GpCRC

Gastroparesis
Clinical Research Consortium

Gastroparesis Registry (GpR)

Protocol

Confidential

1 December 2009

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Gastroparesis Registry Protocol

Design synopsis

Objectives

- To establish a registry of patients with gastroparesis for the study of the epidemiology, etiology, and degree of morbidity associated with gastroparesis.
- To prospectively and systematically follow a well-characterized cohort to define the natural history and clinical course of gastroparesis.
- To provide a reliable resource for rapid recruitment of well-characterized patients with gastroparesis for therapeutic clinical trials, pathophysiological, molecular, histopathologic, or other ancillary studies. These subsequent clinical trials or other ancillary studies will each be conducted under separate study protocols with separate consent processes.

Type of study

- Observational

Population

- Patients at least 18 years of age
- Gastroparesis patients with delayed gastric emptying
- Patients without nausea, but with other symptoms suggestive of gastroparesis and with delayed gastric emptying
- Patients with symptomatic nausea and vomiting, but without delayed gastric emptying

Inclusion criteria

- Symptoms of gastroparesis of at least 12 weeks duration (do not have to be contiguous) with varying degrees of nausea, vomiting, abdominal pain, early satiety, postprandial fullness
- Completion of a 4-hour scintigraphic low fat Egg Beaters gastric emptying study
  - Patients with either or both abnormal 2 hour (>60% retention) and 4 hour (>10% retention) gastric emptying will be enrolled and classified as definite gastroparesis
  - Patients with normal gastric emptying, but with symptoms of gastroparesis may be enrolled and classified as possible gastroparesis
- Age at least 18 years at initial screening visit
- Ability and willingness to participate in follow-up

Exclusion criteria

- Inability to comply with or complete the gastric emptying test by scintigraphy
- Presence of other conditions that could explain the patient's symptoms:
  - Pyloric or intestinal obstruction
  - Active inflammatory bowel disease
  - Eosinophilic gastroenteritis
  - Neurological conditions such as increased intracranial pressure, space occupying or inflammatory/infectious lesions
  - Acute liver failure
  - Advanced liver disease
  - Acute renal failure
  - Untreated chronic renal failure (serum creatinine >3 mg/dL)
- Total or subtotal gastric resection (patients with prior fundoplication or postvagotomy

gastroparesis after pyloroplasty or antrectomy with Billroth I, Billroth II, or Roux-en-Y gastrojejunostomy 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

Study duration
- Recruitment: Up to 700 patients until 31 March 2010
- Follow-up: 48-192 weeks (1-4 years)

Visit schedule
- Screening/entry into Gastroparesis Registry: enrollment must occur within 16 weeks of initiation of screening
- Follow-up visits at 16 weeks, 32 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, 128 weeks, 144 weeks, 160 weeks, 176 weeks, and 192 weeks

Outcome measures
- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
- Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
- Scintigraphic gastric emptying test
- HbA1c and glucose levels
- Body mass index
- Health related quality of life (SF-36)
- Brief pain inventory
- Nutritional intake
- Investigator Derived Independent Outcome Measure Scores (IDIOMS)
- Management of gastroparesis
- Beck Depression Inventory
- State Trait Anxiety Inventory
- Rome III questionnaires
- Survival at the end of study period

Sample size
- Separately justified for each hypothesis
- Specification of primary outcome measure for hypothesis
- Type I error ≤ 0.05 and power ≥ 0.80
- Specification of primary comparison groups
- Specification of minimum clinically meaningful effect size for the primary outcome
- Specification of method for handling missing data
- No adjustments for multiplicity of comparisons

1. Background and rationale

1.1. Historical background

Gastroparesis is a devastating disease affecting predominantly young women (females outnumber males by a ratio of 4:1, with an average 34 years of age).[1] The symptomatic profile of gastroparesis includes nausea (90% of patients), vomiting (>80%), pain (~50%), early satiety (60%) and bloating (75%) and 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 at large. Gastroparesis remains difficult to treat, in large part because of the lack of knowledge of the underlying pathophysiology of this disease. 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, the lack of generally available, reliable methods for physiological testing and the inaccessibility of tissue for histopathological correlation. Given the complexity of the problem, and the profound degree of morbidity currently associated with this disorder, a compelling need exists to study patients in a systematic, concerted manner. Such studies can best be achieved by recruiting patients and collecting data from multiple centers as part of a large network of investigators focused on this disorder. In recognition of this fact, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through the mechanism of RFA-DK-05-004, established the Gastroparesis Clinical Research Consortium in 2006.

1.2. Gastroparesis Clinical Research Consortium

The Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of six clinical centers, one satellite center, and one Data Coordinating Center (DCC). Clinical centers are responsible for proposing protocols, participating in their overall development, recruiting patients, conducting the research, and disseminating research findings. The individual clinical centers participate in a cooperative and interactive manner with one another and with the DCC in all aspects of the GpCRC. The DCC supports protocol development; provides sample size calculations, statistical expertise, forms, and data analysis; supports manuscript preparation; and provides overall study coordination and quality assurance, including coordination of the activities of the Data and Safety Monitoring Board, the Steering Committee and other standing committees. The DCC also collaborates with the NIDDK Biosample (plasma, serum) and Genetics (DNA) Repositories for specimen banking.

A Steering Committee composed of the principal investigators of each clinical center in the Network, the principal investigator of the DCC, and the NIDDK Project Scientist represents 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.

1.3. Mission of the GpCRC and overall objectives

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

1.4. Gastroparesis Registry

In order to achieve part of the overall objectives of the GpCRC, the GpCRC will construct and implement the **Gastroparesis Registry (GpR)** as an observational study to clarify the epidemiology, natural history, clinical course, and other outcomes of gastroparesis. The Gastroparesis Registry will consist of patients that meet specific criteria of gastroparesis that are recruited at the six clinical centers and satellite centers of the GpCRC. The Gastroparesis Registry will be used to collect data on patients with gastroparesis for the study of the epidemiology, etiology, and impact of gastroparesis. The patients in the Gastroparesis Registry will be a well-characterized cohort that will be followed to examine the natural history and clinical course of gastroparesis. Patients enrolled in the Gastroparesis Registry will be evaluated and treated according to the standards of care for this disorder, which has been formulated by the American Gastroenterological Association and the American Motility Society. The Gastroparesis Registry standards of care have been outlined by the GpCRC investigators and will be implemented through the study Standard Operating Procedures (SOPs). The Gastroparesis Registry will also serve as a means to readily identify well-characterized patients for enrollment in subsequent clinical and translational research studies. Fasting plasma, serum, and DNA samples will be collected and stored for ancillary studies of etiology and pathogenesis of gastroparesis.

2. Objectives and hypotheses

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

- To establish a registry of patients with gastroparesis for the study of the epidemiology, etiology, and degree of morbidity associated with gastroparesis.
- To prospectively and systematically follow a well-characterized cohort to define the natural history and clinical course of gastroparesis.
- To provide a reliable resource for rapid recruitment of well-characterized patients with gastroparesis for therapeutic clinical trials, pathophysiological, molecular, histopathologic, or other ancillary studies. These subsequent clinical trials or other ancillary studies will each be conducted under separate study protocols with separate consent processes.

Detailed epidemiological, clinical, physiological and patient outcome data will be collected in the GpR, 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.

2.1. Hypotheses to be tested

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

- A grading system (mild, compensated, chronic failure) for gastroparesis can be developed that predicts the subsequent clinical course of patients.
- Most patients with gastroparesis have a disease course with episodes of exacerbations.
- The delay in gastric emptying predicts the clinical course of patients with gastroparesis.
- 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 no correlation with symptoms.
- Markedly accelerated early emptying (more than 75% emptied at 1 hour) relates to symptoms, whereas mildly accelerated emptying (50-75% emptied at 1 hour) has no correlation with symptoms.
- Weight loss in gastroparesis correlates with reduced fasting ghrelin levels.

- The clinical course of gastroparesis will vary 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 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.
- Symptom progression in diabetic gastroparesis relates to worsening autonomic dysfunction, dysrhythmias, fundic relaxation impairment, and visceral hyperalgesia.
- Control of gastropathy symptoms in diabetes (as opposed to improved emptying) leads to better glycemic control (decreased hemoglobin A1c).
- Patients with type 1 diabetes mellitus and type 2 diabetes mellitus with HbA1c greater than 8.5%, 7.5 to 8.5% and 6.5 to 7.5% will have different upper GI symptoms, different gastric dysrhythmias and different rates of gastric emptying.
- The clinical course of idiopathic gastroparesis patients with positive autoimmune markers will differ from patients without the autoimmune markers.
- Symptom resolution in postviral gastroparesis relates to improved gastric emptying, gastric dysrhythmias, fundic accommodation, visceral hyperalgesia.
- Symptoms in postfundoplication gastroparesis show improvement over the first 2 post-operative years that does not relate to improved vagal function (i.e. non-vagal pathways are recruited).
- Severe abdominal pain is infrequently the predominant symptom in patients with gastroparesis.
- Lifetime stressful events and a history of abuse relate to symptom severity in gastroparesis.
- Symptoms of gastroparesis fluctuate over time and worsen in the last half of the menstrual cycle.
- A subset of patients with gastroparesis have evidence of an inflammatory process. These patients have a slow downhill course.
- Nausea, but not vomiting or abdominal pain, is associated with the decreased quality of life in patients with gastroparesis.
- Specific genetic markers can be identified in patients with familial forms of gastroparesis.
- A heritable component of gastroparesis is detectable in patients with type 2 diabetes mellitus.
- 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.
- A subset of patients with gastroparesis will also have subtle or overt dysmotility of the small and/or large intestine which will adversely impact prognosis.
- Patients with type 2 diabetes mellitus have high prevalence of upper GI symptoms, gastric dysrhythmias, and gastroparesis (comparable to literature for patients with type 1 diabetes mellitus).

3. Scientific background

Gastroparesis is a disorder of gastric neuromuscular sensory and motor function that affects patients (most of whom are women) in the prime of their life. Inadequate understanding about the pathogenesis of this condition, coupled with a general lack of awareness of the disease amongst most clinicians has led to a haphazard and often ineffective approach to treatment. The traditional concept of gastroparesis being defined as a disorder of delayed gastric emptying has dominated physician thinking for decades and has influenced the management approaches to these patients. 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. Second, prokinetic agents are frequently ineffective as sole therapeutic agents. Third, preoccupation with gastric emptying has distracted attention 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.[2]

3.1. Clinical symptoms

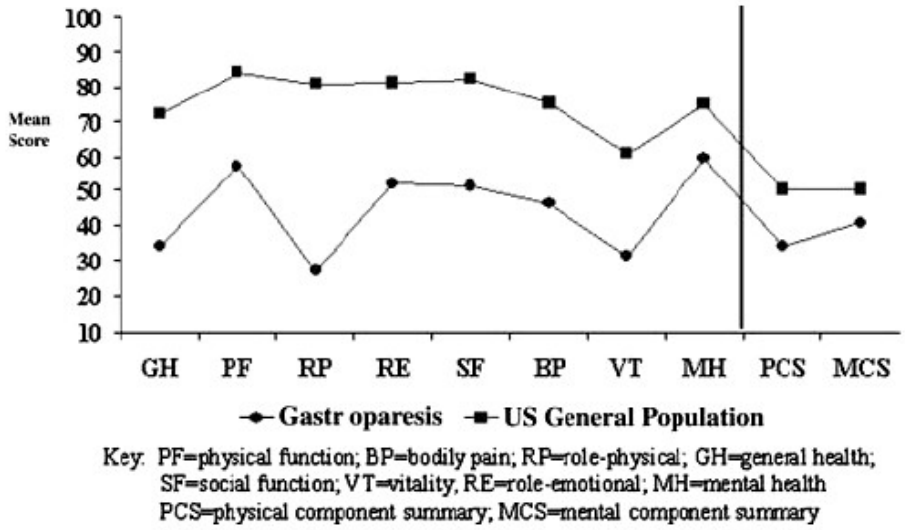
Although nausea and vomiting are the most well recognized and frequent symptoms of gastroparesis (Table 1), epigastric pain can be the most challenging and resource-consuming issue to address in selected individuals. In the more severe cases, the pain of gastroparesis may result in narcotic dependence.

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%

Although there is a paucity of data on the true prevalence and incidence of gastroparesis in the community, it is clear that it imposes a huge burden of disease on its sufferers. Indeed, one can only extrapolate from personal experience of what it must feel like to experience chronic unrelenting nausea, abdominal pain, and an inability to enjoy even simple foods. This is reflected in quality of life surveys such as that shown in Figure 1.

Figure 1. SF-36 quality of life scores in patients with gastroparesis.[3]



3.2. Epidemiology and natural history

The prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition.[4] Diabetes mellitus is the most common systemic disease associated with gastroparesis. A similar number of patients present with gastroparesis of an idiopathic nature. Postsurgical gastroparesis, often with vagotomy or damage to the vagus nerve, represents the third most common etiology of gastroparesis. Published data from specialized centers 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.[5,6] Furthermore, 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.[7]

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. The natural history of gastroparesis is poorly understood and, even in diabetics, symptoms may fluctuate considerably with many patients reporting 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.[9]

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. Many therapies for gastroparesis relieve symptoms only in subsets of patients or are associated with significant side-effects. 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.[3,9] 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 simpler 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

3.3. 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 (Figure 2). 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.

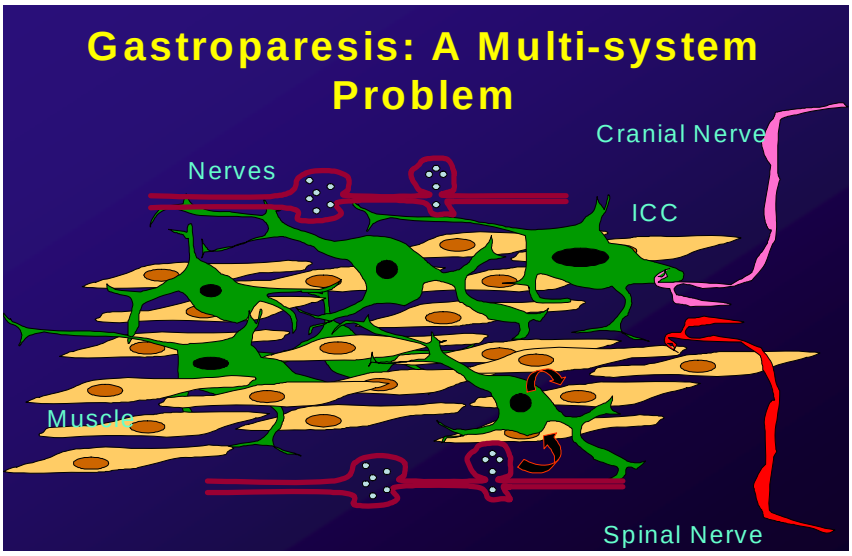


Figure 2. Gastroparesis: a multi-system approach

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, intrinsic nerves of the stomach, ICCs, and gastric smooth muscle. However, what is lacking is knowledge about the relative importance of the various dysfunctional elements and the relative influences of metabolic or immunologic alterations on each component.

Further, it is difficult to confidently apply the results of animal studies to humans with gastroparesis for several reasons. First, there are no systematic human pathological studies available. The few scattered case reports that exist vary tremendously in terms of the methodology used, the emphasis on certain tissue elements, and the clinical profile of the patients. It is not surprising therefore that there is a great disparity in the reported findings. Another reason to be cautious is that gastric physiology may differ in fundamental ways between humans and rodents. Hence, the reported changes in key molecules or cell types may have different implications for each species. As an example, a prominent theme in the experimental literature is the loss of expression of neuronal nitric oxide synthetase (nNOS) in diabetes. Systemic inhibition (either pharmacologically or genetically) of nitric oxide results in profound delays in gastric emptying in mice and rats. However, the effects of manipulation of nitric oxide (NO) appear to result in the opposite effect in humans, at least in acute studies. Thus systemic nitroglycerin slows down gastric emptying in healthy volunteers despite inhibition of pyloric contractility;[10] conversely, intravenous L-NMMA, a NOS inhibitor, enhances antral contractions and gastric emptying without any changes in electrical rhythm.[11]

Much of the clinical literature has assumed that the major defect in diabetic gastroparesis reflects vagal dysfunction.[5] 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 subjects 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).[12-19] 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.[20] Pathological findings in humans have also been mixed. Guy and co-workers 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;[21] a single report also showed loss of myelinated axons in the cervical vagus.[22] However, Yoshida and co-workers found no abnormalities in the abdominal vagus on light microscopy in five diabetics (2 with gastroparesis).[23]

In recent years, especially in experimental animal models, 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[24] and changes in axonal processes but not cell bodies were reported in the esophagus of 18 out of 20 diabetic patients.[22] 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.[25] A larger study of 18 nondiabetic controls and 16 patients with long-standing diabetes (5 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.[23]

Adequate investigations in euglycemic diabetics have not been performed to define organic defects in the absence of metabolic disruption. Finally, a recent study has reported the presence of a circulating antibody against L-type calcium channels on smooth muscle in 8 of 16 patients with type 1 diabetes; this antibody acts at the dihydropyridine binding site and can produce disruption of the normal contractile response in smooth muscle to nerve stimulation.[26]

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 these 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.[27] 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.[28] 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 marked decrease of substance P/tachykinin immunoreactive

staining in nerve fibers and myenteric neurons.[29] 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,[30] 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. However at this time, there is little scientific evidence to suggest that these other factors represent key therapeutic targets for control of gastroparesis symptoms.[5]

Potential therapeutic targets: pathophysiological changes in gastroparesis

- Delayed emptying of solids and liquids
- Accelerated emptying of liquids
- Gastric hypersensitivity to balloon distention
- Impaired relaxation
- Fundal hypocontractility
- Antral hypomotility
- Pylorospasm
- Antropyloroduodenal uncoordination
- Gastric arrhythmia
- Autonomic neuropathy
- Hypercoagulation and/or vascular disease

3.4. 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 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 99mTc 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.[31] There may be significant day-to-day variability (up to 20%) in rates of gastric emptying.[32] 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.[33]

Tests occasionally used in gastroparesis diagnosis and management are listed in Table 2.

Table 2: Clinical and research diagnostic tests for gastroparesis[5]

Test	Advantages	Disadvantages
Gastric emptying		
Upper gastrointestinal barium radiographic study	Assess for mucosal lesions	Nonphysiologic Radiation exposure (moderate)
Scintigraphy	Gold standard, noninvasive Able to assess solid and liquid emptying	Radiation exposure (minimal)
Breath tests using ^{13}C	Noninvasive	Need normal small intestinal absorption, liver metabolism, pulmonary excretion
Ultrasonography for serial changes in antral area	Noninvasive, physiologic	Requires expertise for interpretation, primarily measures liquid emptying
Magnetic resonance imaging	Noninvasive	Expensive, time consuming Need specialized centers and software
Gastric contractile activity		
Antroduodenal manometry	Assess contractility in fasting and postprandial periods	Invasive, needs expertise to interpret
Gastric barostat	Measures proximal stomach relaxation and contraction	Invasive Research technique
Gastric myoelectrical activity		
EGG	Noninvasive	Movement artifact may make recording difficult to interpret
Gastric accommodation		
Gastric barostat	Measures proximal stomach accommodation response	Invasive, research technique Balloon may interfere with accommodation
Satiety test	Measures combination of accommodation and sensitivity	Simple Not well standardized or accepted

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.[19] However, a normal EGG does not correlate with normal gastric emptying and its relation to symptoms is unclear.[33]

3.5. Treatment

Recently, consensus guidelines for the treatment of gastroparesis have been published.[4] 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 3: Antinauseant medications for treatment of gastroparesis[4]

Class of agent	Examples
Dopamine D_2-receptor antagonists	
With prokinetic activity	Metoclopramide, domperidone
Without prokinetic activity	Prochlorperazine, trimethobenzamide
Serotonin 5-HT_3-receptor antagonists	Ondansetron, granisetron, dolasetron, tropisetron
Tricyclic antidepressants	Desipramine, nortripthyline, amitriptyline
Muscarinic M_1-receptor antagonists	Scopolamine, hyoscyamine, clinidium
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.

Although in most cases, rigorous investigations have not assessed therapeutic responses as a function of symptom severity, a number of basic recommendations can be made. For mild symptoms (grade 1), dietary modifications should be tried. 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 glycaemic control to minimize effects of hyperglycaemia on gastric function. For individuals with grade 2 compensated gastroparesis, treatment recommendations commonly involve a combination of antiemetic (Table 3) and prokinetic medications (Table 4) given at regularly scheduled intervals to relieve more chronic symptoms of nausea, vomiting, fullness, and bloating.

Table 4: Prokinetic medications for treatment of gastroparesis[4]

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
5-HT_4-receptor agonists	Tegaserod	Cisapride†	Renzapride, mosapride
Muscarinic receptor agonists	Bethanechol		
Acetylcholinesterase inhibitors	Physostigmine, neostigmine		
CCK receptor antagonists			Loxiglumide, dexloxiglumide

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

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 3 and 4). Chronic care of these individuals may include enteral or parenteral nutritional support with endoscopic and/or surgical intervention (Table 5).

Table 5: Criteria for initiation of enteral nutritional supplementation[4]

Severe weight loss, unintentional weight loss >5-10% of usual bodyweight over 3-6 months
Repeated hospitalizations for refractory gastroparesis requiring i.v. 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 everyday 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.

3.6. Management of refractory gastroparesis

Recently, two new 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, no controlled trials are available and 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 one small controlled study and several case series to reduce nausea and vomiting in patients with refractory diabetic, idiopathic, and postsurgical gastroparesis. Currently, there is one approved device (Enterra, Medtronic, Inc.) for gastric stimulation[5]. 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 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. Further, there may be significant issues with lead dislodgement. Finally, the overall response rate is probably less than 70%, with most patients continuing to be somewhat symptomatic.

4. Case definitions

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 has the advantage of widespread acceptance and ready availability in the community and will provide a more uniform group of patients, at least in the initial phases of GpCRC.

4.1. Gastroparesis

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

- Symptoms of nausea, vomiting, abdominal pain, bloating, and early satiety for at least 12 weeks (not necessarily contiguous)
- Scintigraphic evidence of delayed gastric emptying (using a standardized low fat Egg Beaters meal with any combination of 2 and 4 hour retention of greater than 60% or greater than 10% respectively)
- 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, at least in the initial phases of GpCRC.

Overlap with other functional dyspepsia: The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety, and post-prandial 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 (FD) 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 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, any patient with nausea (regardless of the degree of other dyspeptic symptoms) who has delayed gastric emptying will be classified as gastroparesis.

Gastroparesis with delayed emptying: defined as above with the following diagnostic categories:

- Diabetic
- Post-surgical
- Idiopathic
- Others, such as Parkinsonism, pseudo-obstruction

4.2. Patients without nausea but with other symptoms suggestive of gastroparesis with delayed gastric emptying

Patients without nausea will qualify for enrollment in this category if they present symptoms suggestive of gastroparesis such as early satiety, bloating, and post-prandial discomfort and delayed gastric emptying. It is expected that some of these patients will meet the Rome III criteria for the postprandial distress syndrome subset of functional dyspepsia.

4.3. Symptomatic nausea and vomiting without delayed gastric emptying

Patients will qualify for enrollment in this category if they meet all the criteria for gastroparesis defined above 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. This disorder has previously been defined by the Rome II consensus criteria as “functional” vomiting. Many of these individuals satisfy the Rome III definitions of chronic idiopathic nausea or functional vomiting.

4.4. Target composition

It is expected that 80% of patients will meet the definition of gastroparesis as above with delayed gastric emptying. We will cap the number of the patients with symptomatic nausea and vomiting without delayed gastric emptying (as described in section 4.3 above) to 20%. Patients will be recruited predominantly from outpatient clinics either in gastroenterology, diabetes or primary care settings. Inpatients with the diagnosis of gastroparesis may also be invited to participate once they are discharged from the hospital and more stable medically.

5. Screening and enrollment

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, abdominal pain, early satiety, post-prandial fullness,
- Completion of a 4-hour scintigraphic low fat Egg Beaters gastric emptying study
  - Patients with either or both abnormal 2 hour (>60% retention) and 4 hour (>10% retention) gastric emptying will be enrolled and classified as definite gastroparesis (Gp)
  - Patients with normal gastric emptying, but with symptoms of gastroparesis may be enrolled and classified as possible gastroparesis or gastroparesis-like with normal gastric emptying (GLNGE)
- Age at least 18 years at initial screening visit
- Ability and willingness to participate in follow-up

5.2. Exclusion criteria

- Inability to comply with or complete the gastric emptying scintigraphy
- Presence of other conditions that could explain the patient's symptoms:
  - Pyloric or intestinal obstruction
  - Active inflammatory bowel disease
  - Eosinophilic gastroenteritis
  - Neurological conditions 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 or greater)
  - Acute renal failure
  - Untreated chronic renal failure (serum creatinine >3 mg/dL)
- Total or subtotal gastric resection (patients with prior fundoplication or postvagotomy gastroparesis after pyloroplasty or antrectomy with Billroth I, Billroth II, or Roux-en-Y gastrojejunostomy 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 Data Coordinating Center to start enrollment in the Gastroparesis Registry. 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 Gastroparesis Registry has been identified, details will be carefully discussed with the patient. 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

Screening, consent, and follow-up overview: Many of the Gastroparesis Registry (GpR) patients will likely come from the current patient rosters of the GpCRC investigators and new patients referred to them for evaluation and treatment of gastroparesis. Patients may be referred from physicians outside the Consortium and some patients may refer themselves to be included in the Registry. Patients considered by the clinical center investigator as likely to be eligible for enrollment in the Registry 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 a reasonable standard of care. Patients who are thought to be eligible will be invited to screen for enrollment in the Registry. Screening may take place over several visits. At the initial screening visit, the details of Registry participation will be introduced. If the patient is agreeable 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.

The screening visits may occur on separate calendar days and may occur over a period of up to 16 weeks. The data collected at these visits and during the retrospective chart review are used to determine eligibility and to establish baseline values. Consent for screening and HIPAA authorization to disclose protected health information with the Gastroparesis Registry must be obtained from the patient prior to initiating any data collection for the Gastroparesis Registry; this consent and authorization must be obtained at the start of the initial screening visit. The consent will include consent for screening and enrollment in the Registry, including follow-up.

The currently projected maximum follow-up on a patient entered into the Gastroparesis Registry will be approximately 4 years. Data will be collected during screening visits to establish baseline values, and then every 16 weeks after enrollment if the patient does not return in the interval for exacerbation of gastroparesis symptoms. If this happens, an interim visit will be keyed in the database to reflect the exacerbation of symptoms. The Appendix 10.2 displays the consent and data collection schedule for screening, enrollment, and follow-up.

6.1. Screening visits

Formal screening begins once the patient has signed the HIPAA authorization and consent for screening and enrollment in the Gastroparesis Registry (GpR). The patient is considered to be registered once the consent is signed. Recording of data on GpR baseline data collection forms may begin once this initial consent and authorization are obtained.

The purpose of the screening visits is to initiate collection of the baseline data needed to determine eligibility. Activities at screening visits include:

- Signature on the Gastroparesis Registry consent form
- Signature on Gastroparesis Registry HIPAA authorization form
- Assignment of GpCRC patient identification number
- Medical/medication history
- Physical examination including vital signs, height, weight, anthropometric measurements
- Review status of laboratory tests including those reflecting glycemic control
- Review status of gastrointestinal tests including endoscopy and X-rays
- Review status of gastric emptying scintigraphy
- 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
- Clinical center coordinator to request prior reports from health care provider
- Questionnaires (PAGI-SYM, PAGI-QOL, Rome III questionnaires, health related quality of life, brief pain inventory, IDIOMS, Block food questionnaire, Beck Depression Inventory, State Trait Anxiety Inventory, and others to be specified).

During the screening visits, the patient completes the questionnaires needed for enrollment in the Gastroparesis Registry and has blood drawn for additional research protocol related laboratory tests and specimen (plasma, serum, and DNA) banking. The patient must attend the screening visit after an overnight fast at least 8 hours and should be instructed to bring a snack to be eaten after fasting blood is drawn. Standards of care for patients with gastroparesis are described in the Gastroparesis Registry Standard Operating Procedures (SOP) Part IV. Other procedures at screening visits include:

- Hematology
- Clinical chemistry
- HbA1c
- Liver panel
- Serology (ANA, Scl-70, CRP, SPEP, Sed rate)
- Fasting blood for plasma and serum banking
- Blood draw for DNA banking (no fasting required)

Gastric emptying scintigraphy: To enter the Gastroparesis Registry with a diagnosis of definite gastroparesis (see section 4.1 for definition), the patient must have a 4 hour scintigraphic evaluation of gastric emptying using a low fat Egg Beaters meal that is available for review by the GpCRC investigator who must confirm that the patient meets the criteria for definite gastroparesis. This may be repeated as part of standard of care for diagnosis or follow-up as determined by the clinical center investigator during screening. The gastric emptying scintigraphy may have been obtained at any time within 6 months prior to enrollment.

6.2. Follow-up visits

Gastroparesis Registry follow-up visits will be scheduled every 16 weeks after enrollment. The date of enrollment will be the date from which the follow-up visits are timed (i.e., the zero time). Each follow-up visit will have a time window around the target date for the visit; the time window is an interval of days during which the visit may be completed, and the data collected at the visit may be used to fulfill the data collection requirements for the visit. Data collected outside the allowable time window for a visit are not useable as data for the visit. Each visit has an ideal date for the visit, a lower window date (opening date for the window) and an upper window date (closing date for the window). The dates for a specific patient are specified on the visit time windows schedule for the patient. This schedule is generated by the clinic data system when a patient is enrolled in the Gastroparesis Registry.

Procedures and forms to be completed at each of the follow-up visits are:

- 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192 weeks visit
  - 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)
  - Physical examination
  - Laboratory data (hematology, clinical chemistry, HbA1c, liver panel) as indicated
  - HbA1c values should be obtained at each follow-up visit for patients with diabetes
  - Various questionnaires such as PAGI-SYM, PAGI-QOL, brief pain inventory, IDIOMS, and others to be specified
  - Rome III questionnaires, Block food questionnaire, health related quality of life, Beck Depression Inventory, State Trait Anxiety Inventory (only at 48, 96, 144, 192 weeks)
  - Blood collection for plasma and serum banking (only at 48, 96, 144, 192 weeks)
  - Laboratory data for ANA, Scl-70, CRP, SPEP, sedimentation rate as indicated
  - Documentation of any additional GI tests performed as part of standard of care

Separate entries will be made in the Gastroparesis Registry data system for symptom flares requiring medical intervention.

6.3. Data form contents

Baseline medical history. The Gastroparesis Registry (GpR) forms will capture the following:

- Demographics
- Onset and duration of symptoms
- Nature and severity of symptoms
- Other GI symptoms particularly chronic pancreatitis
- Presence of diabetes (including gestational diabetes)
- If so, 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 12 months prior to enrollment

- Results from gastric emptying test performed within 6 months prior to enrollment
- Other medical problems particularly any history of connective tissue disorder
- Family history of GI or related illness
- Past medical/surgical events and illness history

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

Physical examination. Initial exam will include:

- Vital signs: Temperature, pulse, blood pressure
- Anthropometrics: Height, weight (without shoes or heavy clothing)
- Laboratory items: All laboratory items listed may be obtained as archival material from the patient's chart or should be collected as part of the standard of care. Maximum acceptable intervals between the date of collection of laboratory results and GpR registration (date of initial screening visit) will be specified in the data collection form. The draw date of the laboratory test must be recorded on the data form.
- Hematology: Hemoglobin, hematocrit, white blood cell count (WBC), platelet count, prothrombin time (PT), partial thromboplastin time (PTT)
- Clinical chemistry and HbA1c: Creatinine, total protein and albumin, sodium, potassium, chloride, bicarbonate, calcium, BUN, glucose and HbA1c.
- Liver panel: Total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase
- Screening etiologic tests: Anti-nuclear antibody (ANA), scleroderma antibody (Scl-70), C-reactive protein (CRP), serum protein electrophoresis (SPEP), sedimentation rate

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

6.4. Plasma, serum, and DNA for banking

Fasting plasma, serum and DNA will be banked for specific Gastroparesis Registry research questions and other GpCRC ancillary studies. Blood will be drawn at the screening/enrollment visit and yearly thereafter on all patients enrolled in the Gastroparesis Registry. 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 or at the NIDDK central repositories (see Gastroparesis Registry Standard Operating Procedures (SOP) I: Clinical Center Operations).

7. Statistical and design considerations

The Gastroparesis Registry is the first 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 compile patient data and specimens to clarify the epidemiology, etiology, and natural history of gastroparesis. The Registry will also be used as a resource for recruitment of patients into randomized, controlled, clinical trials of treatments for gastroparesis. The recruitment goal is up to 700 patients with gastroparesis from 1-4 years of follow-up on each patient.

As the first large study of gastroparesis, the objectives and hypotheses to be examined are intentionally very broad (see Section 2). As the study progresses, additional questions may arise that can be addressed through data or specimens collected for the Registry.

Addressing the specified hypotheses of the Gastroparesis Registry will require the full gamut of statistical analysis procedures, from survival analysis to ROC curves. Nearly all questions will require identification of appropriate subgroups of patients from all clinical centers contributing to the Gastroparesis Registry with analyses tailored to the hypothesis to be addressed.

This process will be accomplished through formal publication proposals corresponding to each hypothesis prepared by members of the GpCRC and approved by the full GpCRC Steering Committee. The DSMB will review approved proposals to ensure that the studies are consistent with the goals of the GpCRC and will periodically monitor progress on these publications. Each of these proposals must include a statistical plan and sample size justification prepared by the Data Coordinating Center. Each proposal must contain the following information:

- Statement of the hypothesis to be addressed
- Specification of the primary comparison groups appropriate for the hypotheses
- Specification of the primary and secondary outcome variables
- Specification of inclusion/exclusion criteria needed to define the subgroup of Registry patients needed for the hypothesis
- Specification of baseline covariates or methods to be used to select the covariates for adjustment of comparisons among the primary comparison groups
- Specification of methods for dealing with missing values or lost to follow-up
- Specification of primary and confirmatory analytic methods to be used

The sample size must be justified by calculations (using nQuery Advisor or similar software), which will include a 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 or estimates of variability (eg, 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.

Since the Gastroparesis Registry 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 subjects issues

The study protocol, consent forms, and data collection forms will be submitted to each clinical center's IRB and to the DCC'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 until the site has IRB approval and the DCC has certified the site for initiation of patient activities. Consent forms must have IRB approval. Sites must provide the DCC 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 subjects enrolled in the Gastroparesis Registry will receive a standard of care for gastroparesis and identified associated medical problems as defined by the GpCRC Steering Committee (see SOP IV: Standards 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.

Prototype consents will be prepared for the study. Individual sites may add material but may not delete material thought to be necessary for informed consent. 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 subject and this fact will be documented in the subject's record.

8.1. 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 subject confidentiality. All records will be kept in locked file cabinets with access limited to Gastroparesis Registry 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).

8.2. Adverse event reporting

The Gastroparesis Registry will monitor and report unanticipated or adverse events to ensure patient safety in compliance with 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies. 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. Since the definitions and reporting requirements for unanticipated events may differ at each participating site, the Gastroparesis Registry definitions and procedures for adverse events are designed to satisfy the Common Rule requirements. While the definitions and monitoring procedures apply most directly to clinical trials, all patients in the Gastroparesis Registry will be monitored for occurrence of adverse events, thought to be associated with the Gastroparesis Registry participation and any adverse events that occur will be reported as appropriate.

Adverse event. An adverse event is any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product or clinical procedure and which may or may not have a causal relationship with the treatment. Adverse events include any unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants. The term "unanticipated problem" includes both new risks and increased rates of anticipated problems.

Serious adverse event (SAE). A serious adverse event is an adverse event occurring at any time during the study that results in death, life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Other events may also be considered an SAE if, based on medical judgement, the event jeopardized the patient to the point of requiring medical or surgical intervention to prevent the occurrence of any of the conditions for an SAE listed above.

Unexpected adverse event. An unexpected adverse event is any adverse event with specificity or severity that is not consistent with the risk information in the study protocol, current investigator brochure, or current package insert.

Adverse events will be recorded on study data forms whether or not they are thought to be associated with the Gastroparesis Registry 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. The SAE form, together with a memo summarizing the circumstances of event and the current status of the patient, must be faxed to the Data Coordinating Center and to the NIDDK project officer within one working day of the discovery of the SAE. Also within one day, the clinical center must notify the NIDDK and Data Coordinating Center of the SAE by telephone or confirmed e-mail. The NIDDK project officer will work with the Data Coordinating Center to transmit the SAE form and memo to all study centers and

to the DSMB when the adverse event is both thought to be unexpected and associated with the Gastroparesis Registry participation.

The DSMB will review reports of unexpected adverse events that are related to participation in the Gastroparesis Registry, and provide comments to the NIDDK project officer within one week of receipt of the report. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the NIDDK sponsor.

The clinical center must submit to the NIDDK project officer and to the Data Coordinating Center a follow-up memo within one month of the SAE (and periodic updates if needed) to report the details of the disposition of the SAE. The NIDDK project officer will work with the Data Coordinating Center to distribute the follow-up memo to the clinical center and to the DSMB.

8.3. Review of adverse events by the DSMB

Summary data on 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.[35]

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.

8.4. Participant withdrawal

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

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10. Appendix

10.1. Participating centers

Clinical Centers

- Stanford University
  - California Pacific Medical Center
- Temple University
- Texas Tech University Medical Center
- University of Michigan
- University of Mississippi Medical Center
- Wake Forest University Medical Sciences

Data Coordinating Center:

- Johns Hopkins University

National Institutes of Health:

- National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Central Repositories:

- Biosample repository: Fisher Bioservices
- Genetics repository: Rutgers, The State University of New Jersey
- Data repository: Research Triangle Institute (RTI)

10.2. Data collection schedule

	Screening visits	Follow-up visits: Weeks from enrollment											
	screen and enroll	16	32	48	64	80	96	112	128	144	160	176	192
Consent, HIPAA authorization	X	.	.	.	.	.	.	.	.	.	.	.	.
Baseline medical history	X	.	.	.	.	.	.	.	.	.	.	.	.
Follow-up medical history	.	X	X	X	X	X	X	X	X	X	X	X	X
Interim event form as needed (A)*	.	A	A	A	A	A	A	A	A	A	A	A	A
PAGI-SYM questionnaire	X	X	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	X	X
Rome III battery	X	.	.	X	.	.	X	.	.	X	.	.	X
Brief Pain Inventory	X	X	X	X	X	X	X	X	X	X	X	X	X
IDIOMS	X	X	X	X	X	X	X	X	X	X	X	X	X
Gastric emptying scintigraphy	X	.	.	.	.	.	.	.	.	.	.	.	.
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Upper gastrointestinal endoscopy	X	.	.	.	.	.	.	.	.	.	.	.	.
Eligibility confirmation	X	.	.	.	.	.	.	.	.	.	.	.	.
Beck Depression Inventory	X	.	.	X	.	.	X	.	.	X	.	.	X
STAI: Self evaluation questionnaire	X	.	.	X	.	.	X	.	.	X	.	.	X
Block Brief Food Questionnaire	X	.	.	X	.	.	X	.	.	X	.	.	X
SF-36 quality of life	X	.	.	X	.	.	X	.	.	X	.	.	X
Hematology*	X	A	A	A	A	A	A	A	A	A	A	A	A
Liver panel*	X	A	A	A	A	A	A	A	A	A	A	A	A
Clinical chemistry*	X	A	A	A	A	A	A	A	A	A	A	A	A
HbAlc†	X	X	X	X	X	X	X	X	X	X	X	X	X
ANA, Scl-70, CRP, SPEP, Sed rate	X	.	.	A	.	.	A	.	.	A	.	.	A
Serum, plasma banking	X	.	.	X	.	.	X	.	.	X	.	.	X
DNA for banking	X	.	.	.	.	.	.	.	.	.	.	.	.

Hematology panel includes hemoglobin, hematocrit, white blood cell count (WBC), platelet count, prothrombin time (PT), partial thromboplastin time (PTT)

Liver panel includes total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

Clinical chemistry panel includes creatinine, total protein and albumin, sodium, potassium, chloride, bicarbonate, calcium, BUN, glucose

* A = as needed

† HbA1c is required at each follow-up visit for diabetic patients

10.3. Whole blood draw schedule

	Study visits (wk)					
Procedure	**screening/ enrollment**	**48**	**96**	**144**	**192**	**Total**
Serology (ANA, Scl-70, CRP, SPEP, Sed rate)	10	.	.	.	.	**10**
Hematology	5	.	.	.	.	**5**
Clinical chemistry	5	.	.	.	.	**5**
Liver panel	5	.	.	.	.	**5**
HbA1c†	5	.	.	.	.	**5**
Fasting* plasma, serum banking	20	20	20	20	20	**100**
DNA banking	20	.	.	.	.	**20**
Total (mL)	**70**	**20**	**20**	**20**	**20**	**150**

Hematology panel includes hemoglobin, hematocrit, white blood cell count (WBC), platelet count, prothrombin time (PT), partial thromboplastin time (PTT)

Liver panel includes total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

Clinical chemistry panel includes creatinine, total protein and albumin, sodium, potassium, chloride, bicarbonate, calcium, BUN, glucose

* 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.

†HbA1c will be obtained at each follow-up visit for diabetic patients only

10.4. 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
CTCAE	-	Common Terminology Criteria for Adverse Events
DCC	-	Data Coordinating Center
DSMB	-	Data and Safety Monitoring Board
EGG	-	electrogastrography
FD	-	functional dyspepsia
GEE	-	generalized estimating equations
GCSI	-	Gastroparesis Cardinal Symptom Index
GLNGE	-	gastroparesis-like with normal gastric emptying
Gp	-	gastroparesis
GpCRC	-	Gastroparesis Clinical Research Consortium
GpR	-	Gastroparesis Registry
HbA1c	-	glycosylated hemoglobin A1c
HIPAA	-	Health Insurance Portability and Accountability Act
ICC	-	interstitial cells of Cajal
IDIOMS	-	Investigator Derived Independent Outcome Measure Scores
INR	-	international normalized ratio
IRB	-	Institutional Review Board
NIDDK	-	National Institute of Diabetes and Digestive and Kidney Diseases
NO	-	nitric oxide
NOS	-	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
PT	-	prothrombin time
PTT	-	partial thromboplastin time
ROC	-	receiver operating characteristic
SAE	-	serious adverse event
Scl-70	-	scleroderma antibody
SOP	-	standard operating procedures
SPEP	-	serum protein electrophoresis
WBC	-	white blood cell count

10.5. Document history

Gastroparesis Registry Protocol (14 September 2006)

Gastroparesis Registry Protocol (1 February 2008)

Numerous editorial and wording changes were made to the following sections:

§Design synopsis:
- Changed Recruitment – "1000 enrolled patients (200/clinical center" to "500 enrolled patients (100/clinical center)"

§5.2 Exclusion criteria
- Changed "Advanced liver disease (Child's B or C)" to "Advanced liver disease (Child's B or C; a CPT score of 7 or greater)"

§6.2 Follow-up visits
- HbA1c values should be obtained at each follow-up visit for patients with diabetes

§8.2 Adverse event reporting
- The 1st paragraph "thought to be associated with the Gastroparesis Registry participation" was added to the last sentence.
- The 6th paragraph "when the adverse event is both unexpected and thought to be associated with the Gastroparesis Registry participation" was added to the last sentence in the paragraph.
- The 7th paragraph "The DSMB will review each SAE report and provide comments to the NIDDK project officer within one week of receipt of the report" was changed to "The DSMB will review reports of unexpected adverse events that are related to participation in the GpR registry, and provide comments to the NIDDK project officer within one week of receipt."

§10.1 Participating centers
- Changed 4th clinical center "University of Texas Medical Branch" to "Stanford University"

§10.2 Data collection schedule
- Changed HbA1c test from "as needed" to "required at each follow-up visit for diabetic patients"

§10.3 Whole blood draw schedule
- HbA1c will be obtained at each follow-up visit for diabetic patients only

Gastroparesis Registry Protocol (1 December 2009)

Numerous editorial and wording changes were made to the following sections:

§Design synopsis:
- Exclusion criteria: removed "(Child's B or C; a CPT score of 7 or greater)"
- Recruitment: replaced this section with "Study Duration"
- Duration to followup: replaced this section with "Study Duration"
- Added new section "Study Duration" with bullets "Recruitment: Up to 700 until 31 March 2010" and "Follow-up: 48-192 weeks (1-4 years)"

§1.2 Gastroparesis Clinical Research Consortium
- In 1st sentence changed "five clinical centers" to "six clinical centers, one satellite center"

§1.4 Gastroparesis Registry
- In 2nd sentence changed "five clinical centers" to "six clinical centers and one satellite center

§3.2 Epidemiology and Natural history
- Grade 2 Compensated Gastric Neuromuscular Dysfunction: removed extra space before "lifestyle adjustments"

§5.2 Exclusion criteria
- Advanced liver disease: replaced CPT with Child-Pugh-Turcotte (CPT)

§7 Statistical and design considerations
- Changed last sentence in the 1st paragraph from "The recruitment goal is 500 (100 per clinical center) patients with gastroparesis from 1-4 years of follow-up on each patient." to "The recruitment goal is up to 700 patients with gastroparesis from 1-4 years of follow-up on each patient."

§10.1 Participating centers
- added 6th clinical center "Texas Tech University Health Science Center"
- added satellite center "California Pacific Medical Center"

§10.2 Data collection schedule
- Hematology: moved partial thromboplastin time (PTT) to 2nd line

§10.4 Glossary
- Added "CPT- Child-Pugh-Turcotte score"