life in patients. This measure also provides two summary scores (physical and mental health) and eight scale scores. It is reliable and internally consistent.

Neuropathy Total Symptom Score (NTSS-6).[60] The NTSS-6 provides a valid assessment of neuropathy sensory symptoms in patients with diabetes.

Block 2005 Food Frequency Questionnaire. This full-length (approximately 110 food item) questionnaire was designed to estimate usual and customary intake of a wide array of nutrients and food groups. It takes 30-40 minutes to complete and is intended for either self- or interviewer-administration. The food list was developed from NHANES 1999-2002 dietary recall data; the nutrient database was developed from the USDA Food and Nutrient Database for Dietary Studies (FNDDS), version 1.0. A series of "adjustment" questions provide greater accuracy in assessing fat and carbohydrate intake. Individual portion size is asked for each food, and pictures are provided to enhance accuracy of quantification. Copyright 2005 ©Block Dietary Data Systems www.nutritionquest.com.

Block Energy Expenditure Survey.[61] This tool is designed to measure total average energy expenditure per day, as well as minutes per day of moderate and vigorous activities, and average MET-minutes by activity type. The form assesses job type and time, frequency and duration of the 26 most relevant daily-life and leisure time activities as determined by analysis of the Human Activities Patterns Survey data. It takes 20-25 minutes to complete.

Nausea Profile and Vomiting questionnaire.[62] The nausea profile (NP) is a subjective symptom checklist with the goal of obtaining a more in-depth description of what patients are experiencing when they report the feeling of nausea. The NP evaluates the experience of 3 dimensions which are involved in the complex feeling of nausea, somatic distress, GI distress and emotional distress.

GpCRC abdominal pain questionnaire. The consortium developed a questionnaire to address abdominal pain in gastroparesis patients.

7. Statistical and design considerations

As noted earlier, the Gastroparesis Registry 2 is a prospective, multi-center, observational study with standardized collection of data on a large cohort of patients with gastroparesis or gastroparesis-like symptoms. The overall objective is to broadly compile baseline and follow-up data, including biospecimens and DNA, on the cohort with the aim of better defining the epidemiology, etiology, and natural history of gastroparesis. In addition, the GpR 2 will serve as a major patient recruitment source for randomized, controlled clinical trials of treatments for gastroparesis. The recruitment goal for the GpR 2 is to enroll over a 30 month period, a total of 500 patients consisting of 270 new patients and 230 patients continuing from the first Gastroparesis Registry. One or more years of follow-up data will be collected on each enrolled patient.

As this is the largest cohort study of gastroparesis, the objectives and hypotheses to be examined are intentionally numerous and cut across many aspects of gastroparesis (e.g., see Section 2). Furthermore, new hypotheses and objectives, not listed in Section 2, are expected to arise later in the study. These might arise as follow-up analyses suggested by information from GpR 2 data analyses related to the objectives and hypotheses in Section 2 or from new information from sources outside the GpCRC. This approach mirrors the successful process that occurred during the first phase of the GpR, in which presentations and publications from accumulating data were made, rather than waiting until the recruitment goal was met.

Addressing the specified hypotheses of the GpR 2 using the multicenter, multivariable, longitudinal cohort data will require a full array of statistical analyses ranging from simple descriptive statistics to multivariable regression models applied to either cross-sectional data or longitudinal data. Given this diversity of analytic plans, it is not possible to have one global sample size calculation for the GpR 2. However, as was done successfully in the first phase of the GpR, proposers of every presentation or publication related to one of the study aims must submit a formal Abstract/Manuscript (AMP) or Study Proposal (SP) application form to the GpCRC Steering Committee stating the aims, rationale, methods and materials needed (e.g., biospecimens or DNA) and giving a detailed statistical plan, including a sample size justification. Every proposal must identify appropriate subgroups of patients for analysis and comparison, drawing patients from all clinical centers. Analyses tailored to the hypotheses to be addressed must also be included in the proposal. For each proposal, the Steering Committee approves, disapproves, or suggests modifications and resubmission to the proposers.

For each publication or ancillary study proposed to the Steering Committee the following considerations must be addressed to ensure that the sample size results in an adequately powered analysis to address the primary aim of the proposal.

- Statement of the hypothesis to be addressed with references to the Protocol,
- Specification of the primary outcome measure for the hypothesis,
- Specification of Type I error < 0.05 and power ≥ 0.80 in sample size determination,
- Specification of primary comparison groups and outcome measures,
- Specification of minimum clinically meaningful effect size for the primary outcome,
- Specification of inclusion/exclusion criteria needed to define the subgroup of Registry patients needed for the hypothesis,
- Specification of methods for handling missing data,
- Specification of adjustments for multiplicity,
- Specification of the method of statistical analysis for primary and secondary objectives

The sample size must be justified by calculations (using PASS 2011 or similar design software), which will include the relative sizes of the subgroups for comparisons (rarely will the ratio be 1:1), Type I error of 0.05 or less, a power of 0.80 or higher, specification of a clinically meaningful effect size, and estimated event rates (categorical outcomes) or estimates of variability (e.g., SD of primary outcome measure), and a rationale for achievement of the sample size in a reasonable period of time, either from existing patients in the registry or from patients to be recruited in the future, or both, and, if appropriate, adjustments for missing data. Adjustments to Type I errors for multiplicity of comparisons are not needed for hypotheses pre-specified in Section 2.1. Other hypotheses that are not pre-specified and that arise as a result of data analyses will be identified in publications as exploratory and needing further confirmatory data.

As noted above, each publication or presentation requires a separate statistical plan and sample size justification; however, it is useful to illustrate the statistical power and minimum clinical meaningful effect sizes that will be detectable for a few major subgroups. Table 5 shows four major subgroup comparisons reflecting the expected patient mix of the target 500 patients in the GpR 2: (1) patients with delayed (n=400) vs. not delayed (n=100) gastric emptying, and, among the patients with delayed gastric emptying, (2) diabetic (n=120) vs. idiopathic (n=200), (3) Type 2 (n=50) vs. Type 1 (n=70) diabetics, and (4) patients with post-Nissen fundoplication (n=80) vs other types of gastroparesis (n=320). These examples provide a mix of small, intermediate, and large subgroups for comparison, which represent the range of subgroup sizes likely to arise in GpR 2 analyses related to study aims and objectives. The type of outcome measure that must be analyzed to address a particular study aim influences the sample size considerations. Both categorical (either binary or more than 2 categories) and continuous or quasi-continuous (ordered) outcome measures may be needed. The sample size is strongly dependent on the event rates (for binary categorical outcomes) or, for continuous outcome measures, the variability, expressed in standard deviation (SD) units. Using the extensive database collected during the first phase of the GpR, we developed estimates useful for study planning in GpR 2. These estimates are shown in Table 6 (for continuous outcomes) and Table 7 (for binary outcomes). Potential outcome measures shown in Tables 6 and 7 may be used either in cross-sectional analyses (baseline data) or longitudinal data analyses (baseline and repeated follow-up measures).

Table 5. Illustrative GpR 2 Subgroup Comparisons

Major Subgroup Comparisons	Expected Subgroup Size Smaller	Larger
Delayed Gastric Retention: No vs Yes	100	400
Patients with Delayed Gastric Retention:		
Diabetic vs. Idiopathic	120	200
Diabetes: Type 2 vs Type 1	50	70
Post-Nissen vs Other Gastroparesis	80	320

Table 6 presents the measures of variability and the minimal clinically important effect sizes (in SD_Δ units) for continuous outcome measures of direct interest in GpR 2: PAGI-SYM, GCSI and related subscales, six measures of quality of life and/or depression, BMI, three laboratory measures from serum, and two and four hour gastric emptying times. The following information for each of several potential outcome measures is displayed: the overall mean at baseline, the standard deviation of the measure at baseline (SD_b), the coefficient of variation ($CV = SD_b/mean_b$), and for longitudinal studies, SD_Δ, the standard deviation of the change in the measure from baseline to follow-up, and the

intra-class correlation coefficient of repeated within-person measures (r). GpR 2 analyses of baseline or follow-up data using more variable outcome measures such as total hospitalizations (CV=2.0), C-reactive protein (CV=1.7), or 2-hr (CV=0.7) or 4-hr (CV=0.9) gastric emptying times will need larger sample sizes than studies using less variable outcomes such as GSCI (CV=0.4), the SF-36 quality of life scales (CV=0.3), or HbA1c (CV=0.2).

Table 6 also shows, for each potential outcome measure, the minimum clinically important effect size (in SD units) detectable with 80% statistical power and 0.05 two-sided Type I error for four subgroup comparisons with longitudinal outcome measures of change from baseline to 48 weeks, where the smaller subgroup ranges across the sizes shown in Table 5: (1) Diabetes mellitus vs. idiopathic groups,(2) Type 2 vs. Type 1diabetes,(3) Post Nissen fundoplication vs. other gastroparesis, and (4) Patients with gastroparesis symptoms without vs. with delayed 4 hour gastric empting by scintigraphy. In every case, across outcomes measures and subgroup sizes, the GpR 2 sample size provides adequate power to detect minimum clinically important effect sizes of 0.5 SD_{Δ}, or smaller; the smallest effect size is 0.10 SD_{Δ} and the average effect size in the Table 6 is 0.30 SD_{Δ}.

Table 6: Measures of Variability and Minimum Clinically Important Effect Sizes (in SD_Δ) units) detectable with 80% power and 0.05 Type I error for Changes in Continuous Outcome Measures from Baseline to 48 Weeks

							Smaller Subgroup‡§			
							DM	T2DM	Post-Nissen	Not Delayed
Continuous Outcomes	**Mean***	**SD_b†**	**CV†**	**Δ†**	**SD_Δ†**	**r†**	**MDE**	**MDE**	**MDE**	**MDE**
Symptoms:										
PAGI-SYM: (0-5)										
GCSI	2.9	1.0	0.4	-0.4	1.1	0.44	0.34	0.55	0.37	0.33
Nausea/Vomiting Sub-scale	2.5	1.4	0.6	-0.4	1.4	0.56	0.31	0.50	0.34	0.30
Postprandial Fullness Sub-scale	3.4	1.1	0.3	-0.6	1.3	0.31	0.38	0.62	0.41	0.37
Bloating Sub-scale	3.0	1.6	0.5	-0.2	1.5	0.57	0.30	0.48	0.32	0.29
Upper abdominal sub-score	3.0	1.6	0.5	-0.5	1.5	0.53	0.29	0.48	0.32	0.29
Total hospitalizations in past year	1.9	3.9	2.0	-0.4	3.2	0.66	0.22	0.35	0.24	0.22
Depression/Quality of Life										
BDI score (0-63)	18.8	11.2	0.6	-0.5	9.9	0.61	0.26	0.40	0.28	0.25
State anxiety score (0-80)	44.7	13.6	0.3	0.2	13.9	0.48	0.28	0.46	0.30	0.27
Trait anxiety score (0-80)	44.0	12.5	0.3	0.4	10.8	0.63	0.25	0.40	0.27	0.25
PAGI-QOL total score (0-5)	2.5	1.1	0.4	0.3	0.9	0.64	0.25	0.40	0.26	0.24
SF-36 physical component (0-100)	33.7	10.5	0.3	1.7	9.4	0.60	0.26	0.41	0.28	0.25
SF-36 mental component (0-100)	37.9	12.8	0.3	1.5	12.1	0.56	0.27	0.43	0.29	0.26
Anthropometric:										
BMI kg/m^2	27.0	7.3	0.3	0.5	2.6	0.94	0.11	0.18	0.12	0.11
Laboratory measures:										
C-reactive protein (CRP) mg/dL	0.7	1.2	1.7	0.8	0.4	0.95	0.10	0.16	0.11	0.10
ESR (mm/hr)	18.3	19.0	1.0	1.0	15.1	0.69	0.23	0.37	0.25	0.23
HbA1c (%) (for Diabetics only)	7.9	1.9	0.2	0.2	1.9	0.48	*n/a*	0.46	*n/a*	*n/a*
Gastric emptying (scintigraphy):										
% retention at 2 hours	55.4	23.4	0.7	7.0	22.2	0.55	0.27	0.43	0.29	0.26
% retention at 4 hours	25.1	23.4	0.9	6.7	21.2	0.59	0.26	0.42	0.28	0.25

* Based on data from the GpR Phase I (N=570 participants)

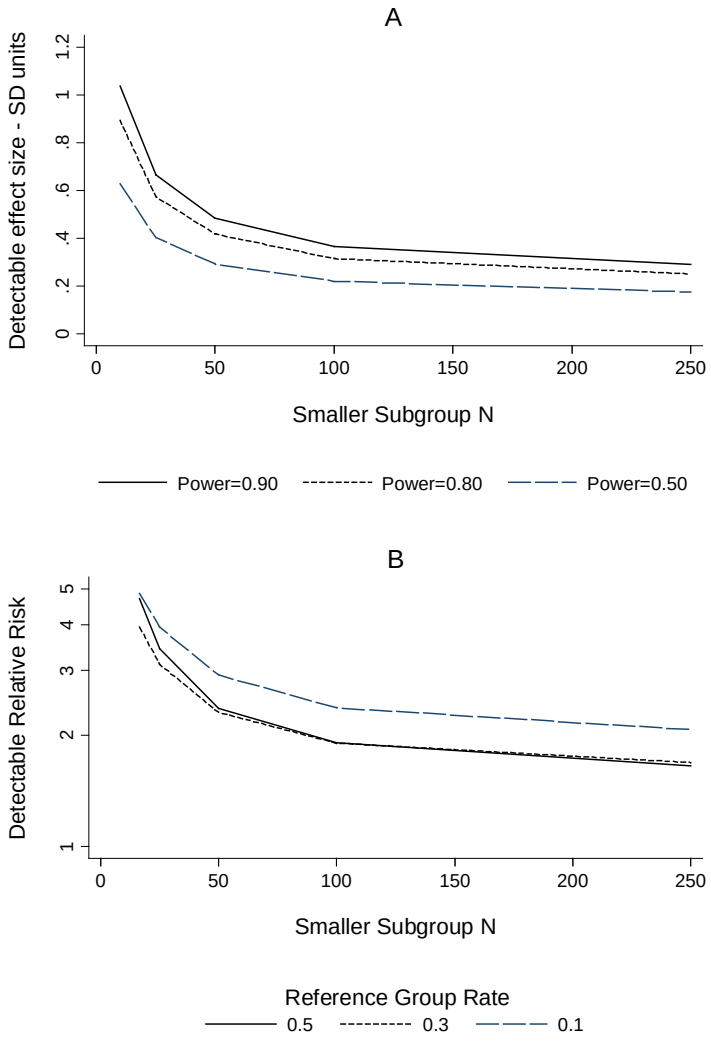
† SD_b defined as standard deviation (SD) of the mean baseline outcome; CV defined as the coefficient of variation of the baseline outcome data; Δ defined as the mean change in outcome from baseline to 48 weeks; SD_Δ defined as the SD of the change in the outcome measure at 48 weeks; r defined as the intra-class correlation of the measure across time; MDE defined as the minimal detectable effect size (in SD_Δ units) at 80% power, 0.05 type I error, and r, the correlation between baseline and 48 week measures.

‡ The smaller subgroup is compared to the larger one: DM is all diabetes (N=120) vs idiopathic (N=200), T2DM is Type 2 Diabetes (N=50) vs Type 1 (N=70), Post-Nissen is Post Nissen Fundoplication (N=80) vs others with gastroparesis (N=320); all 6 subgroups must have delayed retention at 4 hour on baseline GES. Not Delayed (N=100) vs Delayed retention (N=400) at 4 hour baseline GES.

§ MDE, expressed in SD_Δ units, determined from Stata v12 software's "Sample size and power determination for tests of means with repeated measures" (***sampsi_repmeas***) and the method, ANCOVA, correcting for the mean at baseline. Conversion of the MDE to units of the outcome is computed by multiplying the MDE in Table 6 by Δ (mean change of outcome).

As a further aid to sample size justification for analyses related to GpR 2 aims, Figure 1, Panel A shows detectable effect sizes in multiples of SD as a function of the size of the smaller of two subgroups with Type I error = 0.05 and 3 choices for statistical power: 0.50 (inadequate power), 0.80 (good power), and 0.90 (excellent power). Given the subgroup size in the smaller comparison group vs a larger subgroup ($500 - N_{smaller}$) and outcome measure of interest, Panel A of Figure 1 can be used to find the minimum clinically important detectable effect in SD units; the effect size can be easily converted to the units of the outcome measure of interest using Table 6 (see footnote §). If the comparison subgroup size is smaller than specified above, then the power will be less than 0.80 for that detectable effect size, or fixing the power at 0.80, the detectable effect size will be larger.

Figure 1. (A) Detectable Effect Size (in SD units) with Power = 0.90, 0.80 and 0.50 and (B) Detectable Relative Risk with Power = 0.80 and Reference Group Effect Rates of 0.5, 0.3 and 0.1 for Analyses Comparing Two Subgroups with Type I error = 0.05 and Total Sample Size of 500



Other studies may require categorical outcomes rather than continuous outcomes. In most cases, a binary event can be defined as the outcome measure in order to judge the adequacy of the sample size, which depends on the Type I error, power, sizes of the subgroups to be compared, and the event rate in the reference subgroup. Table 7 contains information on event rates in reference groups for comparisons of important categorical outcome measures derived from the database from the first phase of the GpR, some of which indicate improvement over time at 48 weeks (GCSI, PAGI-QOL, SF-36, BDI) and others indicate status at baseline (gastric failure, BMI category, CRP/ESR inflammatory markers, and degree of gastric retention). This mix of important variables is not exhaustive, but the general approach illustrated applies to other categorical outcomes not in Table 7.

Table 7. Event Rates for Binary Outcome Measures in Reference Subgroups of Interest

Binary Outcomes	Smaller Subgroup* Gastroparesis			Not Delayed‡
	Diabetes	T2DM	Post-Nissen†	
	Rate	Rate	Rate	Rate
Improvement at 48 weeks from baseline:				
Improvement in GCSI (- 0.75 point or less)	0.32	0.29	0.27	0.39
Improvement in PAGI-QOL (0.5 point or more)	0.32	0.30	0.17	0.48
Improvement in SF-36 mental (3.0 points or more)	0.42	0.40	0.33	0.43
Improvement in SF-36 physical (3.0 points or more)	0.42	0.47	0.50	0.41
Improvement in BDI (-5.0 points or less)	0.26	0.24	0.23	0.26
At baseline:				
Gastric failure vs Mild/Compensated	0.44	0.39	0.41	0.22
Not overweight (BMI > 25 kg/m^2) vs Overweight	0.34	0.14	0.71	0.39
Inflammation§ vs not	0.55	0.57	0.35	0.35
Severe 4 hr Gastric Retention vs < 35% retention	0.45	0.32	0.52	*n/a*

* The smaller subgroup is compared to the larger one: DM is all diabetes (N=120) vs idiopathic (N=200), T2DM is Type 2 Diabetes (N=50) vs Type 1 (N=70), Post-Nissen is Post Nissen Fundoplication (N=80) vs others with gastroparesis (N=320); all 6 subgroups must have delayed retention at 4 hr on baseline GES. Not Delayed (N=100) vs Delayed retention (N=400) at 4 hour baseline GES.

† Post-Nissen Fundoplication subgroup outcome distributions estimated from the GpR post-surgical group (N=23).

‡ Delayed emptying defined as % gastric retention on scintigraphy at 2 hrs >60% OR gastric retention at 4 hrs > 10%

§ Inflammation defined as CRP > 1.0 mg/dL and /or ESR > 20 mm/hr

¶ Event rates > 0.5: Use 1 – (event rate) to determine power for a given detectable relative risk in Figure 1, Panel B

The event rates in Table 7 can use be used in combination with Figure 1, Panel B to find the minimum clinically important relative risk when comparing two subgroups of varying sizes with power = 0.80 and Type I error = 0.05. Detection of relative risks of 2.0 or smaller is possible for event rates near 0.5, even for subgroups as small as 100. Similar sizes of subgroups are needed for event rates near 0.3; if the event rate is as low as 0.1, only relative risks greater than 2.5 will be detectable. Since for this graph, the 2 subgroup sizes must add to 500, then if the combined subgroup size is smaller than 500, the power to detect that relative risk will be less than 0.80.

The calculations presented in Figure 1 assumed two-sided Type I error = 0.05, and a total sample size = 500. The detectable effect size plot in Panel A of Figure 1 assumed power of 0.5, 0.8, and 0.9, and used as the test statistic an ANCOVA with a correlation between baseline and follow-up measures = 0.5 and used Stata (StataCorp 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) for the calculations. The detectable relative risk plot in Panel B of Figure 1 assumed power = 0.80 and an uncorrected chi-square as the test statistic using the sample size

software of Dupont and Plummer (Dupont W, Plummer WD: Power and Sample Size Calculations: A Review and Computer Program, Controlled Clinical Trials 1990; 11:116-28).

Since the Gastroparesis Registry 2 will generate longitudinal data over time, analytic methods must account for, as applicable, time to events, repeated measurements, counts, or other discrete responses. For time to event data, we will use the Cox proportional hazards regression model with covariates tailored to the hypothesis under investigation. For hypotheses involving repeated measurements, events, counts or other discrete responses, we will use either of two approaches: (1) generalized linear models with generalized estimating equations (GEE) with robust variance estimation to account for the clustering; or, (2) multilevel generalized linear mixed models with random coefficients to account for within patient clustering as well as other sources of variations like clinic effects.

8. Human participants issues

8.1. Overview and IRB approval

The Gastroparesis Registry 2 study is not a treatment study. Patients will continue to receive care for their clinical condition. The study protocol, consent forms, and data collection forms will be submitted to each clinical center's IRB and to the SDRC's IRB. Additionally, each clinical center will submit to their IRB any recruitment materials to be used at their site. A site may not initiate any patient contact about the Gastroparesis Registry 2 until the site has IRB approval and the SDRC has certified the site for initiation of patient activities. Consent forms must have IRB approval. Sites must provide the SDRC with copies of the initial IRB approval notice and subsequent renewals, as well as copies of the IRB approved consent statements. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (Black or African American, Hispanics or Latino, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander) as well as non-Hispanic white subjects. We anticipate that the patients recruited from diverse sources, including community and tertiary referral populations, will capture the entire spectrum of gastroparesis.

All participants enrolled in the GpR 2 will receive a standard of care for gastroparesis and identified associated medical problems as defined by the GpCRC Steering Committee (see SOP IV: Standard of Care for Patients with Gastroparesis). This will include provision of health care counseling and educational materials at enrollment and on an ongoing basis during follow-up.

8.2. Informed consent

Template consents will be prepared for the study. Sites may reformat and reword information to conform to their local requirements. A signed consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record.

8.3. Participant confidentiality

All laboratory specimens, evaluation forms, reports, and other records that are part of the study data collection and entry materials will be identified by coded number only to maintain participant confidentiality. All records will be kept in locked file cabinets with access limited to the GpR 2 investigators. All computer entry and networking programs will identify patients by patient identification number. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB or DSMB. Clinical information may be reviewed during site visits, but use of personal identifiers will be avoided. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and NIH requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

8.4. Concerns related to specimen banking

It is anticipated that serum, plasma, and DNA from the participants will be stored for future studies related to gastroparesis and possibly other diseases. These samples will be stored in NIDDK central repositories. The GpCRC Steering Committee will develop specific guidelines addressing the issues such as (a) obtaining a separate informed consent, (b) storage, (c) transportation of the material, (d) who will have access to the material, and (e) what investigations are to be conducted.

8.5. Participant withdrawal

If a participant chooses to withdraw from the GpR 2, all data collected up to the point of withdrawal will remain in the GpR 2, but no further data may be collected. This is consistent with HIPAA guidelines and regulations.

9. Safety monitoring

GpR 2 is an observational multicenter study and each participating clinical center will follow local IRB guidelines to monitor and report unanticipated or adverse events to ensure participant safety. Since the adverse event definitions and reporting requirements for unanticipated events may differ at each participating site, the GpR 2 definitions and procedures for adverse event reporting are designed to satisfy a wide spectrum of interpretations of the Common Rule requirements.

9.1. Risks related to participation

Questionnaires: The questionnaires ask about symptoms, quality of life, and exercise and eating habits, and require approximately 2 hours to complete. If patients have high scores on the psychological questionnaires, they could be referred to a clinical psychologist or psychiatrist.

Blood drawing*:* Blood draw may cause mild discomfort, such as swelling, temporary sensation of pain, burning, or a bruise that may develop and last for a few days. Less common risks include a blood clot at the site of puncture, swelling of the vein and surrounding tissues, and possible bleeding from the puncture site.

***Electrogastrography (EGG) with nutrient bar meal or water load*:** EGG recording involves placement of EGG electrodes on the abdominal skin. There may be some soreness in removing the EGG electrodes. The nutrient bar used for the caloric meal has approximately the same caloric intake as the egg sandwich meal for a gastric emptying test. During the water load test, the patient drinks water until they are full. Diabetics will have their glucose checked at the beginning and the end of the tests, with appropriate measures being taken if hypoglycemia or hyperglycemia is detected.

Wireless motility capsule: The SmartPill® wireless motility capsule transit test used in this protocol is approved for patient evaluation and is performed at many institutions for evaluation of patients. Risks of the ingestion and passage of the SmartPill® capsule through the GI tract are minimal. The capsule is usually excreted from the body in 30 hours in normal subjects. There have been no complications in the 326 subjects who have ingested the SmartPill® in the clinical studies for gastroparesis and constipation. In all subjects, the capsule was evacuated. In one patient with gastroparesis, there was prolonged gastric retention of the SmartPill® in the stomach. In our study, patients will keep a diary documenting bowel movements. If the subject retrieves the SmartPill®, it will be suggested that they return it to the study site. In addition, the result of the SmartPill® test will often indicate elimination of the capsule by a decrease in temperature. This was done in most subjects undergoing a completed clinical trial for gastroparesis. In a recent study, all patients with constipation passed the SmartPill®[50].

Autonomic function testing: Autonomic testing in this study uses an electrocardiogram to measure cardiac electrical activity. There may be some discomfort when removing the recording pads on the chest. In addition, autonomic function testing takes blood pressure and pulse when the patient changes from a lying down to standing position. Some patients may develop lightheadedness when standing. If this happens, the patient will promptly lie down.

Gastric emptying scintigraphy test: The gastric emptying of solids and liquids for enrollment into the registry is performed for the patient's clinical evaluation. In this study, a repeat gastric emptying

scintigraphy of solids only is performed 48 weeks after enrollment. *Radiation Exposure.* The effective dose to a patient per test from the 0.5 -1 microcurie Tc-99m egg meal is estimated to be 37-53 millirem (adult male and adult female, respectively), assuming normal transit times. This is below the total average annual dose a person in the United States receives from natural background radiation. Natural annual background exposure averages 300 millirem (3 mSv). Although no immediate harmful effects are expected, there is a very small, theoretical (that means not proven) long-term health risk from this small amount of radiation exposure. The amount of radiation to which participants may be exposed to could be higher or lower than this value depending on their body weight or size.

General risks: The condition of the patient may or may not get better or may become worse while they are in the Gastroparesis Registry 2 study. This is not a treatment study. During the study, patients will still be getting clinical care by their physician.

Stopping medications for gastroparesis: For participation in this study, prescribed medications may need to be stopped temporarily for the testing required for the study: gastric emptying tests, wireless motility capsule, and electrogastrography. These medications include those that speed up stomach emptying. Medicines like this include metoclopramide (Reglan), erythromycin, and domperidone (Motilium). Medications that slow down the movement through the GI tract include anticholinergic agents such as Levsin and NuLev and pain medications such as Percocet, Tylenol #3, Vicodan, Dilaudid, Fentanyl patch, and others. If patients are taking any of these medications and they are helping their symptoms, if they are stopped, their symptoms may return or worsen. The stopping of medications is for a short time only (1 week) and is not felt to cause any undue hardship on the patient.

Safety issues related to patient privacy: There is a potential risk to patient privacy. Every effort will be made to maintain patient's privacy. It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity is maintained in their data submission to the Scientific Data Research Center. Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses (i.e., available only to local clinic staff). All study material will be maintained in strict confidence.

9.2. Monitoring

An independent Data and Safety Monitoring Board (DSMB), appointed by the NIDDK, is responsible for providing input to the NIDDK regarding approval of the protocol for the GpR 2 study and for monitoring the accumulated interim data as the study progresses to assess patient safety and data quality. The DSMB is a multi-disciplinary group with a written charge provided by the NIDDK. The DSMB serves in a consultative capacity to the NIDDK, which will communicate with the investigators regarding the DSMB deliberations.

The DSMB meets to provide input to the NIDDK regarding approval of the protocol and supporting documents. After the study commences, the DSMB meets twice a year to review safety data and other performance issues. The DSMB may request more frequent meetings if necessary to fulfill its charge or at the discretion of the NIDDK Program Official. It may also request additional safety reports on a more frequent basis. For example, all serious adverse events are reported to the DSMB quarterly for their consideration and recommendations as they occur. The DSMB Charter provides more specific information and defines the roles, responsibilities, and activities of the DSMB.

9.3. Adverse event definitions and reporting

The Gastroparesis Registry 2 study will monitor and report adverse events to ensure patient safety in compliance with 45 CFR Part 46, Subpart A the "Common Rule". The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants, IRBs, appropriate institutional officials, and the Department or Agency Head The FDA Guidance for Clinical Investigators on Adverse Event Reporting to IRBs - Improving Human Subject Protection[63] document also provides recommendations for adverse event reporting, while specifically focusing on unanticipated event reporting. The FDA recommends that careful review of whether an adverse event is an unanticipated event that must be reported to IRBs should be considered while adhering to local IRB guidelines. While the definitions and monitoring procedures apply most directly to clinical trials, all patients in the Gastroparesis Registry 2 will be monitored for occurrence of adverse events thought to be associated with Gastroparesis Registry 2 participation. Any adverse events that occur will be reported as appropriate. When applicable, signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or severe using Version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[64]

Definitions

Adverse event. An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

Life-threatening adverse event. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event (SAE). An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events will be recorded on study data forms whether or not they are thought to be associated with Gastroparesis Registry 2 participation or prior participation in a GpCRC study. Adverse events may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits.

Serious adverse events must be reported upon discovery at the clinical center. This will involve completing a data form describing the severity and details of the event together with a memo

summarizing the circumstances of event and the current status of the patient, which must be emailed or faxed to the Scientific Data Research Center.

Review of adverse events by the DSMB

Summary data of adverse events will be monitored by the DSMB at its semi-annual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events by clinic, or in other subgroups requested by the DSMB. Where applicable, signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or severe using the Common Terminology Criteria for Adverse Events.[64]

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

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11. Appendix

11.1. Participating centers

Clinical Centers

- Johns Hopkins University Medical Center, School of Medicine
  - *California Pacific Medical Center (2012-Aug 2017)*
  - *Stanford University (2012-Aug 2017)*
- Massachusetts General Hospital (effective Oct. 2016)
- Temple University
- Texas Tech University Medical Center
- *University of Michigan (2012-Aug 2017)*
- University of Louisville
- Wake Forest University Medical Sciences

Scientific Data Research Center:

- Johns Hopkins University, Bloomberg School of Public Health

Pathology Center:

- The Mayo Clinic

National Institutes of Health:

- National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Central Repositories:

- Biosample repository: Fisher BioServices
- Genetics repository: Rutgers University Cell and DNA Repository (RUCDR)
- Data repository: Information Management Services (IMS)

11.2. Data collection schedule

	Screening visits	**Follow-up visits: Weeks from enrollment**									
	Screen and enroll	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**
Consent, HIPAA authorization	X	.	.	.	.	.	.	.	.	.	.
Baseline medical history	X	.	.	.	.	.	.	.	.	.	.
Follow-up medical history	.	X	X	X	X	X	X	X	X	X	X
Upper gastrointestinal endoscopy	X	.	.	.	.	.	.	.	.	.	.
Gastric emptying scintigraphy*	X	.	X	.	.	.	.	.	.	.	.
PAGI-SYM questionnaire	X	X	X	X	X	X	X	X	X	X	X
PAGI-QOL questionnaire	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X
EGG with SmartBar®, SmartPill®	X	.	.	.	.	.	.	.	.	.	.
Autonomic function testing with ECG	X	.	X	.	.	.	.	.	.	.	.
EGG and water load test	X	.	X	.	.	.	.	.	.	.	.
Rome III questionnaire	X	.	X	.	X	.	X	.	X	.	X
Eligibility confirmation	X	.	.	.	.	.	.	.	.	.	.
Neuropathy Total Symptom Score-6	X	X	X	X	X	X	X	X	X	X	X
Beck Depression Inventory	X	X	X	X	X	X	X	X	X	X	X
STAI: Self-evaluation questionnaire	X	X	X	X	X	X	X	X	X	X	X
Patient Health Questionnaire (PHQ-15)	X	X	X	X	X	X	X	X	X	X	X
Nausea Profile and vomiting questionnaire	X	X	X	X	X	X	X	X	X	X	X
Block 2005 Food Questionnaire	X	.	X	.	X	.	X	.	X	.	X
SF-36v2 Quality of Life	X	.	X	.	X	.	X	.	.X	.	.X
Block Energy Expenditure Survey	X	.	X	.	X	.	X	.	X	.	X
Brief Pain Inventory	X	.	X	.	X	.	X	.	X	.	X
GpCRC abdominal pain questionnaire	X	.	X	.	X	.	X	.	X	.	X
Interim event form as needed (A)	.	A	A	A	A	A	A	A	A	A	A
Hematology, metabolic/ lipid panel, ANA, hs-CRP, ESR, TSH, vitamin B12 & vitamin D levels	X	.	.	.	.	.	.	.	.	.	.
HbAlc†	X	X	X	X	X	X	X	X	X	X	X
Serum, plasma banking	X	.	X	.	X	.	X	.	X	.	X
DNA for banking	X	.	.	.	.	.	.	.	.	.	.

Hematology (complete blood count): white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count

Comprehensive metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, and liver panel including total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

Lipid panel: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides

ANA= antinuclear antibody, hs-CRP= high sensitivity C-reactive protein, ESR= erythrocyte sedimentation rate, TSH=thyroid stimulating hormone, vitamin B12 and 25-hydroxy vitamin D levels

* The gastric emptying scintigraphy prior to enrollment is for solids and liquid emptying; whereas the gastric emptying test at 48 weeks will be quantitating gastric emptying of solids only.

† HbA1c is required during screening for all and at each follow-up visit for diabetic patients only

11.3. Whole blood draw schedule

	Study visits (week)						
Procedure	**screening/ enrollment**	**48**	**96**	**144**	**192**	**240**	**Total**
Hematology, metabolic/ lipid panel, ANA, hs-CRP, ESR, TSH, vitamin B12 & D levels	25	.	.	.	.	.	**25**
HbA1c* (5 mL x 11 visits for diabetics)	5	5	5	5	5	5	***55**
HbA1c* (non- diabetics)	5						5
Fasting† plasma, serum banking	20	20	20	20	20	20	**120**
DNA banking	20	.	.	.	.	.	**20**
Total (mL) (diabetics)	**70**	**25**	**25**	**25**	**25**	25	**220**
Total (mL) (non-diabetics)	**70**	**20**	**20**	**20**	**20**	20	**170**

Hematology (complete blood count): white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count

Comprehensive metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, total protein albumin, and liver panel including total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

Lipid panel: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides

ANA= antinuclear antibody, hs-CRP= high sensitivity C- reactive protein, ESR= erythrocyte sedimentation rate, TSH= thyroid stimulating hormone, vitamin B12 and 25-hydroxy vitamin D levels

*HbA1c is required for all during screening and will be obtained at each follow-up visit (weeks 24, 48, 72, 96, 120, 144, 168, 198, 216, and 240) for diabetic patients only

†Fasting is defined as nothing by mouth except water in the 8 hours prior to blood draw. Fasting visits need to be scheduled for early morning and the patient must attend the visit after an overnight fast of at least 8 hours

11.4. Glossary

ALT	-	alanine aminotransferase
ANA	-	anti-nuclear antibody
ANS	-	autonomic nervous system
AST	-	aspartate aminotransferase
BMI	-	body mass index (kg/m^2)
BUN	-	blood urea nitrogen
CPT	-	Child-Pugh-Turcotte score
CRP	-	C-reactive protein
CTT	-	colon transit time
CTCAE	-	Common Terminology Criteria for Adverse Events
DSMB	-	Data and Safety Monitoring Board
EGD	-	esophagogastroduodenoscopy
EGG	-	electrogastrography; electrogastrogram
FD	-	functional dyspepsia
GCSI	-	Gastroparesis Cardinal Symptom Index
GCSI-DD	-	Gastroparesis Cardinal Symptom Index-Daily Diary
GEE	-	generalized estimating equations
GET	-	gastric emptying test
GI	-	gastrointestinal
Gp	-	gastroparesis
GpCRC	-	Gastroparesis Clinical Research Consortium
GpR	-	Gastroparesis Registry
GpR 2	-	Gastroparesis Registry 2
HbA1c	-	glycosylated hemoglobin A1c
HIPAA	-	Health Insurance Portability and Accountability Act
ICC	-	interstitial cells of Cajal
IRB	-	Institutional Review Board
MI	-	motility indices
MMC	-	migrating motor complex
NIDDK	-	National Institute of Diabetes and Digestive and Kidney Diseases
NO, NOS	-	nitric oxide, nitric oxide synthetase
PAGI-SYM	-	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index
PAGI-QOL	-	Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life
ROC	-	receiver operating characteristic
SAE	-	serious adverse event
SB	-	small bowel
SBTT	-	small bowel transit time
SDRC	-	Scientific Data Research Center
SOP	-	standard operating procedures
TSH	-	thyroid stimulating hormone
VAS	-	visual analog scale
WBC	-	white blood cell count
WMC	-	wireless motility capsule

11.5. Document History

Gastroparesis Registry 2 Protocol (March 2, 2012)

Gastroparesis Registry 2 Protocol (October 9, 2013)
§ Design Synopsis:

- Revised **Recruitment targets** to: A total of 500 patients are to be enrolled in the Gastroparesis Registry 2 (GpR 2): 270 new patients and 230 patients continuing from the first Gastroparesis Registry
- Revised sample size from 750 to 500

§ 1.5. Gastroparesis Clinical Research Consortium

- Updated the number of satellite clinical centers to two

§ 4.3 Target composition

- Revised the composition for new recruitment goal: Assuming the goal of 500 patients are entered into GpR 2 and assuming similar types of enrollment as in the first registry this will result in the following types of patients: 200 idiopathic gastroparesis patients, 50 idiopathic patients with normal gastric emptying, 120 with diabetic gastroparesis, 30 diabetic patients with normal gastric emptying, 80 post-Nissen gastroparesis patients, and 20 post-Nissen patients with normal gastric emptying

§ 6.7.4 Autonomic function testing

- Revised the section to reflect the ANSAR ANX 3.0 system testing protocol

§ 7. Statistical design and considerations

- Revised the target numbers for the individual groups to be analyzed
- Updated tables 6 and 7

§ 11.1 Participating Centers

- Added University of Louisville and Johns Hopkins University
- Removed University of Mississippi
- Changed contractor for NIDDK Data Repository

§ 11.5 Document History added

Gastroparesis Registry 2 Protocol (October 12, 2016)
§ Design Synopsis:

- Revised **Follow-up period:** to 48-240 weeks (1-5 years); up to 5 years follow-up depending on date of enrollment
- Revised **Screening and Enrollment:** added visits at 216 and 240 weeks
  Follow-up visits will occur at 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 weeks

§ 1.2 Gastroparesis Clinical Research Consortium

- Changed Data Coordinating Center to Scientific Data Research Center and DCC to SDRC throughout
- Removed the specific number of clinical centers

§ 1.4 Gastroparesis Registry
- Changed follow-up times by one year: GpR 2 is to have up to five years of follow-up data for patients in the GpR 2 and up to 9 years of follow-up data for patients who participated in the initial GpR study

§ 6.3 Follow-up visits:
- Added follow-up visits at 216 and 240 weeks

§ 8.1 Overview and IRB approval
- Changed DCC to SDRC throughout

§ 9.1 and 9.3
- Changed Data Coordinating Center to Scientific Data Research Center throughout

§ 11.1 Participating Centers
- Added Massachusetts General Hospital

§ 11.2 Data Collection Schedule
- Added follow-up visits for weeks 216 and 240

§ 11.3 Blood collection schedule
- Added blood collection for HbA1c, plasma and serum banking at f240 visit
- Clarified blood collection amounts for HbA1c for patients with and without diabetes

§ 11.4 Glossary
- Removed Data Coordinating Center; added Scientific Data Research Center