Gastroparesis
Clinical Research Consortium

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (APRON)

Standard Operating Procedures

Part I: Clinical Center Operations

August 2013

APRON SOP Part I: Clinical Center Operations

Contents

APRON SOP Part I: Clinical Center Operations

1. Design overview

1.1. Design synopsis

Title

- **Ap**repitant for the **R**elief **o**f **N**ausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (APRON)

Sponsor

- NIDDK

Type of study

- Phase 3 randomized clinical trial
- Multicenter, double-masked, placebo-controlled trial of 2 parallel treatment groups

Objective

- To determine whether treatment with aprepitant or placebo results in symptomatic improvement of nausea in patients with chronic nausea and vomiting of presumed gastric origin.

Treatment groups

- Group 1: Aprepitant (125 mg q.d.)
- Group 2: Aprepitant-placebo (q.d.)

Population

- Age 18 years or older at registration with nausea, vomiting, and other symptoms suggestive of patients with chronic nausea and vomiting of presumed gastric origin, with or without delayed gastric emptying

Study duration

- Up to 4 weeks of screening prior to randomization
- 4 weeks of treatment starting at randomization
- 2 weeks of washout period
- Length of recruitment: 16 months

Sample size justification

- Total of 120 patients in 2 groups of equal size (60 per group)
- Primary comparison: aprepitant vs. placebo
- Error protection: Type I = 0.05 and Type II = 0.10 (90% power)

Number of clinical sites

- 8

Inclusion criteria

- Age 18 years or older at registration
- Gastric emptying scintigraphy within 2 years of registration
- Normal upper endoscopy or upper GI series within 2 years of registration
- Symptoms of chronic nausea or vomiting compatible with gastroparesis or other functional gastric disorder for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥21
- Significant nausea defined with a visual analog scale (VAS) score of ≥25 mm on a 0 to 100 mm scale

Exclusion criteria

- Another active disorder which could explain symptoms in the opinion of the investigator
- Use of narcotics more than 3 days per week
- Significant hepatic injury defined by significant ALT and AST elevations > 2 x ULN or a Child-Pugh score of 10 or greater
- Contraindications to aprepitant (e.g., hypersensitivity or allergy)
- Concurrent use of warfarin, pimozide, terfenadine, astemizole, or cisapride
- Pregnancy or nursing
- Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study
- Failure to give informed consent

Outcome measures

- ***Primary:*** The primary outcome measure is a binary (0,1) variable indicating improvement in nausea or not in the mean of available VAS scores over the 28 day treatment period compared to the mean of VAS scores during the 7 day baseline period. The criteria for improvement are either a 25 mm or more reduction in mean VAS or attaining a mean VAS during the treatment period of < 25 mm.
- **Secondary outcome measures** will be defined to address the following areas:

  (1) Gastrointestinal symptoms
  - Subscores for the GCSI: nausea/vomiting, postprandial fullness, bloating
  - Subscores for the GCSI Daily Diary
  - Individual symptom scores for nausea, retching or vomiting
  - Global overall relief of symptom questionnaire
  - Clinical global patient impression

  (2) Physiology
  - Satiety test: Volume of Ensure® consumed during satiety testing
  - Electrogastrography: Percent time in EGG dysrhythmias (outside 2.5-3.75 cycles per minute)
  - Side effects to treatment requiring stopping medication

1.1. Design synopsis

Randomization

- Centrally administered randomization stratified by clinical center and blocked by calendar time

Visit schedule

- Screening: at least 1 visit separated by at least 1 calendar day from date of randomization; screening period can last no more than 4 weeks after registration
- Randomization: final pre-treatment interview, dispensing of study drug
- Follow-up visits: every 2 weeks after randomization throughout the 6 week study

Statistical analysis

- Analyses will be on an "intention-to-treat" basis. Patients without VAS nausea scores recorded during the period of treatment will be counted as not improved (i.e., 0) for the primary outcome
- Secondary, sensitivity analyses on a per-protocol basis will also be carried out, excluding patients from both groups who do not complete at least 50% (2 weeks) of the 4 weeks on assigned treatment, but conclusions about the primary objective will be based on the intention-to-treat analysis.

Safety monitoring

- NIDDK appointed DSMB will monitor the data for safety and efficacy for outcomes such as toxicity and any other outcomes or events identified as safety-related

1.2. Data collection schedule

	Screening and randomization visits		Follow-up visits Weeks from randomization		
Assessment/Procedure	**screening**	**rz**	**2**	**4**	**6**
Consent	X	.	.	.	.
Gastric emptying scintigraphy results review	X	.	.	.	.
Upper endoscopy results review	X	.	.	.	.
Baseline medical history	X	.	.	.	.
Initial VAS nausea assessment	X	.	.	.	.
Provide supplies of Daily Diaries	X	X	X	.	.
Collection of Daily Diaries	.	X	X	X	.
Gastrointestinal Disorders/PAGI-SYM	X	.	X	X	.
GSRS questionnaire	X	.	.	X	.
SF-36 QOL questionnaire	X	.	.	X	.
Beck Depression Inventory-II	X	.	.	X	.
Nausea Profile	X	.	X	X	.
State Trait Anxiety Inventory	X	.	.	X	.
Brief Pain Inventory	X	.	X	X	.
PHQ-15 questionnaire	X	.	.	X	.
Satiety test with electrogastrography	X	.	.	X	.
Electrocardiogram (ECG)	X	.	.	.	.
Physical exam	X	.	.	X	.
Study drug dispensed	.	X	.	.	.
Follow-up medical history including review of adverse events	.	.	X	X	X
CBC, CMP, glucose, HbA1c*	X	.	.	X	.
Plasma banking	.	X	.	X	.
DNA banking	.	X	.	.	.
Pregnancy test	.	X	.	.	.

Physical exam includes measurement of weight, vital signs (temperature, heart rate, blood pressure), general physical findings

CBC: Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

CMP: Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, BUN, creatinine, ALT, AST, magnesium, albumin, total protein. billirubin, and alkaline phosphate

* Glucose, hemoglobin A1c will be obtained in patients with diabetes.

1.3. Whole blood draw schedule: mL of blood to be drawn at screening and follow-up visits

	Study visit (wk)				
Procedure	Screening	rz	2	4	**Total**
Complete blood count	5	.	.	5	**10**
Complete metabolic panel, HbA1c*	5	.	.	5	**10**
Blood for DNA banking	.	20	.	.	**20**
Blood for plasma banking	.	10	.	10	**20**
Total (in mL)	**10**	**30**	**.**	**20**	**60**

Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

Complete metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, BUN, creatinine, ALT, AST, magnesium, albumin, total protein, billirubin, and alkaline phosphate.

* Glucose, hemoglobin A1c will be obtained in patients with diabetes.

2. Eligibility and enrollment

2.1. Inclusion and exclusion criteria

Inclusion criteria

Patients with nausea, vomiting, and other symptoms suggestive of gastroparesis, with or without delayed gastric emptying, will be studied. In order to qualify for inclusion in the trial, patients must satisfy the following inclusion criteria:

- Age 18 years or older at registration
- Gastric emptying scintigraphy within 2 years of registration
- Normal upper endoscopy or upper GI series within 2 years of registration
- Symptoms for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
- Significant nausea defined with a visual analog scale (VAS) score of ≥ 25 mm on a 0 to 100 mm scale
- Women of child bearing age should have a negative pregnancy test before entry into the study

Exclusion criteria

Patients who satisfy any of the following exclusion criteria will be ineligible for enrollment in the trial:

- Another active disorder which could explain symptoms in the opinion of the investigator
- Use of narcotics more than 3 days per week
- Significant hepatic injury as defined by significant alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations of greater than 2xULN or a Child-Pugh score of 10 or greater
- Contraindications to aprepitant such as hypersensitivity or allergy
- Concurrent use of warfarin, pimozide, terfenadine, astemizole, or cisapride
- Pregnancy or nursing
- Any other condition which, in the opinion of the investigator, would impede compliance or hinder the completion of the study
- Failure to give consent

2.2. Calculation of Child-Pugh-Turcotte score

Child-Pugh-Turcotte (CPT) score for severity of liver disease will be calculated as follows:

	Points
1. Serum albumin (g/dL; recorded on the LR form)	
greater than 3.5	1
2.8 – 3.5	2
less than 2.8	3
2. Serum total bilirubin (mg/dL; recorded on the LR form)	
less than 2.0	1
2.0 – 3.0	2
greater than 3.0	3
3. Prothrombin time (INR; recorded on the LR form)	
less than 1.7	1
1.7 – 2.3	2
greater than 2.3	3
4. Ascites: use all available information from all sources and best medical judgement	
None	1
Mild, easily managed	2
Severe, refractory	3
5. Encephalopathy: use all available information from all sources and best medical judgement	
None	1
Mild, easily managed	2
Severe, refractory	3

Child's stage A: 5-6 points
Child's stage B: 7-9 points
Child's stage C: 10-15 points

2.3. Calculation of Gastroparesis Cardinal Symptom Index (GCSI)

Gastroparesis Cardinal Symptom Index (GCSI) score for gastrointestinal symptoms will be calculated using the Patient Assessment of Upper Gastrointestinal Disorders – Symptoms Severity Index (PAGI-SYM) as follows:

The GCSI score will be calculated as the sum of the three symptom sub-scale scores. GCSI score can range from 0 to 45, with higher scores reflecting greater symptom severity.

Points:

None	Very mild	Mild	Moderate	Severe	Very Severe
0	1	2	3	4	5

Nausea/vomiting subscore: (sum of these 3 items) ____

1. nausea (feeling sick to your stomach as if you were going to vomit or throw up) 0 1 2 3 4 5
2. retching (heaving as if to vomit, but nothing comes up) 0 1 2 3 4 5
3. vomiting 0 1 2 3 4 5

Postprandial fullness/early satiety subscore: (sum of these 4 items) ____

4. stomach fullness 0 1 2 3 4 5
5. not able to finish a normal-sized meal 0 1 2 3 4 5
6. feeling excessively full after meals 0 1 2 3 4 5
7. loss of appetite 0 1 2 3 4 5

Bloating subscore: (sum of these 2 items) _____

8. bloating (feeling like you need to loosen your clothes) 0 1 2 3 4 5
9. stomach or belly visibly larger 0 1 2 3 4 5

Total GCSI score: (sum of 3 subscores) _____

The total GCSI score must be ≥21 during screening to be eligible for randomization into the APRON trial. The GCSI is calculated on the Assessment of Gastrointestinal Disorders (GD) form.

2.4. Guidelines for repeat determinations of eligibility

While certain inclusion and exclusion criteria are more objective and are unlikely to change, others are more subjective and may change over time. Thus, participants who are deemed ineligible at the time of initial screening may be re-screened at a later time as follows:

- Age <18 years – the participant may be re-screened after his or her 18th birthday
- Use of narcotics greater than 3 days per week – participant may be re-screened when use of narcotic medications is less than or equal to 3 days per week.
- Use of warfarin, pimozide, terfenadine, astemizole, or cisapride – the participant may be re-screened after completing a 1 week washout
- Unable to complete gastric emptying scintigraphy – the test may be repeated and the participant may be re-screened when clinically indicated

Participants who are deemed ineligible at the time of initial screening may NOT be rescreened if:

- Symptoms of gastroparesis with a Gastroparesis Cardinal Symptom Index (GCSI) score of < 21 - participant may not be rescreened
- Nausea visual analog scale < 25 mm on a 0 to 100 mm scale - participant may not be rescreened

2.5. Co-enrollment in Gastroparesis Registry 2

When an active GpR 2 participant is randomized into APRON Trial, the visit schedule and requirements of APRON take precedence over the requirements of the GpR 2 Study. When a GpR 2 participant is randomized in APRON Trial, complete the GpR 2 Closeout (CO) form to 'temporarily suspend' the patient's participation in the GpR 2 Study. Otherwise, data forms for GpR 2 visits will be due until the GpR 2 Closeout (CO) form is keyed. The patient remains enrolled in the GpR 2 while participating in APRON, but the patient is not subject to completion of GpR 2 visits. You do not need to complete the Missed or Incomplete Visit (MV) form for the missed GpR 2 follow-up visits. The patient will complete APRON follow-up visits and forms.

Since the APRON Trial has a duration of only up to 10 weeks, the clinical coordinator should consult the APRON candidate's GpR 2 visit time window and schedule the patient's APRON screening visit a minimum of 10 weeks prior to the next scheduled GpR 2 follow-up visit. In doing so, a 'co-enrolled' patient can complete APRON Screening (up to 4 weeks) and the remaining 6 weeks of treatment and follow-up within the 6-month interval between GpR 2 follow-up visits without interruption of the GpR 2 study visits. The APRON Closeout (CO) form should be completed at the APRON 6 week (f6) visit, or at the close of the f6 visit window.

- Ask the patient to read and sign the APRON consent form
- Complete and key the APRON RG form but do NOT issue a new patient ID number and code. GpR 2 patients enrolling in APRON will keep the previously assigned patient ID number
- Blood for plasma banking
  - Whole blood must be collected and processed for plasma banking at the biosample repository even if plasma and serum were already banked for the GpR 2
- Blood for DNA banking
  - If DNA samples were not obtained for this patient before, and the patient now consents to DNA banking, have the patient sign the APRON genetic consent, collect a sample, and complete the APRON Genetic Consent and Blood Collection Documentation (CG) form
  - If the DNA amount on the sample obtained when the patient screened for the GpR 2 was satisfactory, the patient does not need to sign the APRON genetic consent or donate blood. However, complete the APRON CG form to document that blood for DNA banking was collected in another study.
  - If the DNA amount on the sample obtained when the patient screened for the GpR 2 was unsatisfactory (less than 50 μg), have the patient sign the APRON genetic consent form, obtain the replacement sample, and complete the APRON CG form. The GpR 2 CG form should remain in the data system
- Lab results reported on the GpR 2 Laboratory Results (LR) form may be recorded on the APRON LR form if they were obtained within 4 weeks of registration in APRON
- All interviews and patient questionnaires (baseline history, quality of life, and patient health) must be completed for APRON patients

2.5. Co-enrollment in Gastroparesis Registry 2

The GpR 2 protocol specifies dual gastric emptying procedures of solids and liquids. The APRON gastric emptying scintigraphy (GES) protocol specifies 'solids only' gastric emptying procedures. *Can GpR 2 'solids only' gastric emptying scintigraphy data be used in APRON?* Yes - as long as the following criteria are met:

- GpR 2 patients who wish to enroll into APRON may have the GpR 2 'solids only' gastric emptying data transferred to the APRON gastric emptying scintigraphy documentation (GE) form if the GES procedure took place within two years of registration into APRON, and
- The GpR 2 'solids only' gastric emptying scintigraphy procedure must be performed as a 4-hour test

If the patient is randomized in APRON, complete the GpR 2 Closeout (CO) form to temporarily suspend the patient's participation in the GpR 2. Retain all GpR 2 forms completed for the patient in the patient's GpCRC file. Retain the patient's GpR 2 visit windows schedule since it will be needed once the APRON trial is completed.

GpR 2 Standard Operating Procedures I, section 6.30 provides additional instructions to transfer patients from APRON Trial to GpR 2 Study, but if you cannot find the answer to your question, call or email the Data Coordinating Center.

2.6. Randomization and eligibility checking

Randomization steps

- Collect and key all required screening data collection forms within 4 weeks of registration date
- Run electronic check on eligibility (i.e., run the Randomization Task and resolve any missing items or ineligibility conditions)
- Run the Randomization Task and confirm that you want to randomize the patient "now"; this task will officially randomize the patient in APRON and the randomization assignment, study drug bottle number, and materials needed in follow-up will be generated (i.e., labels, visit time windows); this task will categorize each patient into one of two treatment groups:
  - Aprepitant 125 mg
  - Aprepitant - placebo 125 mg

Overriding eligibility criteria

- Requests for overriding eligibility criteria must be made in writing (via email) to the DCC (direct the request to Aynur Ünalp-Arida). The request must specify the eligibility criteria for which the override is requested.
- The DCC may require agreement to the override from other GpCRC investigators
- Override requests require time to review and the review process will not be shortened; therefore, requests should be submitted at least one week prior to the end of the screening window.

Randomization date

- The date the clinical center runs the Randomization Task and confirms that the patient is to be randomized "now" and the treatment group is assigned.
- The "time zero" for reckoning the time windows specified on the patient's APRON visit time window guide.

3. Certification

3.1. Certification overview of APRON

What is certification?

- It is an internal (i.e., related to the study) procedure designed to identify the staff responsible for specific data items, data collection procedures, or decisions about eligibility
- It is a managerial and quality assurance tool for the study

Who and what does it apply to?

- It applies to:
  - APRON trial staff
  - Each clinical center
- Certification for the APRON trial is required before any patient visits or data collection may occur; patients may not begin any screening examinations, sign any consent statements, or complete any study forms until the clinical center has been certified for the study
- It is recommended that more than one staff member be certified for a role

Why do we require it?

- Primary purpose is to ensure adherence to study protocol and standardization of procedures for patients over the duration of the study.
- Study procedures should be carried out in the same manner within and across clinical centers, per protocol.
- It identifies the staff and sites that carry out study procedures and identifies to staff that they and their site are a part of the APRON trial.
- It provides a mechanism for tracking who collected key data items or made key decisions.
- The certification process standardizes training of staff and defines the requirements of the facility and equipment in an organized fashion. Completion of these items are required before study specific activities may begin.

APRON certification

- Certification requirements for APRON will be distributed to clinical centers in a numbered Policy and Procedure Memorandum (PPM).

3.2. Clinical center certification

General comments

- Each clinical center participating in the APRON trial must be certified
- Completion of the Clinical Center Certification (CC) form
- IRB approval for the APRON protocol and consent statements

Purpose of clinical center certification

- Provide information regarding how the clinical center will conduct different aspects of the protocol and who will staff the study
- Guide a clinical center through the steps of getting ready for the APRON trial
- Provide a checklist of what needs to be in place before patient activities begin

Requirements for certification of a clinical center

- Complete the APRON Clinical Center Certification (CC) form
- Certify at least one person for each role that requires certification (a person may be certified for more than one role): Study Physician, Clinical Coordinator, and Data Entry Technician
- Obtain IRB approval of the most current APRON protocol and consent documents
- Participate in a start-up telephone conference call with the Data Coordinating Center Personnel
- Receive written notice of approval (e-mail) from the Data Coordinating Center

3.3. Personnel certification

Staff roles requiring certification

- Clinical Coordinator
- Study Physician
- Data Entry Technician

Requirements

- Personnel requesting certification in APRON
  - Read the APRON trial protocol and Standard Operating Procedures (SOP) I: Clinical Center Operations
  - Complete the APRON Personnel Certification and Knowledge Assessment (PC) form; this form identifies the roles applied for, requires signed assurances of data confidentiality and integrity, and tests general knowledge about the APRON Trial (open book)
- Additional requirements for Study Physician
  - Study Physician must be an MD, preferably a gastroenterologist
  - Read SOP IV: Standard of Care
- Additional requirements for Data Entry Technician
  - Read SOP III: Web-based data management system
  - Complete the web-based data management system tutorial (personnel previously certified for the Data Entry Technician role do not need to complete the data system tutorial a second time)

Process

- All APRON staff must send the completed PC form to the DCC
- The DCC will send written notice of approval for certification or pending certification
- Each clinic staff member will be issued a Personnel Identification Number (PIN)

Personnel Identification Numbers (PINs)

- Each clinic staff member certified for at least one role will be issued a PIN which will consist of 3 digits – the first digit will identify the clinical center and the next two digits will be a sequential number assigned by the Data Coordinating Center
- The PIN is used when completing forms
- The Data Entry Technician uses his/her PIN when signing on to the web-based data management system
- Staff can be certified for more than one role but will have only one PIN

Personnel Certification forms

- PC Personnel Certification and Knowledge Assessment

3.4. Personnel decertification

General comments

- GpCRC personnel, regardless of study or position, must be decertified at the close of a GpCRC study or after termination of employment on GpCRC studies.
- Enables the Data Coordinating Center to accurately track personnel working on GpCRC studies

Process

- Complete the Decertification Request (DC) form by the person requesting decertification, a clinical coordinator, or the study physician
- Form must be signed by a clinical coordinator or the principal investigator
- Form must be submitted to the Data Coordinating Center via email or fax

Personnel Decertification forms

- DC - Decertification Request form

4. Human subjects

4.1. Background

Consent to participate in the APRON trial must be completed prior to initiation of screening the patient. In signing the consent, the patient agrees to study procedures offered to and performed on him/her for screening, as well as during the follow-up visit.

The consent process is a dynamic process involving explanations, time to think, questions, clarifications, and advice that a patient may seek from relatives, friends or anybody else considered relevant. We wish to inform the prospective participant as much as possible and as accurately as possible about what will be offered to him/her, how it will be done, what are the reasonable risks and benefits, what are the alternatives, and what is expected of the patient. We wish to answer patients' questions in a consistent and complete way.

The APRON trial consent process has three major stages:

- The patient is asked to consent to screening and randomization into the APRON trial. If the patient does not agree to have plasma samples sent to the Repository, the patient may not participate in the study and should not sign the study consent. The signed study consent requires blood (10 mL) to be collected for processing of plasma for future use such as measurements of study drug levels in plasma, and metabolomics.

- The patient is asked to consent to the collection, storage, and use of blood samples for genetic research using DNA from blood processing. Agreement by the patient to sign this consent is voluntary.

- The patient is asked to sign the HIPAA authorization to disclose protected health information

Once the consent forms have been signed, proceed with the completion of the APRON Registration (RG) form. At the end of the screening process, the patient is asked to re-affirm their consent on the Randomization (RZ) form.

4.2. Institutional Review Board process

Two template consent statements have been prepared for distribution to your institutional IRB for the APRON trial. Additions and/or editing of the template consents may be required at individual institutions. Deletion of material and/or major rewording of text may need to be explained and justified. Once a consent form has been approved by an institution's IRB, it cannot be changed without the IRB's approval.

The two template consent statements include:

- Consent for screening and enrollment in APRON, and
- Consent for the collection, storage, and use of blood samples for current and future genetic research

Clinical centers are expected to use these materials in their submissions to their Institutional Review Boards (IRBs). Each clinic must send copies of the consent statements stamped with their IRB's approval to the Data Coordinating Center for approval prior to initiating patient activities in the APRON trial. Data Coordinating Center staff will review and compare each clinical center's approved consents to the template consents. After review, the Data Coordinating Center will forward consents to the NIDDK Repository. The NIDDK Repository will review each clinical center's consents and issue an approval letter. Once the approval letter is received, the specimen shippers will be sent to the clinical center.

The study protocol, consent forms, and data collection forms will be submitted to each clinical center's IRB and to the Data Coordinating Center's IRB. Additionally, each clinical center will submit to their IRB any recruitment materials to be used at their site. A clinical center may not initiate any patient contact about the APRON trial until the site has IRB approval for the APRON trial and the Data Coordinating Center has certified the site for initiation of patient activities. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

HIPAA authorization forms will be prepared by each clinical center according to local clinical center institutional requirements and guidelines.

4.3. Consent administration

APRON consents

It is assumed that patients referred to a clinical center for screening have heard about the APRON trial, but their level of knowledge and expectations may differ. We wish to standardize the consent administration across clinical centers as much as possible. Administration of the APRON consents involves two tasks:

(1) An APRON staff member must sit down with the patient and review the contents of the statement; explain the risks, benefits, and responsibilities of participation; review the alternatives to participation; and answer questions.

(2) An APRON certified study physician (i.e., a APRON certified gastroenterologist) must sign the consent statement, taking overall responsibility for the patient's informed and voluntary consent.

Staff at each clinical center should be designated to carry out these tasks. The rationale for requiring that the consent statement be signed by a study physician is to assure that the physician has primary responsibility for the conduct of the study.

Generally, patients should be given the consent statements to read at least a day before signature is requested. The consent should be reviewed with the patient by the staff member. Another option is that the consent statement may be read to the patient, pausing to explain issues as needed. This activity should take place in a quiet, private and relaxed setting in the clinical center.

The patient should sign the consent statement in the presence of the APRON staff member after all questions have been answered and when the patient has asserted orally that he/she is ready to sign the consent. After the patient has signed and dated the consent, the patient should meet with a APRON study physician, at which time the physician will sign the consent statement; ordinarily this meeting should take place on the same day that the patient signed the consent statement. The physician should ask the patient to confirm his/her voluntary consent and query the patient about any questions or concerns the patient may have about participation. Both signatures on the consent form must be in a non-erasable ink pen. If the physician cannot meet with the patient on the same day that the patient signs the consent statement, the physician may sign on another day. It is good practice to make an entry in patient's chart that the consent form was discussed and consent was obtained.

Banked Plasma

The APRON study consent includes the collection and banking of plasma for future use, such as measurement of study drug levels or metabolomics studies. If the patient does not agree, or does not wish to have plasma samples collected by the study, the patient should not sign the study consent.

Consent for genetic research

The consent for collection and banking of blood for genetic research should be administered in the same way that the APRON consent is administered, except that it should not be signed until the patient has been determined to be eligible for the APRON trial. The blood sample will be used as a source for DNA to study the relationship between genes and gastroparesis.

4.4. Time considerations for obtaining consent

- The **APRON Consent and HIPAA authorization** must be obtained at the start of the initial screening visit; documents from the referring physician (if any) should have been reviewed prior to the visit and the patient judged eligible for screening prior to the visit. Signature and date of signature of this consent is required prior to sending the patient for any APRON trial diagnostic tests, including collection of 10 mL of blood for processing of plasma to be banked for future use such as measurement of study drug levels or metabolomic studies. A check for signature of this consent statement occurs on the APRON Registration (RG) form.

- **APRON Consent for Collection, Storage, and Use of Blood Samples for Current and Future Genetic Research** must be obtained after eligibility for the APRON trial has been established at screening. Signature of this consent is required prior to drawing blood for genetic research for the APRON trial; a check for signature of this consent statement occurs on the APRON Genetic Consent and Blood Collection (CG) form. Signature of this consent statement is not required for APRON trial eligibility (i.e., the patient may choose not to participate in the genetic research component of the APRON trial).

- A patient should be given the consent statements to review prior to the initiation of screening visit. The patient should be allowed sufficient time to reflect about the APRON procedures, pose questions, and consult with other individuals that he/she considers relevant to their participation in the APRON trial. Patients may request and should be given time to "think it over" at home and come back at a later time. Whenever a consent is first given to a patient for review, it should be made clear to the patient that the consent should not be signed until requested by a APRON staff member. The consents may be mailed to the patient prior to screening visit.

4.5. Consent handling

- Signed consent statements are important legal documents. These signed statements should be kept in a locked and secure location in the patient's APRON clinical center file together with his/her other APRON forms and documents. These forms are not part of the individual's institutional medical record, but part of his/her study record in the APRON trial. Consent statements will be examined during site visits.

- Consents should be annotated with the patient's study identifiers (ID number and code).

- The APRON trial consent statement is an "all or none" form. The patient either accepts it in its entirety and signs it, or does not. The patient must consent to the evaluation procedures, the follow-up evaluations, and the banking of his/her plasma for studies such as the measurement of study drug levels or metabolomic studies. If the patient refuses any part, the patient may not enroll in the APRON trial.

- The APRON trial Consent for Collection, Storage, and use of Blood Samples for current and future genetic research has been made a separate consent statement so that the patient can opt out of genetic research and still participate in the APRON trial.

4.6. Informing participants of changes to consent statement after randomization

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As new data become available during the conduct of the APRON trial, the consent statements may need to be changed to reflect the current assessment of risks and benefits to participants in the trial.

Procedures for dissemination of revisions of consent statements from the DCC

- Changes deemed necessary will be made to the prototype consent statements
- Revisions of the prototype consent statements will be distributed to sites via a numbered Policy and Procedure Memorandum (PPM) with instructions to submit the revised consent to their IRB

Procedures for reviewing changes to consent statements with participants

- Clinical center personnel will develop a chronology of IRB approved changes to the consent statements used at their site
- At each follow-up visit, staff will use the chronology of consent changes to review with the participant any changes to the consent since the last visit. This review does not require obtaining the participant's signature on a new consent statement, unless the local IRB requires obtaining a signature.
- Review changes to the consent statements with participants at follow-up visits
- This review process is not intended to be a reaffirmation of consent. The clinical center, if required by their local IRB, may develop procedures for reaffirmation of consent.

4.7. Consenting patients who 'rolled over' from Gastroparesis Registry 2 to APRON

If the patient previously enrolled in the Gastroparesis Registry 2

- Consent as for a new APRON patient

If the patient previously consented to DNA banking as part of any other GpCRC studies such as the Gastroparesis Registry 2, Gastroparesis Registry, or NORIG

- Patient does not need to sign new consent for DNA banking as part of APRON if the volume of the blood sample obtained was satisfactory.

4.8. HIPAA considerations

APRON study staff have access to patient health information and to patient identifiers, such as name, address, and telephone number. Study records are to be kept in a secure place. Only people working on the APRON trial should have access to these records. However, these records could be reviewed to make sure that the trial is being conducted according to protocol. People who may see study records are:

- Officials of your institution
- Your institution's research ethics committee
- Monitors from the GpCRC Data Coordinating Center at the Johns Hopkins University, or other individuals selected by the GpCRC Steering Committee to monitor the study
- Members of the Data and Safety Monitoring Board (DSMB) to monitor overall progress of the study
- Government officials from the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), or the Food and Drug Administration (FDA)

Each clinical center should take steps to protect patient privacy. The assigned patient ID number and code should be used to identify patients on forms and in the data files. Personal information such as name, address, and telephone number should be kept only at the clinical center where a patient completes visits.

People outside the clinical center who will receive APRON trial data include:

- The GpCRC Data Coordinating Center at the Johns Hopkins University in Baltimore, Maryland (or its successor) to maintain the central study database
- The GpCRC Data and Safety Monitoring Board to review the APRON data for performance and safety
- The NIDDK Genetics Repository at Rutgers, the State University of New Jersey in New Brunswick, New Jersey (or its successor) will receive patients' blood to obtain DNA; the blood samples for a particular patient will be identified by the patient's study ID number and code, not by name
- The NIDDK Biosample Repository at Fisher Bioservices in Germantown, Maryland (or its successor) will receive patients' plasma; the samples for a particular patient will be identified by the patient's study ID number and code, not by name
- The GpCRC investigators, as well as outside researchers, to analyze and report APRON trial data. Patient identity will not be disclosed in any reports or publications resulting from the trial. While the APRON trial is ongoing, the use of the APRON trial data must be approved by the GpCRC Steering Committee and by the research ethics committee at your institution.

4.8. HIPAA considerations

Patient agreement to enter the APRON trial indicates that the patient also agrees to the use of the data as described above. If a patient does not agree to the described uses of the data, the patient may not participate in the APRON trial. The only exception is refusal to provide blood for DNA banking for genetic research; patients may refuse to provide blood for genetic research and still enroll in the APRON trial.

5. Study visits

5.1. Overview of visit schedule

Patient-related activities of the APRON trial can be divided into 4 phases:

- Screening for eligibility (1-2 visits over a maximum of 4 weeks)
- Randomization to treatment (1 visit)
- Treatment phase (2 visits over 4 weeks)
- Post treatment washout phase (1 visit at 6 weeks)

The screening phase may be conducted over 1-2 visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit. The visit schedule is a guide for the centers and allows flexibility in completion of screening procedures, however, a randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening forms keyed to the data system.

Screening (must be completed within 4 weeks of registration date)

- s: The patient should be in a fasting state (no food or drink after midnight except for 4 oz (120 mL) of water the night before) for this visit. The patient will sign the consent at or prior to the screening visit. The patient will undergo a history and physical examination to identify other illness and contraindications for participation such as use of narcotics for pain more than 3 days per week (including fentanyl patches), use of antimetics, use of warfarin, pimozide, terfenadine, astemizole or cisapride, or allergy to egg. On the Baseline Medical History (BH) form, the patient will be asked to respond to the Clinical Global Patient Impression (CGPI). The coordinator will give the patient the Daily Diary - Screening Only (DS) form for completion each night before bed. The patient will also undergo an eletrogastrography with satiety testing as detailed in SOP I section 6.5 and will complete the following questionnaires:
  - Gastrointestinal Symptoms Rating Scale (GSRS)
  - Upper Endoscopy Documentation (EG) - within 2 years
  - Health-related quality of life questionnaire (SF-36)
  - Beck Depression Inventory (BDI-II)
  - Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM)
  - State Trait Anxiety Inventory (STAI)
  - Brief Pain Inventory (BPI) focusing on abdominal pain
  - Patient Health Questionnaire (PHQ-15)
  - Nausea Profile

Anthropometric assessments (body weight, body height, waist circumference, hip circumference, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature), and general physical findings will be collected and recorded. Patients will have an ECG performed at this visit. Laboratory test results that need to be recorded from chart review or obtained as part of screening include: a complete blood count (CBC): white blood cells, red blood cells, hemoglobin, hematocrit, platelets; a metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine; and a hepatic panel: albumin, total protein, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin. Hemoglobin A1c is required for diabetic patients.

Randomization

- rz: Patients will have 10 mL of blood drawn for plasma banking and 20 mL of blood drawn for DNA banking if necessary. The last form to be completed before drug dispensing should be the Randomization form (RZ) which reaffirms the patient's consent to participate in the APRON trial.

  The Daily Diaries (DS) screenings completed by the patient at home will be keyed; if not already keyed.

  Women of childbearing potential must have a negative pregnancy test. Randomization occurs when the clinical center staff runs the enrollment task on the web based data management system and the patient is found to be eligible. A randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and all required baseline data has been keyed to the data system.

  Once the patient is randomized to the APRON trial, the specific numbered medication bottle to be given to the patient will be generated. This number is patient specific and will correspond to numbered bottles of medication which have been sent to the clinical center's research pharmacy (or clinical coordinator if not using a pharmacy) by the GpCRC Drug Distribution Center. The research pharmacy (or clinical coordinator) will issue the assigned numbered bottle to the patient. Each patient's random treatment assignment will be generated for that specific patient and will not be transferable to another patient. Once the assignment has been generated, the patient should be issued the assigned study drug (in person) and instructed about when to take the study drug and monitoring for potential adverse effects. The patient should also be given the Daily Diary - Follow-up (DD) form for completion each night before bed.

  The study drug dispensed at the time of randomization will be either a 125 mg capsule of aprepitant or a matching placebo capsule. Once the study drug is dispensed to the patient, remove the two tear-off portions of the label and affix one to your clinical center's drug inventory log and one to the Study Drug Dispensing and Return (RD) form. The RD form should be entered in the data system at the end of the visit to document study drug dispensing at randomization and maintain accurate drug inventory records.

Follow-up

- f2: Obtain a medical history including the global overall relief of symptoms question. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Brief Pain Inventory (BPI), Nausea Profile and Adverse Event Report. Review study drug adherence and tolerance. The Daily Diary Follow-up (DD) form completed by the patient at home will be collected. An additional Daily Diary Follow-up (DD) form will be provided to the patient for completion each night before bed.

- f4: Patient should be in a fasting state (no food or drink after midnight the night before). The Daily Diary Follow-up (DD) form completed by the patient each night during the last two weeks of treatment phase of the APRON trial will be collected by the clinical center staff. Patients will undergo an electrogastrography with satiety testing; medical history including the global overall relief of symptoms question, physical exam (temperature, heart rate, respiratory rate, blood pressure); 20 mL blood draw for laboratory test and plasma banking; and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), Beck Depression Inventory (BDI-II), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI) focusing on abdominal pain, Patient Health Questionnaire (PHQ-15), Nausea Profile and Adverse Event Report. Review study drug adherence and tolerance of the study drug with the participant. Collect the medication bottle dispensed at the randomization visit with unused study drug.

- f6: Obtain a medical history including overall relief of symptoms. Complete the Adverse Event Report. The Closeout (CO) form should be completed at the f6 visit for all patients randomized in APRON as outlined in SOP I, section 6.30.

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Screening		
s	RG	Registration (document consent, sociodemographics, assign IDs)
	PL	Patient location (patient contact information)
	BH	Baseline medical history
	PE	Physical exam including electrocardiogram
	EG	Upper endoscopy documentation
	GE	Gastric emptying scintigraphy documentation
	LR	Laboratory results
	GD	Assessment of Gastrointestinal Disorders
	GS	Gastrointestinal Symptoms Rating Scale
	QF	SF-36 Health Survey
	BD	Beck Depression Inventory
	SE	State-Trait Anxiety Inventory
	PI	Brief Pain Inventory
	PQ	Patient Health Questionnaire
	ST	EEG and Satiety Test
	NP	Nausea Profile
	DS	Daily Diary (Screening Visit)
Randomization		
rz	CG	Genetic consent and blood collection documentation
	BP	Blood processing for plasma
	RD	Study drug dispensing and return
	PL	Patient location (update as needed)
	DD	Daily Diary (Follow-up visits)
	RZ	Randomization
Follow-up phase		
2 week follow-up visit		
f2	FH	Follow-up medical history
	GD	Assessment of Gastrointestinal Disorders
	NP	Nausea Profile
	PI	Brief Pain Inventory
	PL	Patient location (update as needed)
	AE	Adverse Event Report
	DD	Daily Diary (Follow-up Visits)
4 week follow-up visit		

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
The patient should be in a fasting state for follow-up visit f4.		
f4	FH	Follow-up medical history
	PE	Physical examination
	BP	Blood processing for plasma
	GD	Assessment of Gastrointestinal Disorders
	GS	Gastrointestinal Symptoms Rating Scale
	ST	EEG and Satiety Test
	AE	Adverse Event Report
	QF	SF-36 Health Survey
	BD	Beck Depression Inventory
	NP	Nausea Profile
	GC	Gastroparesis Cardinal Symptom Index Daily Diary Documentation
	SE	State-Trait Anxiety Inventory
	PI	Brief Pain Inventory
	PQ	Patient Health Questionnaire
	RD	Study drug dispensing and return
	LR	Laboratory results
	PL	Patient location (update as needed)
6 week follow-up visit		
f6	FH	Follow-up medical history
	PL	Patient location (update so study results can be mailed at a later date)
	CO	Closeout form
	AE	Adverse Event Report

5.3. Guide for screening visit

The screening visit may be conducted over 1-2 visits. Clinical centers may alter the order of the visits or modify the procedures done during a particular visit to meet their needs. This visit guide allows flexibility in completion of screening procedures, however, a randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening forms keyed to the data system.

Procedures

- Patient should be in a fasting state (no food or drink after midnight the night before)
- Obtain signed consent for the APRON trial (consent form and HIPAA authorization form)
- Obtain permission to abstract data from patient's medical records
- Obtain patient location information
- Initiate data collection for screening and baseline values
  - Physical exam and anthropometric measurements (height, weight, waist circumference, hip circumference, temperature, blood pressure, resting radial pulse, respiratory rate, electrocardiogram)
  - Interview for baseline medical history (responses may be modified or expanded upon chart review)
  - Laboratory testing (hematology, metabolic panel, hepatic panel)
  - Upper endoscopy results documentation
  - Gastric emptying scintigraphy results documentation
  - Electrogastrography with satiety testing
  - Questionnaires regarding gastroparesis symptom severity, quality of life, pain, and depression

Data collection forms

- Forms completed for all patients
  - RG Registration (document consent, sociodemographics, assign IDs)
  - PL Patient Location (patient contact information)
  - BH Baseline Medical History
  - PE Physical Examination with electrocardiogram
  - EG Upper Endoscopy Documentation
  - GE Gastric Emptying Scintigraphy Documentation
  - LR Laboratory Results
  - GD Patient Assessment of Upper Gastrointestional Disorders Symptom Severity Index (PAGI-SYM)
  - GS Gastrointestinal Symptoms Rating Scale
  - QF SF-36 Health Survey
  - BD Beck Depression Inventory
  - SE State-Trait Anxiety Inventory
  - PI Brief Pain Inventory

- DS Daily Diary (Screening Visit)
- PQ Patient Health Questionnaire
- ST Electrogastrogram and Satiety Test
- NP Nausea Profile

Form to be completed by the patient for 7 days before bedtime

- DS Daily Diary - Screening visit

Forms for clinical center use only

- PL - Patient Location
- Medical records release (use local form)

Before the patient leaves the clinical center

- Register patient on clinic data system

After the patient leaves the clinical center

- Key completed data forms
- Set up a APRON trial chart for patient and file the completed forms.

5.4. Randomization visit

Procedures

- Requests for randomizations will be made by clinical centers using the web based data management system.
- A randomization assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement, has had all required baseline data keyed to the database and the clinical center staff indicate they wish to randomize the patient.
- The Daily Diary Screening visit (DS) must be completed and keyed before the patient is randomized. Because this is a long form, clinics may collect the DS form prior to randomization visit by mail or at a second screening visit at least one week after the first visit
- Once patient is successfully randomized into the APRON trial, the study drug bottle number assigned to the patient will be generated
- Patient is given the assigned study drug bottle with a number unique to the patient, instructed about starting the drug and monitoring for adverse effects, and begins taking study drug.
- Once the study drug is dispensed to the patient, remove the tear-off portions of the label and affix one to your clinical center's drug inventory log and one on the Study Drug Dispensing and Return (RD) form. The RD form should be entered in the data system at the end of the visit to document study drug dispensing at randomization and maintain accurate study drug inventory records.
- Patient is given Daily Diary Follow-up visits (DD) form

Data Collection Forms

– CG - Genetic consent and blood collection documentation
– BP - Blood processing for plasma
– DS - Daily Diary - Screening visit
– NP - Nausea Profile
– RZ* - Randomization checklist
– RD* - Study Drug Dispensing and Return

**(These data collection forms should be keyed into the data system last. The RD form should be keyed after drug has been dispensed)*

Comment

- The date of randomization visit is the date for reckoning all follow-up visits
- Use visit windows guide generated at randomization to schedule the first follow-up visit and prepare forms and labels that will be used at visit f2. The f2 visit may not be scheduled sooner than 1 week (7 days) after randomization.

5.5. Visit windows: randomization and follow-up

- **Randomization** must occur within 4 weeks (28 days) of registration date
- **f2**: window runs from week 1 through 3 weeks, ideal date is 2 weeks (14 days) after randomization date
- **f4**: window runs from (3 weeks+1 day) through 5 weeks, must be at least 8 days after f2; ideal date is 4 weeks (28 days) after randomization date
- **f6**: window runs from (5 weeks+1 day) through 7 weeks, must be at least 8 days after f4; ideal date is 6 weeks (42 days) after randomization date

5.6. Interim (unscheduled) visits or telephone contacts

- Unscheduled visits or telephone contacts may occur as needed. No time windows or minimum time separations are imposed for such visits or contacts.

- Data are not collected at interim visits (i.e., data forms are not completed) unless reporting an exacerbation of gastroparesis symptoms, study drug side effects, death or a serious adverse event.

- If gastroparesis symptom exacerbations or study drug side effects occur for a APRON trial participant between scheduled APRON trial visits, complete the Adverse Event Report (AE) form.

- The AE form is used to document (1) events that impact the patient's treatment or participation in APRON (e.g., temporary interruption or permanent cessation of study medication), or (2) adverse events thought to be associated with study drug that do not meet the criteria for Serious Adverse Event/IND Safety Report (SR) form, or (3) other event that clinical center staff feel should be reported now rather than wait until the next follow-up visit and that is not recorded on another APRON form. Adverse events associated with APRON study medication that are serious, unexpected, and have reasonable possibility of being caused by APRON study drug should be reported on this (AE) form, as well as recorded on the IND Safety Report (SR) form.

- Use visit code n even if reporting an event discovered during a regular follow-up visit. If more than one event is reported on the same calendar day (i.e., same date in item 4 for all events), use visit code n for first event, n1 for second event.

- Complete and key the AE form for any event that meets the criteria above. The short name (item 18) and the severity grade (item 19) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.gpcrc.us under Documents. Fax the DCC Attention: Ivana Vaughn and Erin Corless: (1) a copy of this form; (2) A narrative description of the event; (3) A copy of your report to your IRB if severity grade is 3 or higher (Fax 410-955-0932).

6. Study procedures

6.1. Assignment of study identifiers

What

- The GpCRC uses 2 identifiers for patients
  - ID number (4 digits)
  - ID code (3 alphabetic characters)
- These identifiers help assure confidentiality of patient identity

Materials

- ID number and code labels received from the Data Coordinating Center
- Registration (RG) form

When

- Screening visit (s)

By whom

- Clinical Coordinator

Procedures

- Complete the APRON Registration (RG) form; if the patient remains eligible at the close of the form, assign the ID number and code by peeling a label off the label sheet and affixing it to the specified item on form RG or note ID assigned previously in GpCRC
- Do not assign a new ID for previous GpCRC patients registering for APRON; use the ID assigned in the previous GpCRC study
- The patient will be known by these IDs for the duration of the GpCRC, including participation in any other GpCRC studies
- Key the Registration (RG) form into APRON web-based data management system; this must be the first form keyed and **no other forms may pre-date the date of the RG form**
- The Registration (RG) form should be keyed for each patient screened for APRON, including patients already enrolled in the Gastroparesis Registry 2

Comments

- Once an ID number and its associated ID code are assigned, these IDs must be used by the patient for the duration of the GpCRC and cannot be changed
- Do NOT reassign or reuse IDs assigned to patients found to be ineligible or who refuse enrollment

6.2. Screening Contact Log (SL form)

What

- Screening Contact Log

Purpose

- To record information on patients who are contacted as prospective participants for APRON

When

- Record prospective participants contacted regarding consenting and registration each week

Procedure

- Document your contact with each prospective participant on a single line of the Screening Contact Log (SL) form
- Each line should be numbered sequentially and the patient identifier may be a name or chart number (this information is not keyed to the data system)
- Complete items a-i for every prospective participant contacted
- Number the Screening Contact Log (SL) forms in sequential order
- Weekly or once you have filled a Screening Contact Log form please key the entire form to the web-based data management system.
- Key any partial forms during the last week of each month to ensure that your clinical center's recruitment efforts may be summarized accurately in the monthly performance reports
- Retain the SL forms in your clinical center's APRON files along with other study forms

6.3. Gastric emptying scintigraphy documentation (GE form)

Egg Beaters Gastric Emptying Scintigraphy

The standard scintigraphy meal will consist of a low fat Egg Beaters meal radiolabelled with 0.5 -1 mCi 99Tc, which is scrambled and cooked. This is served with 2 pieces of toast, jam, and water. The meal has a caloric value of 255 kcal (nutritional composition: 72% carbohydrate, 24% protein, 2% fat, and 2% fiber).

Items needed for Egg Beaters Gastric Emptying Scintigraphy
- Egg Beaters (egg substitute): 99% real eggs, cholesterol free, fat free, low calorie
  (120 g Egg Beater, 60 kcal, approx two large eggs)
- 2 slices of bread (120 kcal),
- Strawberry jam (30 g, 74 kcal)
- Water (120 ml).
- Technetium-99m 0.5 -1 mCi

Gastric emptying studies are generally performed in the morning. Patient should be fasting overnight or for at least 6 hours. (It is all right for the patient to have taken medications with no more than 4 oz (120 mL) of water on arising.) Patients should generally stop medications that can affect gastric emptying for 3 days prior to the test. This includes prokinetic agents, narcotic analgesics, and anticholinergic agents.

To prepare the meal, the Egg Beaters is poured into a bowl, sprinkled with 0.5 - 1 mCi 99Tc sulfur-colloid marker on top, mixed, and cooked in a microwave. Alternative is to use a skillet (nonstick frying pan). The Egg Beater mixture is stirred once or twice during cooking and is cooked until it has the consistency of an omelet (3-5 min). The bread is toasted. Jelly is spread on the bread, and a sandwich is made of the jellied bread and cooked egg mixture. The subject completes the sandwich meal within 10 minutes. The staff technologist records how long it takes the subject to consume the meal and the amount of the meal and water they consume.

Immediately after meal ingestion, the subject will be placed in front of a gamma camera with images taken in the 140 keV 99Tc peak with a 20% window (140 keV ± 10%). One minute of anterior and 1 minute of posterior measurements will be taken. Subsequent images are taken at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after meal ingestion and times of the images should be recorded (The 30 minute and 3 hour time points are optional, but should be obtained if possible. The 0 minutes, 1, 2, and 4 hour time points are required for APRON trial randomization.) In the time between images, subjects can be sitting, standing, or walking but should remain in close proximity to the nuclear medicine section.

Analysis is performed using the geometric mean of the anterior and posterior images for each time point which are then corrected for decay. Results are expressed as percent remaining in the stomach.

Gastric Emptying Scintigraphy Documentation (GE form)

- The Gastric Emptying Scintigraphy Documentation (GE) form is used to record results from a gastric emptying scintigraphy to determine eligibility for the APRON trial.
- Complete the GE form at screening visit s
- The 4 hour gastric emptying scintigraphy must be performed within 2 years prior to registration, or during screening, preferably at an APRON clinical center.
- Any necessary information not contained in the report (amount of meal or water consumed, time to consume meal) should be gathered from the patient or technician immediately after the test.
- The Study Physician should complete the GE form using the gastric emptying scintigraphy report.
- A copy of the scintigraphy report should be attached to the GE form as the source document.

6.4. Upper Endoscopy Documentation (EG form)

Purpose

- To document the results of the upper gastrointestinal endoscopy to determine APRON patient eligibility

When

- Screening visit s (the upper gastrointestinal endoscopy must have been performed within 2 years prior to the registration date)

- As needed during follow-up

Procedure

- Study Physician or Clinical Coordinator completes the form using the available reports (surgical and histology) of the upper gastrointestinal endoscopy procedure
- The EG form should be completed using the available reports of the upper gastrointestinal endoscopy procedure. Upper gastrointestinal and Endoscopy with Ultrasound (EUS) reports may be used if all of the required components of the EGD are available. Attach a copy of the available GI procedure reports as the source document.
- If a **Stop** or **Ineligible** is checked for any item, the patient is ineligible for the APRON trial unless the item can be resolved within the 28 day screening window (i.e., re-scheduling an EGD).
- The EG form **can not be keyed to the data system** if there are any Stop or Ineligible items present.
- The form should be retained in a study file for further evaluation as appropriate or in the file for ineligible patients. Attach a copy of the endoscopy report as the source document.

6.5. Electrogastrogram and Satiety Test (ST form)

Pre-test procedures

The patient should fast after midnight the night before the test (nothing to eat or drink except for 4 oz (120 mL) of water the night before). The patient is generally scheduled for a morning appointment at about 8 am for the electrogastrogram (EGG) and satiety test. The EGG will be performed using 3CPM equipment. For each EGG study, the clinical center needs to have:

- At least 4 cans of regular vanilla Ensure® (lactose free) available and refrigerated for each subject. Each can is regular vanilla Ensure® (lactose free) 8 fluid ounces; 237 mL, 250 calories
- A cup that has a 150 mL measured mark for the Ensure®.
- 3 EGG leads
- A dedicated quiet area for the EGG recording
- A reclining chair
- A blanket
- Metric ruler
- 3CPM EGG equipment

Test protocol

On the morning of the EGG and satiety test, the patient will arrive fasting, that is, nothing to eat or drink except for 4 oz of water after midnight the night before the test. Subjects 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. Diabetic patients will have blood glucose measured by fingerstick prior to the test. Only patients with levels between 60 and 275 mg/dL will be allowed to proceed with the test. Patients who do not meet this criteria will either return on another day or be managed at the site with insulin or other measures, at the discretion of the investigator.

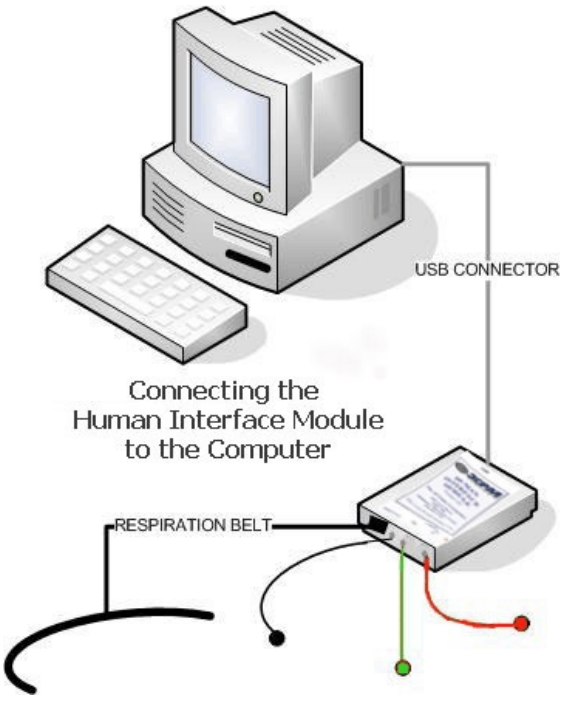
At the time of the visit, the APRON trial questionnaires and physical examination should be performed first, prior to the EGG and satiety test. Patient should be weighed. The patient should be encouraged to use the bathroom. Take the Ensure® out of the refrigerator just prior to starting the EGG baseline recording.

Electrogastrography is the recording of the electrical activity of the smooth muscle, nerves, and interstitial cells, in the stomach using electrodes similar to those used to record the electrocardiogram (ECG). EGG electrodes are placed on the abdominal skin. Skin preparation for these electrodes will consist of cleaning the skin and then applying pre-gelled electrodes. If needed, the abdominal surface where electrodes will be positioned is shaved. The recording is performed in a quiet room with the subject reclining at a 45 degree angle.

The following practical points will help to ensure a quality EGG recording:

- Record the EGG in a quiet room with subdued light
- Avoid all loud noises or distracting voices
- Position the patient in a comfortable chair or recliner (offer a blanket)
- Instruct the subject to keep arms and legs still, and to avoid any quick body movements.
- Talking should be avoided during the recording. Should an event such as coughing, movement, nausea, talking, etc happen during the baseline or post-stimulation periods of the EGG recording; you can mark the event by placing the mouse cursor over the desired minutes on the EGG tracing (the cursor will change to a pointer finger) and click the left mouse button. A screen will appear that gives you options for marking the event (cough, movement, etc) and a description box if you would like to record something other than the selections available. Once you select or enter the event, choose the "OK" button to complete the recording of the event. You may record an event as many times as one occurs. The object should be to have as many 4 minute segments without any events, so use the event recording only in cases of severe changes in the EGG tracing.

Equipment set-up:



Technique for skin preparation and electrode placement

1. Prepare to position the EGG electrodes as shown in the 3CPM User Manual:

   – The RED EGG lead wire and electrode (+) is placed on the left mid-clavicular line (left side) approximately two inches below the left costochondral margin (lower ribs).

   – The BLACK EGG lead wire and electrode (-) is placed approximately midway between the xiphoid process and the umbilicus, along the line from the xyphoid process to the umbilicus

   – The GREEN EGG lead wire and electrode (ground) is placed is placed two inches below the right costochondral margin (lower ribs) along the right midclavicular line.

2. Preparing the skin
   – Shave off abdominal hair that is present in these locations for electrodes 1, 2, and 3.
   – Gently abrade the skin in the areas of the electrode positions using a course cloth, 4x4 gauze, or "Buff-Puff'.

3. Positioning the electrodes on the skin
   a) Connect the color-coded EGG lead wires to the Human Interface Module, by matching the lead wire color to the corresponding color-coded plug-in as designated on the Module label.
   b) Attach the pre-jelled electrodes to the snap-on ends of the EGG lead wires.
   c) Remove the plastic covers from the adhesive side of the electrode, and place on the skin according to the instructions in #1 above.

4. Positioning and connecting the belt for recording respiration rate
   The subject should be in the recording reclining chair at a 45 degree angle which is comfortable for the subject. Attach the belt across the upper chest with the belt clip placed under the armpits and the entire belt pulled snugly to obtain the clearest respiration signal. Check the EGG leads to verify that they are well adhered to the skin before starting the EGG recording.

   – 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.

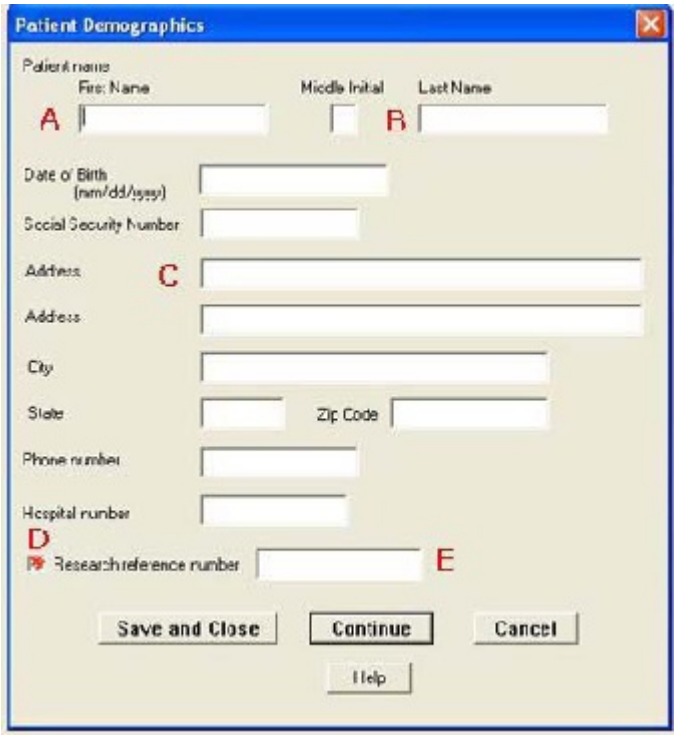
You may elect to start a study for a new patient in one of two ways:

- Select the icon for a new file, from the toolbar just under the top menu.
- Select File from the top menu, then select ***New Study***, and then select ***New Patient***.

De-identifying patient data:

– For EGG recordings in the APRON trial, **do not enter patient addresses, phone numbers, or social security numbers into the Patient Demographics screen**. This will prevent protected health information (PHI) from being displayed, printed, or transferred to Dr. Kenneth Koch at Wake Forest University or the DCC for central reading. It is the responsibility of the clinical center staff to ensure that system protections are utilized to meet HIPAA requirements followed at your institution and implemented by the Gastroparesis Clinical Research Consortium Steering Committee.

– Do not follow the guidelines outlined in the 3CPM User Manual for entering patient demographic for APRON trial research purposes. Instead, enter the participant's information as shown in the figure below:



A. Enter the GpCRC 4-digit ID number in the **First Name** field (i.e., 9000)
B. Enter the 3-letter patient ID code in the **Last Name** field, followed by the study abbreviation (apr) and visit code(i.e., zzzaprf4)
C. Enter the study name in the **Address** field (i.e., APRON etc.).
D. Always check the **Research Reference Number** box.
E. Re-enter the GpCRC 4-digit ID and the 3-letter patient code separated by a hyphen, followed by the study abberviation (apr) and visit code (i.e., 9000-zzzaprf4 for the APRON f4 visit).

Once the demographics have been entered, click on ***Continue*** to continue with the study.
Cancel stops the study without saving any information.
Save and Close saves the patient demographics and ends the study. The patient won't be available if you try to select a patient study as there is no study yet. However, if at a later date, you start a study again with this patient, the program allows you to use the previously entered patient demographics.

When ***Continue*** is selected, you may then enter pre-study information.

Equipment test

This section of the study makes sure that the signals (EGG and Respiration) are stable. Both signals must be stable for 2 minutes. The initial screen shows the Respiratory sensor and Gastric electrodes in large red dots. When these turn green, the system is ready to start the baseline recording. The EGG signal, shown in red is in the top graph. The Respiration signal, shown in black is in the bottom graph.

To start the equipment test, select the ***Start Equipment Test*** button. When both the Respiratory sensor and the Gastric electrodes turn green, the ***Begin Baseline*** button gets enabled. Then to start the Baseline, select this button.

Recording of EGG and respiratory signals

- If you have not yet removed the Ensure® from the refrigerator, remove it now, prior to the 15 minute baseline recording period.

- Allow 2-3 minutes before initiating the study in order to establish a stable skin-to-electrode interface. Obtain the first set of baseline symptoms using the symptoms score sheet (visual analog scale) page 2 of the EGG and Satiety Test (ST) form.

- Once the EGG and respiratory signals are stable, the baseline (pre-prandial) 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, which is comfortable for the subject.

– Select the ***Start Baseline*** button to start the baseline part of the study. The baseline period should last at least 15 minutes. Once the 15 minutes (baseline) have been reached, select the ***Stop Baseline*** button. You will then give the patient the symptoms score sheet (ST form page 3) to complete. You will have the options to select ***Pause Study, Skip Stimulation, and Stimulation Medium***. You will **always** select the ***Stimulation Medium*** button and leave this box open during the satiety test. When the subject has completed the satiety test, you will enter the amount of Ensure® consumed (in milliliters) in this box.

Satiety test

Patients will begin the Satiety Test. For this, subjects will sit up. During the test, subjects will drink regular vanilla Ensure® (1.1 kcal/mL) at a rate of 150 mL every 5 minutes until they feel "**completely full**." The patient's symptoms are recorded every 5 minutes and the total volume of Ensure® consumed will be recorded on page 4 of the ST form.

Instructions to patients for Satiety Test are as follows:

"You will be given a cup of Ensure® to drink every 5 minutes until you feel completely full. You will have up to 5 minutes to drink each cup. You may use all of this time, if needed. After each drink, we will ask about your feeling of fullness on a five-point scale, that is 0, 1, 2, 3, 4, 5 where 0 is not full at all and 5 is completely full. You will stop drinking when you become completely full from the Ensure®. This is not a test to see how much you can drink, but simply to have you drink until you feel completely full."

- After the subject feels completely full, have them complete the symptoms score sheet on page 5 of the ST form. The total volume of Ensure® consumed (ST form page 4) will be entered into the "stimulation medium" box at this time.

- The subject returns to the same 30-45 degree position that they were in for the fasting baseline condition.

- The electrodes should be checked to verify that they are well adhered to the skin before starting the EGG recording for the 30 minute post satiety period (after the drink is completed). The respiratory belt should be checked to verify it is snug.

Starting the EGG study recording (post satiety testing)

Once you have entered the amount of Ensure® that was consumed (in the ***Stimulation Medium box***) you will have two options: the ***Start Study*** and the ***Cancel*** button. You will always select the button "Start Study". You will then select the ***Begin Study*** button; this will start the 30 minute post satiety EGG recording.

- A continuous 30 minute EGG recording is then obtained.

- At the end of the 0-15 minute period, you will have the subject complete a symptoms score sheet (ST form page 6). **Do not select the Finish button** in order for the subject to complete the symptoms score sheet; the EGG should continue to run during this period. At the end of the 16-30 minute postprandial period, you will have the subject complete a symptoms score sheet (ST form page 7). Select the ***Finished*** button. A check box will appear and you will check the ***"Finish the Study***" box and then select the "***OK***" button. Once the study is complete, **save it immediately**. To save the study, click on the icon for saving a file. You can also select **File** from the top menu and then select **Save Patient**. When the study is complete, the raw EGG and respiration signals are displayed for the baseline period. Any events that have been marked are also displayed.

- The electrodes will be removed at this time. This concludes the study.

Selecting minutes for your report:
Important:

1. When selecting minutes: **choose whole minutes only**;
2. Choose **at least 4** consecutive good minutes, up to 15 minutes.
3. Do not select more than 15 minutes for any period.

Once the study is finished you will select good minutes for the Baseline part of the study first. To do this enter the full 15 minute baseline in the box "***Select the Length***" by making the Start Period 0.0 and the End Period 15.0. Once these numbers are entered then check the ***Set Period Length*** check box . You will then enter into the second set of boxes the artifact free ***Start minute*** and ***End Minutes***. (Example: 4.0 start minute and 14.0 end minute) Once the minutes are entered, you will check the ***Set Good Minutes*** check box.

Now you can go to the post baseline period, which is after the patient ingested the stimulation medium (Ensure®). You can do this by using one of the 4 following methods.

1. Select ***Go to next period*** icon, at the top of the screen.
2. Select ***Go to*** from the top menu and then select ***Next period***.
3. Select ***Analyze*** from the top menu and then select ***Post stimulation period 1***. While in this menu item (if you have completed analyzing the baseline period), you will notice that there is a check mark next to the ***Baseline period*** menu item. This indicates that the baseline period has been analyzed.
4. Open the pull-down list at the top of the screen and select ***Post stimulation period 1***. Select the length of the initial period for analysis (minutes 0-15), by setting the ***Start minute*** and ***End minute***.

NOTICE: The first post stimulation period includes all the minutes of the study (0.0 Start Minute and 30.0 End minute). You will change this and select the length of the first 0 to 15 minute period by making the Start Period 0.0 and the End Period 15.0 then check the ***Set Period Length*** check box. The remaining minutes (after the last minute in the period) will create the second post stimulation period (minutes 16-30). **Do not select more than 15 minutes for any period length.**

Select the artifact free good minutes within the period just created by setting the ***Start minute*** and ***End Minutes***. Choose whole minutes only. Choose **at least 4** consecutive good minutes, up to 15 minutes. Enter the artifact free minutes into the select Start and End boxes and then check the ***Set Good Minutes*** check box.

This same procedure (***Post Stimulation Period 2***) is used for selecting the period length for the remaining minutes 16.0-30.0 and for selecting good minutes. Use the EGG report to complete page 8 of the ST form.

Electrogastrogram and Satiety Test (ST form)

The Electrogastrogram and Satiety Test (ST) form is used to document symptoms and results of the satiety test and electrogastrogram in APRON trial participants.

- Complete the ST form during screening (s) and at follow-up visit f4.
- Have the patient respond to symptom evaluations on pages 2-7 by marking a vertical line in each of the visual analog scales on pages 2, 3, 5, 6, and 7. The scales should be measured from left to right with a metric (SI) ruler. Enter the value closest to the patient's vertical line in millimeters (0-100 mm) in items 14, 15, 19, 20, and 21
- Measure the calibration line on page 1 and enter the length of the line in millimeters in item 13.
- Using the EGG report, complete section **F. EGG data**
- The Study Physician and Clinical Coordinator should complete section **G. Administrative information**

Best practices when performing the EGG:

- When selecting minutes: choose whole minutes only; choose **at least 4** consecutive good minutes, up to 15 minutes. Do not select more than 15 minutes for any period.
- Attach a copy of the EGG report to the ST form. Save the raw digital EGG data to one of the USB flash drives provided by the DCC.
- EGG and satiety tests should immediately be saved in at least two locations (1) EGG machine's hard drive and (2) the back-up USB drive provided.
- Web support from 3CPM: http://www.3cpmcompany.com/Product_Support1.htm is now used by 3CPM to track support requests from the individual centers. Each person performing EGG's should create an account on the web support page.

Exporting the EGG files:

The 3CPM Export Manual and an updated EGGSAS Research User manual are posted to the GpCRC website. From the home page www.gpcrc.us, click on Documents, then click on *Electrogastrography* and the last bullet is the Export manual.

The export program does not create a location to hold the exported files. Instead it points by default to the 3CPM folder itself. You must create a folder to export to each time you do an export. Please create a master folder called "APRON Exported Data", then create individual subfolders each time you export a group of patient EGG files. This will organize and archive exported APRON patient data to a specific folder in a way that the data may be tracked and documented. For quality assurance purposes, each clinical center must forward their first two APRON EGG with satiety test recordings to Wake Forest University for review by Dr. Kenneth Koch. These EGG recordings should be de-identified (see prior EGG PPM 26: Certification for electrogastrography (EGG) and satiety testing). Do not enter any patient demographics when prompted. Enter the 4-digit patient ID number under **First Name** and the 3-letter patient code in the **Last Name** field. Follow the directions outlined in section 2.2 of the 3CPM EGGSAS Export program manual to select the studies you wish to export to the "APRON Exported Data" folder.

The EGG file (.egg) and the database file (.mdb) should be emailed to Wake Forest University, to the attention of Judy Hooker (jhooker@wakehealth.edu), and Dr. Kenneth Koch (kkoch@wakehealth.edu). Please copy at least two people from the data coordinating center on the email. If you are unable to email the files, you may send the USB drive to Wake Forest at the address below and they will return the USB flash drive to you once the EGG files are copied.

Judy Hooker/Kenneth Koch, MD
Department of Internal Medicine/Gastroenterology
Wake Forest University Health Sciences
Medical Center Boulevard
Winston-Salem, NC 27157

6.6. Baseline Medical History (BH form)

Who

- APRON patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries:
  - Symptoms of gastroparesis
  - Medical history (answer items based on information from all sources available to you)
  - Medication used currently and in the past month
  - Baseline clinical global patient impression

When

- Screening visit s

How

- Mix of interview data and data obtained by chart review
- Questions on the BH form can be answered by interview with the patient – i.e., use all sources to get the most accurate information that you can
- Show the patient Flash Card #7 for the Clinical Global Patient Impression
- If a **Caution** is checked for any item, further review is necessary by the study physician who will determine whether the diagnosis or condition in the Caution item renders the patient ineligible for or unlikely to comply with the requirements of the APRON trial.
- If a **Stop** or **Ineligible** is checked for any item, the patient is ineligible for the APRON trial unless the item can be resolved within the 28 day screening window (i.e., gastroparesis symptom duration is less than 6 months, medication use will be stopped for a washout period).
- The BH form **can not be keyed to the data** system if there are any Stop or Ineligible items present
- The form should be retained in a study file for further evaluation as appropriate.

6.7. Follow-up Medical History (FH form)

Who

- APRON patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries/reviews
  - Change in patient's symptoms
  - Medical history diagnoses
  - Emergency room visits, hospitalizations, and procedures since the last visit
  - Medication use since the last visit
  - Clinical Global Patient Impression

When

- Visits f2, f4, and f6

How

- Mix of interview data and data obtained by chart review
- Questions on the FH form can be answered by interview with the patient – i.e., use all sources to get the most accurate information that you can
- Show the patient Flash card #7 for the Clinical Global Patient Impression

6.8. Physical Examination (PE form)

Who

- APRON patients

When

- Screening visit s and follow-up visit f4

What

- Vital signs
  - Temperature
  - Blood pressure
  - Resting radial pulse
  - Respiratory rate
- Anthropometry
  - Height
  - Weight
  - Waist and hip circumference
- System review
  - Chest and lungs
  - Heart
  - Abdomen
  - Liver and spleen
  - Nervous system
- Electrocardiogram (ECG) is required during screening. Use Flash card #8 to guide your review of the electrocardiogram. If patient's QTc interval is greater than 450 milliseconds, the patient should be referred to cardiology for further evaluation for prolonged QT syndrome or other cardiac abnormalities. If ECG findings during screening are incompatible with APRON participation, the participant is ineligible.
- A negative pregnancy test for women of childbearing potential is required during screening to be eligible for randomization into the APRON trial.

How

- Ideally, use a stadiometer for height measurement
- Ideally, use the Gulick II tape measure for waist and hip measurement; this device may be obtained from www.fitnessmart.com (608-735-4718, model 67019, listed at $47.50). It is manufactured by Country Technology Inc: 608-735-4718
- See SOP sections 6.9 and 6.10 which detail the protocols for measurement of height, weight, waist circumference, and hip circumference

6.9. Height and weight measurements

Height measurements

- Height may be recorded in inches or centimeters
- Ideally, a wall-mounted stadiometer with a horizontal measuring block (or fixed angle) is used; other height measuring devices are acceptable
- Follow the manufacturer's recommendation regarding method and frequency of calibration of the stadiometer
- The patient stands erect on the platform with his/her back parallel to the vertical mounted measure scale (but not touching the wall), looking straight ahead with his/her head in the Frankfort horizontal plane (the horizontal plane defined by the lower margin of the bony orbit (the bony socket containing the eye) and the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear))
- The horizontal measuring block is brought down snugly, but not tightly, on the top of the head
- Record the height to the nearest tenth of the unit of measurement (1 decimal place)

Weight measurements

- Follow the manufacturer's recommendation regarding method and frequency of calibration of the scale
- Weight may be recorded in pounds or kilograms
- Ideally, weight is measured in the morning after voiding and before breakfast; if this is not possible, try to measure the patient's weight at the same time of day and under the same conditions as the baseline measurements are obtained
- Patient should be wearing light clothing (e.g., short sleeve shirt and shorts, or surgical gown) and socks without shoes; pockets should be empty
- Patient should stand still in the middle of the scale platform with head erect and eyes looking straight ahead
- Record the weight to the nearest tenth of the unit of measurement (1 decimal place)
- Patients who have limb amputations or who are wearing casts should have weight measured, but note this on the form on the margin (the notes may be keyed at data entry in the General Comments area of the keying)

6.10. Waist and hip circumference measurement

- Waist and hip circumference may be recorded in inches or centimeters
- Ideally, a Gulick II Tape Measure will be used. This tape measure is designed to eliminate the guesswork by applying a known amount of tension (4 ounces) to the measuring tape; when used properly, tape tension is always 4 ounces. The self-retracting tape is kept at the desired length until the retract button is pushed
- If an ordinary tape measure (without the special 4 ounce tension indicator device) is used, the measurement will be affected by how tightly the tape is pulled
- Patient should be wearing light clothing (e.g., short sleeve shirt and shorts or surgical gown) and socks without shoes; pockets should be empty
- Ideally, waist and hip circumferences are measured in the morning after voiding and before breakfast; if this is not possible, try to measure the patient's waist and hips at the same time of day and under the same conditions as the baseline measurements are obtained

Waist circumference measurement

- Patient should stand with feet together
- Pull an appropriate amount of tape out of the housing
- Ask the patient to bare his/her waist
- Wrap the tape once around the waist: the measure should be taken around the abdomen horizontally at the midpoint between the highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line
- Mark the midpoint on both sides of the patient using a washable marker
- Patient may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position
- When the tape is positioned in the horizontal plane at the correct height, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
- Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
- Record the measurement to the nearest tenth (one decimal place)
- If the tape cannot be made horizontal across the waist markings, default to the right hip and note this in the margin of the form

Hip circumference measurement

- Ask the patient to adjust his/her clothing to allow measuring the hips over the patient's underwear
- Wrap the tape once around the hips over the underwear: the measure should be taken at fullest part of the hips (maximum extension of the buttocks)

6.10. Waist and hip circumference

- Patient may be asked to assist in passing the tape around the hips by holding the end of the tape in position
- When the tape is positioned correctly, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
- Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
- Record the measurement to the nearest tenth (one decimal place)

6.11. Nausea Profile (NP form)

What
- Nausea Profile

Purpose
- To obtain the patient's frequency and intensity of symptoms due to nausea

When
- Screening visits and follow-up visits f2 and f4

Procedure
- Clinical coordinator should complete section A (center, patient, and visit identification) and apply preprinted MACO labels to page 2 before giving the questionnaire to the patient for completion
- Self administered
- The clinical coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the center. Page 1 should be reattached to page 2 and the clinical coordinator should complete section B.

6.12. Daily Diary – Screening Visit (DS form)

What

- Daily Diary of Nausea Visual Analog Scale and Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)

Purpose

- To assess daily symptom severity in patients with gastroparesis in the APRON trial

When

- Screening visit s

How

- The clinical coordinator should complete section A and attach MACO labels to pages 2-8.
- The clinical coordinator should give labeled pages 2-8 to the patient and instruct the patient to complete one diary each evening before bed for 7 days, scoring the VAS as their nausea severity in the past 24 hours.
- The form should be returned to the clinical coordinator at the randomization visit, by mail, or at a second screening visit at least 7 days later than the first visit. (NOTE: If the form is returned at the randomization visit, the clinical coordinator must complete and key the form and assess eligibility prior to randomization)
- The nausea visual analog scales in items 13, 14, 15, 16, 17, 18 and 19 should be measured left to right with a metric ruler, to the closest millimeter (0-100 mm)
- The Clinical Coordinator should complete sections B and C on page 1
- Pages 2-8 should be reattached to page 1
- If the mean nausea VAS score (item 10b) is less than 25 mm, the patient is ineligible and MAY NOT BE RE-SCRENEENED; complete the RZ form to document reasons for ineligibility and enter the RZ form in the data system

6.13. Daily Diary – Follow-up visits (DD form)

What

- Daily Diary of Nausea Visual Analog Scale and Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD)

Purpose

- To assess daily symptom severity in patients with gastroparesis in the APRON trial

When

- Visits rz and f2

How

- The Clinical Coordinator should complete section A and attach a MACO label to pages 2-15
- The clinical coordinator should instruct the patient to complete one daily diary each day before bed for 14 days, scoring the VAS as their nausea severity in the past 24 hours.
- The form given at the randomization visit should be returned at the f2 visit. The form given at the f2 visit should be returned at the f4 visit
- The nausea visual analog scales should be measured from left to right with a metric ruler, to the closest millimeter (0-100 mm)
- The Clinical Coordinator should complete sections B and C and reatttach pages 2-15 to page 1

6.14. Assessment of Gastrointestinal Disorders

What

- Assessment of Gastrointestinal Disorders

Purpose

- To assess symptom severity in patients with gastroparesis in the APRON trial

When

- Screening visit s and follow-up visits f2 and f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) and apply preprinted MACO labels to pages 2-4 before giving the questionnaire to the patient to complete
- Self administered
- **Clinical Coordinator should check returned questionnaire for completeness, check that item 37 (predominant symptom) response is only one item, and complete the scoring section B items 8-12 before the patient leaves the clinical center**
- Page 1 should be re-attached to pages 2-4
- The total GCSI score is the sum of the 3 subscores in items 8, 9 and 10. The maximum total score is 45
- During screening the total GCSI score must be 21 or greater to be eligible for the APRON trial; if the GCSI is less than 21, the patient is not eligible at this visit but may be re-screened at a later visit using a new GD form. Do not key the form to the data system if an Ineligibility is reached

6.15. Gastrointestinal symptom rating scale (GSRS) (GS form)

What

- Gastrointestinal symptom rating scale (GSRS)

Purpose

- To collect data on the symptoms the patient has been experiencing during the APRON trial.

When

- Screening visit s and follow-up visit f4

How

- Clinical Coordinator should complete section A (Center, patient, and visit identification) on page 1 and apply preprinted MACO labels to pages 2-7 before giving to the patient to complete the questionnaire.
- Self-administered
- The Clinical Coordinator should review pages 2-7 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-7.

6.16. Brief Pain Inventory (PI form)

What

- Brief Pain Inventory

Purpose

- To assess the severity and impact on daily functions of the patient's pain in the APRON trial.

When

- Screening visit s and follow-up visits f2 and f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) on page 1 and apply preprinted MACO labels to pages 2-4 before giving to the patient to complete the survey
- Self-administered
- The Clinical Coordinator should review pages 2-4 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-4.

6.17. State-Trait Anxiety Inventory (SE form)

What

- State-Trait Anxiety Inventory (STAI)

Purpose

- To collect data on the psychosocial aspects of gastroparesis in APRON participants

When

- Screening s and follow-up visit f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) and apply preprinted MACO labels to pages 2-4. The patient should be given pages 2 and 3 to complete
- Self administered
- The Clinical Coordinator should review pages 2-3 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-4 and the Clinical Coordinator should use the scoring key on page 4 to calculate the Y-1 and Y-2 scores to complete item 8 on page 1
- Only items 1-10 on page 1 are keyed into the APRON data system

6.18. Beck Depression Inventory (BD form)

What

- Beck Depression Inventory Questionnaire

Purpose

- To collect data on the psychosocial aspects of gastroparesis in APRON participants

When

- Screening visit s and follow-up visit f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) and apply preprinted MACO labels to pages 2-9 before giving the questionnaire to the patient to complete.
- Self administered
- **Clinical Coordinator should check returned questionnaire for completeness and complete the scoring section items 8-11 before the patient leaves the clinical center.**
- The score is the sum of 21 items. If the patient has made more than one choice for an item, use the highest scoring item. The maximum total score is 63.

  The box below provides guidelines on depression level for patients within certain scoring ranges.

Total Scores	Range
0-13	minimal
14-19	mild
20-28	moderate
29-63	severe

- Special attention should be paid to item 2 and to item 9. Patients admitting to suicide ideation (as measured by item 9) and/or hopelessness (as measured by item 2) with a rating of 2 or 3 should be flagged for further clinical care.

- Special attention should be paid to item 16 (changes in sleeping pattern) and item 18 (changes in appetite). There are seven answer options (0, 1a, 1b, 2a, 2b, 3a, 3b). If a patient indicates a different answer for either of these questions as compared to when they last completed the form, this should be noted for clinical care.

- Implement a plan of action per the APRON protocol and your clinical center's guidelines for caring for patients with:
  - a total score between 29-63 or
  - a response of 2 or 3 on item 2 or item 9

6.19. SF-36 Health Survey (QF form)

What

- The SF-36 Health Survey is a 36-item patient reported survey

Purpose

- To obtain the patient's views of his/her health

When

- Screening visit s and follow-up visit f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) and apply preprinted MACO labels to pages 2-7 before giving the questionnaire to the patient to complete
- Self administered
- Clinical Coordinator should review the returned questionnaire for missing responses and resolve any problems before the patient leaves the clinical center

6.20. Patient Health Questionnaire (PHQ-15) (PQ form)

What

- Patient health questionnaire is a 15-item patient reported measure

Purpose

- To obtain the patient's views of his/her health during the APRON trial

When

- Screening visit s and follow-up visit f4

Procedure

- Clinical Coordinator should complete section A (Center, patient, and visit identification) and apply a preprinted MACO label to page 2 before giving the questionnaire to the patient to complete
- Self administered
- Clinical Coordinator should review the returned questionnaire for missing responses and resolve any problems before the patient leaves the clinical center

6.21. Laboratory Results (LR form)

What

- Form LR records laboratory results for tests done during screening and follow-up
  - Hematology
  - Hepatic panel
  - Metabolic panel, including magnesium
  - Hemoglobin A1c (required only for diabetic patients)

When

- **All** laboratory results are required during screening and f4
- When laboratory results are available during other follow-up visits

Instructions for form LR

- The measures on form LR are intended to be obtained by chart review, both at screening and during follow-up
- During screening, if the chart review tests are outside the 4 week time window or the test conditions can't be ascertained or differ from what is required, the chart review tests cannot be entered on the LR form and the tests should be repeated
- During follow-up, the results must be within the time window for the follow-up visit

6.22. Plasma collection for Biosample Repository (BP form)

Purpose

- Collection of whole blood from APRON patients for plasma banking
- Separation of plasma at clinical center: ten - fourteen 0.5 mL aliquots of plasma are to be aliquoted in 2.0 mL cryogenic vials
- Store plasma aliquots at -70° C prior to batch shipping to the NIDDK Biosample Repository at Fisher BioServices each month
- Conduct activities of aprepitant levels, metabolomics and other ancillary studies approved by GpCRC and if additional funds are available

Forms / Materials

- BP - Blood Processing for Plasma
- Preprinted MACO labels for heparin (green top) tube and BP form
- Choose one of the cryovial label sets provided by the DCC, ensuring the patient ID is correct
- Barcode scanner
- SS - Specimen Shipment log
- NIDDK Biosample Repository shipper

When

- Screening (s) or Randomization (rz) visit
- Follow-up visit f4
- Batch shipments: Monthly or more often as needed

By whom

- Phlebotomist
- Clinical Coordinator
- Person responsible for shipping to NIDDK Biosample Repository must have formal, documented training to package and ship hazardous goods, per DOT/IATA guidelines

Equipment

Blood tubes/aliquot vials

- One 10 mL sodium heparin (green top) tube - *provided by clinical centers*
  - Model/product number: Becton Dickinson product number #367874
  - 100 tubes/pack @ $48.45

- 10-14 2.0 mL cryogenic vials - *provided by clinical centers*
  - vials should be able to withstand -196 degrees C
  - vials should be self standing (flat bottom, not curved), externally threaded, 13.5 mm wide x 48.3 mm tall, with silicone washers
  - Vendors contact information:
  1) Cyrogenic Storage Systems and Supplies (CIC)- Model #CV200-2
     243 Lawyers Road, NW
     Vienna, VA 22180
     703-319-8247
     877-738-8247 (toll free)
     703-938-9351 (fax)
  2) Corning External Thread Cryogenic Vials
     Catalog # 430659
     50 per pack, 500pk/case: $266.50
     Telephone: 1-800-492-1110; 1-800-325-3010
  3) Fisher Scientific
     1-800-766-7000
     Catalog #10-500-26
     100/pack ($54.60)
     Telephone: 1-800-766-7000

Labels

- Preprinted MACO labels for whole blood collection tubes (10 mL heparin tube) and for Form BP – MACO *labels are printed at the clinical center via web-based data management system; use MACO ML-5000 1" x 1 ½" labels, 50 labels/page*
- Preprinted polypropylene labels for 2.0 mL cryogenic vials – *provided by the DCC*

Equipment

- Centrifuge
- -70° C freezer
- Swing out rotor
- 5 mL pipettes

Preparation for blood collection

Apply labels to cryovials

- Attach the blue plasma polypropylene cryovial labels for aliquots #01-14 to the vials when the vials are at room temperature (Label for aliquot #00 goes on the BP form)
- Leave the cap on the vial when labeling; the inside of the vial is sterile
- Apply the label to the vial so that the long edge of the label is parallel to the floor when the vial is held in an upright position. The label should not trail off the bottom of the vial or over the cap
- While holding the vial in an upright position, affix the colored portion of the label to the vial first

- Wrap the clear tail around the perimeter of the vial. The end of the clear tail should overlap the colored portion of the label
- Press firmly on the entire label. Verify that all edges of the label adhere to the vial
- When possible, allow newly labeled cryovials to set at room temperature for several hours prior to subjecting them to colder temperatures. (24-48 hours is optimal)

Blood collection and processing procedures

- Blood for plasma to be centrifuged, aliquoted, and frozen within one hour
- If sample appears to have hemolyzed; do not aliquot. Re-draw blood.
- Patient instructed to fast 8 hours prior to blood draw
- Ensure that heparin tubes have not expired (*check that date shown above "Exp" in lower right corner of tube label is later than current month*).
- Collect whole blood into one heparin (green top; Becton-Dickinson #367874) tube.
- Affix the patient and visit specific MACO label to the heparin tube
- Completely fill vacutainer tube
- Mix gently by inversion 5 times
- Within 30 minutes, centrifuge at 1800 x g for 15 minutes at 4° C, preferably with a swing out rotor
- Immediately after centrifugation, insert a 5 mL pipette below surface of plasma
- Remove the clear plasma while avoiding blood cells
- Transfer plasma into aliquots of 0.5 mL each into 10-14 labeled 2.0 mL cryovials
- Freeze at -70° C immediately
- Discard the any remaining labeled cryovials with the same LS code
- Discard all red serum polypropylene cryovial labels with the matching LS code

Note: Plasma aliquots may be stored at -20° C for a few hours and a maximum of up to one day before transfer to -70° C . Make arrangements with your laboratory technicians as needed to ensure samples remain frozen during the transfer.

Blood Processing for Plasma (BP) form

- Complete the Blood Processing for Plasma (BP) form
- Affix duplicate MACO label for the heparin plasma tube to the BP form
- Affix the blue plasma cryovial label for aliquot #00 to the BP form

Packaging Procedures

- Check that 1 absorbent pad is in the Saf T Pack Bio hazard plastic bag
- Insert frozen cryovial into small cardboard boxes with dividers. Place only one tube into each cardboard divider. Each cardboard box may hold 81 cryovials
- Insert each cardboard box with cryovials into its own plastic bag and seal
- Place each plastic bag with specimen box into its own STP-710 Tyvek envelope and seal.

- Place each Tyvek envelope into STP-111 inner brown cardboard box. No more than 3 Tyvek envelopes containing boxes with cryovials can be placed into the STP-111 inner brown cardboard box. If shipping only 1 or 2 specimen boxes, fill the rest of the space inside the cardboard inner box with bubble wrap to prevent movement
- Tape the inner cardboard box closed before placing the styrofoam cooler
- Place cardboard box in upright position in bottom of styrofoam cooler
- Surround the STP-111 inner brown cardboard box with abut 8 kg of 2" blocks or nuggets of dry ice
- Fill excessive room left in the insulated freezer box with bubble wrap to stabilize specimens in transit
- Place the polystyrene lid onto the freezer box
- Place the "Empty Packaging" cover and shipping form on the top of the cooler lid
- Place a completed Specimen Shipment Log with Excel spreadsheet attached on top of the cooler lid
- Close and seal outer cardboard box with tape

Labeling Shipper:

- Place a checkmark in the block on the outer cardboard box next to "BIOLOGICAL SUBSTANCE, CATEGORY B". Do not cover this marking with labels.
- Affix a label with your name and return address to the side of the box in the "Shipper:"
- Affix the repository address label to the side of the box in the "Consignee:"
- Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms
- Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the right of the dry ice label
- Use the preprinted Federal Express air bill to ship specimens to the NIDDK Biosample Repository. Complete return address (leave "Sender Federal Express account number" blank). Section 6, Special Handling: Check "Yes, Shippers Declaration not required," check "Dry Ice" block and entry" "1 x 8" kg. Section 7, Enter "1"under "Total Packages" and the total weight of 24 lbs. Place completed Federal Express Airbill on side of box adjacent to the labeled side. Call Federal Express at 1-800-463-3339; give them the account number in section 7 of the Airbill

  Do not write on exterior of box

  Do not ship frozen packages on Friday; the repository is closed on weekends

Shipping samples to the NIDDK Biosample Repository

- Specimens are to be batch-shipped monthly to Fisher BioServices on Monday, Tuesday, or Wednesday
- Aliquots will be stored locally at the clinical center at -70° C prior to shipping

6.22. Plasma collection for Biosample Repository (BP form)

- Ship specimens in the STP 320 Saf T Pak shipper (provided by the NIDDK Biosample Repository); each shipper can accommodate aliquots for 16 patients, depending on the number of aliquots obtained for each patient (maximum capacity of each shipper is 230 aliquots)
- Open the template Excel file used for shipments and scan each cryovial using the barcode scanner provided to your clinical center. The file should have the filename GpCRC_Site6xx_shipdate.xls. Replace the xx with the last 2 digits for your clinical center's site ID and replace ship date with the date of shipment.
- The Excel shipping file has column headings for barcode number, Site ID-Patient ID, Patient code, date collected, plasma, volume, units of measure, study number and visit code. You must complete all of these columns.
- Complete Section A: Center ID, shipment, and study information and Section B: Clinic administrative information of the Specimen Shipment Log (SS) form. The Excel spreadsheet will replace Section C: Specimen shipment information. **Enclose a printed copy of the Specimen Shipment Log and the Excel spreadsheet with each shipment of specimens.**
- Keep a notebook of all original completed Specimen Shipment Logs (Form SS) and spreadsheets so that you have a record of all shipments to the Biosample Repository
- Email the Excel spreadsheet to the Biosample Repository at bio-niddkrepository@thermofisher.com with the Fed Ex tracking number in the subject line of the email.

6.23. Blood collection for Genetics Repository (CG form)

Purpose

- Collection of whole blood from APRON patients who consent for genetic research
- Shipment of whole blood to the NIDDK Genetics Repository at Rutgers University for DNA banking

Forms

- APRON consent for genetic research
- Genetic Consent and Blood Collection Documentation (CG) form
- NIDDK Genetics Blood Collection form

When

- Screening (s) or randomization (rz) visits or any time during follow-up if unable to obtain during screening or due to a low yield of DNA from initial collection (less than 100 micrograms of DNA), for participants who have not previously consented to DNA banking
- Ship same day as blood collection; **Monday - Friday**

By whom

- Clinical Coordinator and Study Physician (to obtain consent)
- Phlebotomist (to obtain whole blood)
- Person responsible for shipping whole blood to NIDDK Genetics Repository must have formal, documented training to package and skip hazardous goods, per DOT/IATA guidelines

Equipment

- Two 10 mL NaEDTA vacutainer tubes (purple top) - *provided by NIDDK Genetics Repository*
- Preprinted MACO whole blood tube labels and form CG labels - *provided by clinical centers (printed from web based data management system; clinical center provides MACO ML-5000 labels (1" x 1 ½ ", 50 labels per page, www.macolabels.com/ml-5000.html*
- Shipper - *provided by NIDDK Genetics Repository*
  - One model 470 Thermosafe Safety Mailer (styrofoam body and lid)
  - One 2 ½" x 9" pre-cut section of absorbent materials
  - Two 18" strips of red waterproof tape
  - One press-lock plastic bag
  - One corrugated shipping carton with locking tabs
  - One assembly instructions for Model 472 Thermosafe Safety Mailer

6.23. Blood collection for Genetics Repository

Blood collection procedures

- Collect blood into two 10 mL NaEDTA (purple top) tubes
- Invert each tube gently 6 times to mix blood with additives
- Keep blood at room temperature
- Check that patient ID information on preprinted MACO tube labels matches information recorded onto the NIDDK Genetics Initiative Phlebotomy form
- Phlebotomist should sign and date the section: To Be Completed by Phlebotomist on the NIDDK Genetics Initiative Phlebotomy form

Applying labels to tubes

- Apply the MACO labels over the paper vacutainer labels already on the tubes.
- Leave the cap on the tube when labeling; the inside of the tube is sterile

Packaging procedures

- Ship whole blood at ambient room temperature same day to the NIDDK Genetics Repository
- Package the whole blood tubes in the body of the Safety Mailer (Model 472 Thermosafe Safety Mailer)
- Tear off one section of absorbent materials along perforates and place it so it exactly covers cavity of the Safety Mailer
- Place lid of Safety Mailer over body and absorbent material and press down firmly so that lid closes properly. Reposition absorbent material so that it does not get caught between the lid and body
- Peel backing from two 18" long pieces of red waterproof tape and seal the Safety Mailer lid to the body; peel backing from second piece of tape and continue sealing the mailer, overlapping the first piece of tape about two inches on both ends
- Place the sealed Safety Mailer into the press-lock plastic bag. **Do not seal the bag**.
- Place the NIDDK Genetics Initiative Phlebotomy form in the mailer box outside the plastic bag
- Slide the Safety Mailer and open press-lock bag into the corrugated carton
- Seal the press-lock bag and close carton using the locking tabs
- Place sealing tape (not included) over them

Shipping procedures

- Use the preprinted Federal Express shipping label, marked for *Priority Overnight Delivery*, to ship whole blood to the NIDDK Genetics Repository, Monday - Friday
- Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY "B" label to the outside cardboard box
- Call Federal Express, 1-800-Go-FEDEX (1-800-463-3339) for courier. *Due to inconsistent Federal Express delivery around holidays and likelihood of closure of the Genetics Repository on holidays, do not schedule deliveries on the day before or the day of a national holiday. Check with Federal Express and with the Genetics Repository if there is any question about delivery availability or closure.*

- Ship whole blood to:
  Rutgers University/Cell Repository/NIDDK
  604 Allison Rd., Room C120A
  Nelson Laboratory
  Piscataway, New Jersey 08854-8000

Genetics Repository Web Portal System
Rutgers University Cell and DNA Repository - (RUCDR) implemented Laboratory Information Management System (LIMS) software to track shipments. **Please note that the system is not compatible with Mac systems.**

- Please call 732-445-4429 with ANY questions about computer configuration for immediate support. The list of requirements are posted here: https://rucdrlims.rutgers.edu/starlims10.rucdrlims/support/default.htm

- Additionally, they have set up a support email account to specifically address LIMS questions. The address is starlimshelp@biology.rutgers.edu.

Establishing a Username and Password

http://rucdrlimsregister.rutgers.edu/

- Go to the URL listed above and then just follow the directions on the page. You will receive a confirmation email. You will then be contacted to establish your account.

Training videos

- There are training videos for several functions on their website: http://www.rucdr.com/training.htm
- **RUCDR STARLIMS Request for Supplies** (http://rucdrlimstraining.rutgers.edu/reqsupply_video.htm)

This video tutorial will teach you how to order supplies such as collection kits, phlebotomy forms and FedEx AirBills through the RUCDR STARLIMS system. The video will guide you through the appropriate steps of requesting supplies from the RUCDR. Should you need any additional help after watching the video, please contact our RUCDR STARLIMS helpdesk by phone at 732.445.4429 or email at starlimshelp@biology.rutgers.edu.

- **RUCDR STARLIMS Sample Submission** (http://rucdrlimstraining.rutgers.edu/presubmission_video.htm)

This video tutorial will teach you how to preregister your samples through the RUCDR STARLIMS system. By watching the video, you will learn the steps required to correctly preregister your samples before they are sent to the RUCDR.

6.23. Blood collection for Genetics Repository

Logging in to the System

- The URL for the RUCDR StarLIMS system is https://rucdrlims.rutgers.edu/starlims10.rucdrlims/start.lims Enter your username and password. If you ever forget your username or password there are options on this screen to retrieve a lost password or username. You will need to remember what email address you used to create your account to use this function!

Sample Submission

- Use the STARLIMS system to notify the NIDDK Genetics Repository that blood is being shipped and provide the Federal Express tracking numbers and the NIDDK ID numbers. Notification may be via:
  - STARLIMS system: https://rucdrlims.rutgers.edu/starlims10.rucdrlims/start.lims
  - Fax: 1-732-445-1149
  - Telephone: 1-732-445-1498

6.24. Study drug dispensing and return (RD form)

Purpose

- To document dispensing and return of study drug and accounting for unused capsules and empty study drug bottles

When

- Randomization and follow-up visit f4

Dispensing of study drug

- Study drug is to be dispensed to patient at randomization
- The RD form should be completed at the rz visit to document the bottle dispensed.
- At the f4 visit, the patient should return the bottle of study drug to the coordinator. The RD form should be completed to document the capsules and bottle returned.

Drug supply

- Aprepitant and placebo aprepitant: 125 mg capsule; 35 capsules per bottle, to be taken orally once a day (qd) with lunch.

Checks on return of study drug

- Unused study drug to be returned by patient at f4 visit

By whom

- Clinical coordinator or pharmacist

Procedures at clinical center

- Maintain study drug inventory of current drug supplies
- Maintain log of study drugs returned, destroyed or disposed
- Study drug supplies are shipped to arrive within 2 working days of order
- Notify the DCC if your supplies are low or if you do not receive an expected shipment

Handling and disposal

- Unused portions of open bottles in the possession of patients should be considered contaminated and handled accordingly
- Returned capsules should be counted by the pharmacist or clinic coordinator and the number of capsules should be recorded on the RD form
- All unused capsules returned by patients should be disposed per the drug disposal policy of your institution

Storage and stability

- Store in a cool dry place at 77° F (25° C), excursions permitted to 59° F to 86° F (5° C to 30° C).
- Keep container tightly closed

6.25. Standardized management of side effects

Study participants will receive aprepitant or placebo. The overall safety of aprepitant has been evaluated in several thousand individuals receiving highly emetogenic cancer chemotherapy and for prevention of postoperative nausea and vomiting. Aprepitant was given in combination with ondansetron and dexamethasone and was generally well tolerated. However, because of the multiple co-morbidities in these patients, it is difficult to form a reliable estimate of adverse events that can be specifically attributed to aprepitant. More meaningful long term use adverse event data come from trials in patients conducted with major depressive disorders with more than 2,000 patients.

The dose of aprepitant used in these placebo-controlled trials ranged from 40 to 240 mg per day for a duration of up to 10 months. During the trial, if a participant develops non-life threatening side effects attributed to the study drug, the study drug will be stopped only if the participant so desires. If the participant chooses to no longer receive the study drug, the participant will be followed in the trial according to the protocol, in keeping with the "intention-to-treat" paradigm. In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis, or Stevens-Johnson Syndrome, study drug will be discontinued immediately.

Several adverse events are included in the package insert (available on the website under Studies, APRON, Emend package insert). Clinical adverse events reported in trials for chemotherapy induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) include:

- Clinical adverse experiences for the CINV regimen in conjunction with highly and moderately emetogenic chemotherapy (incidence >10%) are: alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea.
- Clinical adverse experiences for the PONV regimen (incidence >5%) are: constipation, hypotension, nausea, pruritus, pyrexia.

The most frequently reported side effects associated with aprepitant (for those without cancer or undergoing chemotherapy) were dry mouth, fatigue and drowsiness. These events were not recognized as clinically significant.

6.26. Adverse event reporting (AE or SR forms)

Definitions

- **Adverse event** (AE) is defined as any unfavorable sign, symptom, state, condition, or laboratory finding in a APRON patient. Adverse events may result from appropriate application of the protocol in relation to the processes of screening, or follow-up of APRON participants, as well as from mistake or misadventure. An adverse event is any untoward medical occurrence that may present itself during treatment with a study drug 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) is defined as any event that suggests a significant hazard, contraindication, or side effect. Serious adverse event includes any event that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. Other events may also be considered a serious adverse event 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 a serious adverse event listed above.
- **Unexpected adverse event** is defined as any adverse event that is not identified in nature, severity, or frequency in the risk information included in the APRON trial protocol or current study drug package insert.
- **Associated with study drug** means that there is a reasonable possibility that the adverse experience may have been caused by the study drugs.

When to complete Adverse Event Report (Form AE)

- All visits after randomization: f2, f4 and f6
- As needed during Screening and Randomization
- As needed between Follow-up visits: record “n” in item 5 for visit code

Reportable APRON events

- Any serious and unexpected adverse event that may reasonably be regarded as caused by, or probably caused by, the study drug. If the adverse event is alarming, the investigator shall report the adverse effect immediately to all clinical centers, the Data Coordinating Center, the NIDDK project scientist, the Steering Committee, DSMB and the FDA.
- Any event threatening the integrity or well-being of the APRON trial (e.g., suspected fraud) is a reportable event. We recognize that this category is not well-defined; however, it is included as a reminder that reportable events can have a broader scope than adverse events that happen to a patient.

- Deciding whether an event is reportable in the APRON trial (i.e., is in either of these categories) will be the responsibility of the study physician of the clinical center. The study chair, the NIDDK project scientist, and staff at the Data Coordinating Center are available for consultation.
- Recent Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection from the FDA can be found here: http://www.fda.gov/cder/guidance/OC2008150fnl.htm or on the GpCRC website www.gpcrc.us – click on *Documents*.

CTCAE v3.0

- Events are reported on the either the Interim Event (IE) or IND Safety Report (SR) form
- The GpCRC uses the Common Terminology Criteria for Adverse Events, (CTCAE v3.0) to categorize and grade adverse events.
- This document is posted on the GpCRC website (www.gpcrc.us – click on *Documents*)
- Use the CTCAE v3.0 to specify the Short Name for the adverse event and the severity grade for the adverse event.

Clinical center responsibilities regarding reportable APRON events that occur at your clinical center

- Your institution's IRB has reporting requirements of its own regarding events occurring in the course of conduct of a trial. These reporting requirements may be more stringent than those adopted by the APRON trial. Regardless of what the APRON trial requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than the APRON's, you may report events locally that you do not report to APRON.
- If such an event occurs, appropriate medical care should be provided immediately in the clinic.
- If a suspected adverse event is reported by telephone several days later, the participant should be evaluated in the clinic by medical staff (preferable) or referred to an appropriate facility for evaluation and management.
- All such events should be documented in the study chart.
- You must notify the Data Coordinating Center about occurrence of events judged reportable to the APRON trial as follows: If an event has occurred that you judge is reportable to APRON, complete the Adverse Event (AE) form. Key this form to the APRON data system. Also send it to the Data Coordinating Center with a narrative description of the event and your subsequent course of action -- describe what happened, the actions taken in response to the event, and the relationship of the event to the APRON study drug or procedures. Please refer to the patient by his/her GpCRC patient ID number and code; do not use the patient's name or other identifiers.

Serious Adverse Event reporting (AE and SR)

- Centers should use the Adverse Event (AE) form to document adverse events and serious adverse events that in the opinion of the investigator are 1) expected, or thought to be associated with study drug but do not meet the criteria for Serious Adverse Event/IND

Safety Report (SR) form or 2) not thought to be associated with the APRON study drug

- Centers must use the IND Safety Report (SR) form to report serious adverse events that satisfy the IND Safety Report requirements outlined in the APRON trial protocol, including the occurrence of a **serious** (fatal or life-threatening, results in significant or persistent disability, results in a congenital anomaly or birth defect, requires or prolongs hospitalization, or represents other significant hazard or serious harm to research subjects or others) **and unexpected** (not included in the APRON protocol or in the package insert of aprepitant) adverse event that, in the opinion of the investigators, is thought to be associated with APRON study drug.
- If the serious adverse event is judged by the study physician to be associated with the study drug and unexpected per the package insert and above definitions, the SR form, together with a memo summarizing the circumstances of the event and the current status of the patient, must be faxed to the DCC and to the NIDDK project scientist within one working day of the discovery of the SAE and confirm receipt via email or telephone.
- The NIDDK project scientist will work with the DCC to transmit the IND Safety Report (SR) form and memo to the DSMB Chairperson and Steering Committee members, all participating center investigators and the FDA no later than 15 days from the discovery of the SAE (no later than 7 days if the SAE is fatal or life threatening).
- The DSMB Chair and NIDDK project scientist will determine if all DSMB members should be made aware of the event at that time, or it is appropriate to wait until the next DSMB meeting.
- The clinical center investigator may also complete an FDA MedWatch 3500 form.
- The DSMB will review each SAE report and provide comments to the NIDDK project scientist 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 scientist and to the DCC 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 scientist will work with the DCC to distribute the follow-up memo to the Steering Committee, all participating center investigators and to the DSMB.
- The DCC will maintain a list of such events for reporting and review at Steering Committee meetings and DSMB meetings.

How to Determine If an Adverse Event (AE) is an Unanticipated Problem that Needs to Be Reported

- Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition, not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

- There should be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. The FDA believes that only the following AEs should be considered as unanticipated problems that must be reported to the IRB:
  - A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
  - A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
  - Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.
  - An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.
  - A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence

Reporting deaths occurring in APRON trial participants

- As soon as a clinical center is aware of a APRON participant's death, the Study Physician and Clinical Coordinator should complete the Death Report (DR) form and send the DCC (Attn: Ivana Vaughn) following: (1) A narrative description of the event including hospitalization information as applicable; (2) A copy of your report to your (IRB), as applicable. See SOP I, section 6.29 for additional instructions for mortality closeout.
- The Death Report (DR) form should be keyed to the APRON data system.

6.27. Procedures for missed or incomplete visits (MV form)

Purpose

- Record data about missed or incomplete visits in the APRON trial

Form

- Missed or Incomplete Visit (MV) form

When

- The MV form should be completed within 7 days of the close of a visit window for any missed follow-up visit or for any follow-up visit with specific study procedures or data collection forms not completed

By whom

- Clinical Coordinator

Procedures for missed or incomplete in-person visits

- For a missed visit:
  - Date of missed visit is the last date of the visit window
  - Indicate reason(s) for missed visit
- For an incomplete visit:
  - Date of incomplete visit is the date on which a partial set of procedures was performed
  - Indicate reason(s) for missed procedures

6.28. Procedures for patients lost to follow-up

Purpose

- Ascertain vital status of patient
- Document reason(s) patient did not attend visit
- Ascertain if patient is lost to follow-up

When

- Whenever patient misses a study visit and is difficult to contact

By whom

- Clinical coordinator

Search strategies

- Contact all persons identified on the Patient Location (PL) form
  - Telephone different times during the day/evening
  - Send letter via regular or certified registered mail to determine if patient is still at listed address
- Check current telephone directory for listings both for the patient and the patient's contacts specified on the PL form. (eg., next of kin, health care professionals)
- Check post office for forwarding address; ask patient's contacts for forwarding address
- Check obituaries
- Check state vital records

6.29. Procedures for mortality closeout (DR form)

Purpose

- Record a APRON participant's death

Forms

- Complete the Death Report (DR) form
- Study Physician should attempt to access the medical records of the participant and submit a narrative on the nature of the death including co-morbidities leading to death, hospitalizations and other pertinent clinical information to the DCC and their local IRB as applicable.

By whom

- Study Physician and Clinical Coordinator

6.30. Transferring patients from APRON to the Gastroparesis Registry 2 (CO form)

Purpose

- To close out a patient's participation in APRON and document the patient's consent to join or re-enter the Gastroparesis Registry 2 (GpR 2)

Form

- Closeout (CO) form

When

- Complete Closeout (CO) form at APRON 6 week (f6) visit or at the completion of the f6 visit window for each patient randomized in the APRON trial.

By whom

- Clinical Coordinator

Instructions

- Ask the patient if he/she consents to re-enter or enroll in the Gastroparesis Registry 2.

- For patients who decline to participate in the Gastroparesis Registry 2 after completion of APRON Trial, inform them that the study results and their treatment assignment will be available to them sometime after the close of the APRON trial.

- Patients willing to enroll into the GpR 2 should sign the most recent version of the Gastroparesis Registry 2 informed consent approved by your IRB (follow your IRB guidelines for re-consenting participants previously enrolled in the GpR 2).

- For patients previously enrolled in the GpR 2, consult the patient's GpR 2 visit schedule (time windows guide) generated at their enrollment to schedule the patient's next GpR 2 follow-up visit.

- For patients who were not previously enrolled in the Gastroparesis Registry 2, a GpR 2 screening visit should be scheduled. Some data from APRON may be used in GpR 2 but additional tests and procedures will need to be scheduled.

- Complete and key the GpR 2 Registration (RG) form but do not assign a new patient ID number and code. APRON patients enrolling in GpR 2 will keep the previously assigned patient ID number.

- *Blood for plasma and serum banking*
  - Whole blood must be collected and processed for plasma and serum banking at

the NIDDK Biosample Repository even if plasma was already banked for APRON.

- *Blood for DNA banking*
  - If DNA samples were not obtained for this patient before and the patient now consents to DNA banking, have the patient sign the GpR 2 genetic consent, collect a sample, and complete the GpR 2 Genetic Consent and Blood Collection Documentation (CG) form
  - If the DNA amount on the sample obtained when the patient screened for the APRON trial was satisfactory, the patient does not need to sign the GpR 2 genetic consent or collect blood. However, complete the GpR 2 CG form to document that blood for DNA banking was collected in another study.
  - If the DNA amount on the sample obtained when the patient screened for the APRON trial was unsatisfactory (less than 50µg), have the patient sign the GpR 2 genetic consent form, obtain the replacement sample, and complete the GpR 2 CG form. The APRON CG form should remain in the data system.

- Lab results (hematology, metabolic panel) reported on the APRON LR form may be recorded on the GpR 2 LR form if they were obtained within 16 weeks of registration in GpR 2 or in the time window for the follow-up visit.

- All interviews and patient questionnaires: (baseline history, quality of life, and patient health) must be completed for GpR 2 patients.

- If the gastric emptying scintigraphy (GES) data used to qualify for entry into APRON is more than 6 months old and/or was a 'solids only' scintigraphy, the data are not transferable to the GpR 2. The GpR 2 protocol specifies that the gastric emptying scintigraphy must be of solids and liquids using 4 hour Egg Beaters® protocol within the last 6 months at a GpCRC clinical center.

- The physical exam (PE) form must be completed for GpR 2 patients.

7. Forms management

7.1. Clinical center ID codes

Alphabetic IDs

- Alphabetic clinic IDs are used on forms, lists, and tables
- Alphabetic clinical center IDs are based on the name of the institution with which the clinical center is affiliated
- Assigned IDs

Johns Hopkins Medical Institutions	JHU
– Stanford University	SU
– California Pacific Medical Center	CPMC
Temple University	TU
Texas Tech University Health Science Center	TTU
University of Louisville	UL
University of Michigan	UMI
University of Wake Forest	WFU

Numeric site IDs

- The NIDDK Genetics and Biosample Repositories use numeric IDs to identify the GpCRC clinical centers
- These will be used on the specimens (whole blood and plasma samples sent to the Genetic and Biosample Repositories, respectively)
- Assigned IDs

Johns Hopkins Medical Institutions	643
– Stanford University	613
– California Pacific Medical Center	613
Temple University	610
Texas Tech University Health Science Center	637
University of Louisville	644
University of Michigan	611
Wake Forest University Health Sciences	614
Johns Hopkins University - DCC	61

7.2. Patient identifiers

What

- Patient ID number
- Patient code

Patient ID number

- 4 characters, all numeric
- ID number labels will be distributed to clinics by the Data Coordinating Center
- The ID number for a patient will remain the same for the duration of the GpCRC, even if the patient enters another GpCRC study or if the patient fails screening and is subsequently re-evaluated – the ID never changes

Ranges of patient IDs assigned to clinics

Johns Hopkins Medical Institutions	JHU	8001	-	8999
– Stanford University	SU	4001	-	4999 (even)
– California Pacific Medical Center	CPMC	4001	-	4999 (odd)
Temple University	TU	1001	-	1999
Texas Tech University Health Science Center	TTU	6001	-	6999
University of Louisville	UL	7001	-	7999
University of Michigan	UMI	2001	-	2999
Wake Forest University Health Sciences	WFU	5001	-	5999

Patient code

- 3 character alpha code assigned by the Data Coordinating Center and printed on the ID number label
- Each patient code is unique across the GpCRC

7.3. Visit ID code

- 1 to 2 character alpha-numeric code
- Determined by purpose of visit and timing with respect to visit windows
- Visit ID codes

s	Screening, baseline data collection
rz	randomization
f2	2 weeks follow-up visit
f4	4 weeks follow-up visit
f6	6 weeks follow-up visit
n	Unscheduled follow-up visit

7.4. General guidelines for forms completion

Ink

- Forms should be completed in ink that is dark enough to photocopy legibly; do not use pencil or colors (e.g., red, green, light blue, or purple) that do not photocopy well

Changing responses on forms

- If an error is made on the form, correct the response by marking through the response with one or two lines and writing the correct response next to or above the original response. The staff member making the correction should put their initials and the date in the margin by the correction. A brief explanation for the change should also be written in the margin; e.g., ‘error', ‘pt changed mind', ‘wrong response checked'.
- Do not obliterate, erase, or white-out incorrect responses
- The idea is to preserve an audit trail of the original response and subsequent changes to it

Multipage forms

- The patient ID number should be written on the top right of every page of every form in the space provided -- protect yourself against ineffective staples and photocopying mishaps

Miscellaneous

- All written responses should be printed legibly so the responses can be keyed to the database
- Do not use abbreviations or short-hand that may not be easily understood or keyed in the written responses
- Numeric data should be recorded in the units prescribed on the form and to the level of precision (number of digits) indicated on the form
- All numbers should be right justified and leading and trailing zeroes should be recorded on the form where applicable (e.g., an age of 8 would be written and keyed as "08").
- All letter codes should be left justified with the remaining spaces left blank (e.g., a visit ID for the screening visit would be completed and keyed as "s").
- The clinical coordinator should review all responses for completeness and accuracy before signing off on the form
- Wherever possible, forms should be completed in real time, not retroactively. Interviews and questionnaires should be completed on the actual data form.
- The data on some forms, such as the Laboratory Results (LR) form, will be transcribed from worksheets or lab reports, but the visit date on the form should correspond to the date the form was initiated
- Staple relevant lab reports and worksheets to the data form; if your lab reports are transferred to you electronically, print a paper copy of the report and staple the copy to the case report form.

7.4. General guidelines for forms completion

Calculations

- All calculations should be performed using a calculator
- Values should be rounded according to the GpCRC data rounding rule (see section on data rounding rule, later in this chapter of the SOP)

7.5. Instruction box

- Each case report form includes an instruction box at the top of the first page. This instruction box gives the purpose of the form, when it should be completed, who administers the form, the respondent, and specific instructions for the form

7.6. Form skips, stops, caution ineligibility symbols

Skip pattern

- Form navigation (skip pattern) instructions are indicated in **boldface**. Skips are designated by an arrow from that response to a box with the number of the next item to be completed.

Stop sign

- Stops are indicated with an arrow from the response to a stop sign – instructions are given that must be fulfilled in order to continue with the form. For example, Form RG (Registration) asks if the patient has signed the consent form; if the response is "no", the form is stopped with the instructions that *'the consent form must be signed prior to continuing with screening'*.

Caution sign

- Items that require further review are indicated with an arrow from the response to a caution sign

Instructions are given regarding completion of the form when a caution is encountered

Ineligibility sign

- Ineligible conditions are designated by an arrow from the response to the symbol:

Other

- Other special instructions are indicated on the form in *italics*. Some examples are:
  – *check only one*: only one of the listed responses should be checked
  – *check all that apply*: one or more of the listed responses may be checked
  – *specify*: a response should be printed on the line(s) provided

7.7. Headers and footers

- Each page of each form includes headers and footers which identify the form and the patient. The top right of the first page of each form has a space to check when the form is keyed [( )keyed]. The top right of subsequent pages is reserved for the patient ID number. The footers include the form abbreviation, form revision number and date, the form name, and the page number. For example:

APRON Patient ID: __ __ __ __

Form RG
Revision 0 (29 Sep 06) RG - Registration Page 2 of 3

- The keyed box should be √ed when the form is keyed; the person keying the form should also date and initial the form by the keyed box
- The patient ID number should be written on each page of the form

7.8. Key fields

- The first 7 items of each form include the key fields which identify the clinical center, patient, visit and study

A. Clinical center, patient and visit identification

1. Center ID: __ __ __ __
2. Patient ID: __ __ __ __
3. Patient code: __ __ __
4. Date form completed: __ __ - __ __ __ - __ __
   day mon year
5. Visit code: __ __
6. Form & revision: __ __ __
7. Study: APRON 4

- The form and revision number will be printed on the forms in item 6; if a form is only used for one specific visit, the visit code will also be printed on the forms
- When a form revision affects the data that are collected, the form revision number and date will change; if this occurs, older revisions of that form should no longer be used for data collection
- If the form is revised without affecting the data collection - i.e., the wording of an item is revised - only the revision date of the form will be changed.

7.9. Missing data

- If a data item is missing and cannot be obtained when the form is completed or reviewed, write the appropriate code in the first left hand space of the empty data field:

  ? = data temporarily missing or inconsistent; to be collected or resolved in the near future; items keyed with a ? will need to be followed up on and resolved
  d = patient does not know the answer
  n = not applicable in this situation
  m = data missing
  r = patient refused

- When using any of the above codes, the entire data field does not need to be filled with the code (e.g., a missing height would be completed as m _ _ _._).

- If data are missing on the form, an explanation for the missing values should be written on the form and keyed to the database in the General Comments section of the keying.

- It is very important to keep the number of missing data items at a minimum, especially at baseline, since many future papers will depend on having a good set of baseline values. If an item is missing at the time the form is filled out, but is expected to be collected in the near future, use a '?' rather than the 'm' code for the item on the form. The 'm' missing code is for items that are truly missing. Coordinators are discouraged from using the 'm' code as a way to get through the data entry checks and enroll a patient; the screening windows should be broad enough to allow you to collect all data within the allotted time window. Also, if the data system will not accept a value because it is out of range, please contact the DCC, so we can make a determination as to whether the range checks need to be adjusted. In the meantime, use a '?' rather than an 'm' on the form. If there is a valid reason that a required baseline laboratory value is missing, please fax the Laboratory Results (LR) form to the DCC along with the reason for the missing value.

7.10. Administrative sign off

- Each form contains a section for administrative sign off
- These items include the Clinical Coordinator PIN and signature and the date the form was reviewed.
- Depending on the form, they may also include the PIN and signature of other staff

It is the standard of practice with NIH funded studies to certify study physicians who assume responsibility for the accuracy and integrity of the sponsored studies. Coordinators are certified separately based on their professional qualifications and privileges even though the functions fulfilled may overlap functions of the study physician.

On the APRON data collection forms that require the Physician's signature, the signature is the assurance that as the clinical center's principal investigator, they are assuming responsibility for the accuracy of the data recorded on the study form. This does not require that the study physician completes the APRON forms or performs the procedures, but does require assumption of responsibility signified by signing the APRON forms. This is also the standard of practice required by the FDA for case-report forms completion.

7.11. Handling forms

Form duplication

- The individual forms and form sets specific to a particular visit are available on the GpCRC website
- You should print forms from the website as needed – if you print copies ahead of time, do not print huge quantities as forms may be revised, especially in the early days of a study

Form storage

- Forms for patients registered but not randomized in the APRON trial should be kept in a single folder or binder in a locked room in a locked cabinet.
- Each patient who is randomized in the APRON trial will have a patient file – either a notebook or file folder which is kept in a locked room or locked filing cabinet. The patient file should contain all APRON trial documents for the patient – consents, forms, appointment schedule, labels, randomization materials. The forms should be arranged in the notebook or folder chronologically by visit. Tabs can be used to separate the visits.

7.12. Data rounding rules

To round data, examine the digits following the last position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged, e.g., if you need to round to _._, then 4.73 rounds to 4.7 and 1.44 rounds to 1.4
- If the first digit following the last data position required for the response is 5 or more, round up the digit in the last data position required for the response, e.g., if you need to round to _._, then 4.78 rounds to 4.8 and 4.75 rounds to 4.8

When completing a calculation for the APRON trial, apply the rounding rule only at the last step, when required to record a quantity on the APRON trial form.

7.13. Data audits and edits

Data audits

- The Data Coordinating Center will serve as the site monitor
- The Data Coordinating Center will conduct monthly data audits as a quality control measure
- Audits may be done by mail or on-site
- During an audit, the APRON forms will be reviewed to see if they were completed and keyed correctly; the APRON forms will also be checked against the source documents (laboratory results, electrocardiograms, electrogastrogram reports) to be sure that values were transcribed correctly.

Source documents include but are not limited to:

- Gastric emptying scintigraphy reports
- Upper endoscopy reports
- Electrogastrogram and satiety test reports
- Gastric imaging study reports
- Laboratory test result reports
- Electrocardiograms
- There are no source documents for questionnaires (the questionnaires are the original documents for the data collection)

Data edits

- Computerized data edits will be sent to the clinics monthly
- The data edits check for consistency and questionable values in the database.

Changes resulting from audits or edits

- Changes made to the APRON forms as a result of an audit or an edit should be marked "per audit" or "per edit" and should be dated and initialed and keyed to the data system using the **Change a data form >** option under **Data Entry >**.

8. Quality assurance

8.1. Site visits

Purpose

- Conduct an audit of selected patient data
- Review documentation and procedures for the APRON trial
- Tour facilities
- Discuss with clinical center personnel any problems that have occurred or that are expected to occur in conducting the trial

The following regulatory and study documents should be available or accessible:

- IRB communications including original approval letters, revision approvals, continuing review approvals, serious adverse event forms, and any communications regarding concerns or special requests from clinical center review board
- Signed and dated consent forms for all participants including the date and signature of a witness
- Documents including APRON trial Protocol, PPMs, and SOPs
- Study forms for participants should be available for data audit

Participants

- At least two DCC personnel will attend the site visit. Representatives from NIDDK may also attend
- GpCRC certified staff from the clinical center

Reviewed during site visit

- IRB documentation
  - Original approval
  - Annual renewals (if applicable)
  - IRB submissions
  - Approval for updated consent forms and protocol
  - Unanticipated or serious adverse event reporting to local IRB

- APRON trial documents
  - Consent forms
  - Directory
  - Drug accountability records
  - Protocol
  - PPMs
  - SOPs

- Enrollment and retention
  - Status
  - Recruitment and retention strategies
  - Problems
  - Losses to follow-up

- Personnel
  - Certification status
  - Personnel changes
  - Backup plans for personnel in event of absence

- Clinical management
  - Adverse event reporting procedures
  - Study procedures
  - Clinical center coordination
  - Scheduling
  - Clinical center concerns or problems

- Participant files
  - Security
  - Organization
  - Consent statements
  - Each patient's APRON forms and their supporting source documents:
    - laboratory test results
    - gastric emptying report and scintigraphy on CD if available
    - upper endoscopy report
    - electrogastrogram and satiety reports

- Specimen shipment
  - Comparison of specimens expected and received
  - Shipping procedures and problems
  - Shipping supplies

- Protocol performance
  - Protocol deviations
  - Exceptions for enrollment and visit window extensions
  - Exceptions on laboratory results obtained outside visit windows

- Forms and data management
  - Monthly form status reports
  - Source documentation
  - Data audit (selected patients)
  - Eligibility criteria
  - Adverse events
  - Death reports

- Previous site visit report
  - Action items follow-up
  - Data audit follow-up

Site visit follow-up

- A list of action items is compiled at the end of the site visit to identify items which require further action. The procedure for site visit action item follow-up is:
  - Clinical centers will be required to respond to action items within 30 days of receipt of the site visit report. Responses should be in writing and sent to the DCC.
  - The DCC will be required to respond to the action items within 30 days of the completion of the site visit report. The DCC will send a written report to the clinical center.

8.2. Performance monitoring

- The DCC will generate recruitment reports that will provide a count of participants screened and randomized at each clinical center

- On a monthly basis, the DCC will generate reports summarizing the performance of all clinical centers. These reports will include information on enrollment and the percentage of expected visits for which documentation has been entered into the APRON data system. Also, for those visits for which data have been entered, the report will show the percentage of missed visits, the completeness of data collection, and the timeliness of data entry.

- Performance reports will be reviewed by the Steering Committee, and the Steering Committee will make decisions regarding actions to be taken in the event that a clinical center is performing poorly.

8.3. Data quality surveillance

General procedures

- Quality assurance of data accuracy will occur routinely through three main procedures: data entry checks, monthly checks for completeness and edits, and form audits
- In addition, detection of problems may occur during data analysis. For example, in preparing reports for Steering Committee meetings, problems may be discovered. Outliers and unusual variations or patterns in the data are examined and may reveal problems.
- Quality assurance of data analysis is achieved by independent replication of key analyses within the DCC and review of reports by multiple individuals before distribution

Data entry checks

- The data system will contain checks during the data entry process of range, logic, and consistency of items within forms
- The data system will perform checks between forms to ensure that the same fields entered on different forms match
- A double data entry system will be used for all forms

Monthly check for completeness and edits

- On a monthly basis, DCC will generate a database report of:
  - number of participants randomized
  - missed visits
  - incomplete visits (missing or pending forms)
  - missed specimen collection or shipment
  - edits (see below)

- Edits are run on the database of the keyed forms monthly. Checks for missing, out-of-range, unusual and inconsistent values, cross-form checks and arithmetic errors are some of the types of checks performed. A listing of edits is sent to each clinical center for resolution within a month. The clinical center must respond to each edit on the listing, document appropriate changes to the forms and make corresponding changes in the database, and file the documentation with the edited data collection form. Items that cannot be corrected (e.g., missing values, unusual measures) are entered into a database at the DCC. These items are excluded from future edits. A hard copy of the edits, with each resolution should be kept in a notebook located at the clinical center.

Forms audits

On a monthly basis the DCC selects and requests copies of forms for specific participants be sent by each clinical center to the DCC for auditing

- Audited forms are compared with the database; discrepancies are noted and queried
- Audited paper forms are also inspected for other problems, which are noted and queried
- Each clinical center will be required to resolve discrepancies from the audit report and fax the resolutions to the DCC within 15 days
- The DCC will generate a summary report of the audit discrepancies by clinical center to be distributed to all APRON clinical centers
- Discrepancy rates over time by clinical center are included in the monthly performance reports and are reviewed by the Steering Committee and the Data and Safety Monitoring Board

GpCRC

Gastroparesis
Clinical Research Consortium

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON)

Standard Operating Procedures

Part IV: Standard of Care for Patients with Chronic Unexplained Nausea and Vomiting of Presumed Gastric Origin

15 January 2013

APRON SOP Part IV: Standard of Care

Contents

APRON SOP Part IV: Standard of Care

1. Introduction

The purpose of this document is to describe a uniform set of practices to be applied by investigators in the Gastroparesis Clinical Research Consortium (GpCRC) in the evaluation and care of patients with gastroparesis or related disorders that are screened and enrolled in the Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin (APRON) trial. These guidelines were developed so that patients with gastroparesis or related disorders will be appropriately evaluated across the clinical centers before being placed in the APRON Trial. Once patients are in the APRON Trial, they will be treated in a generally standard fashion across clinical centers, thereby reducing the extent to which evaluation and care at a particular center will influence diagnosis, treatment, and outcome. In addition, these guidelines are written to delineate the tests and procedures used for routine clinical care of patients with chronic nausea and vomiting of presumed gastric origin. These guidelines were derived by expert opinion as expressed by prior documents by the American Gastroenterological Association, the American Neurogastroenterology and Motility Society, and the American College of Gastroenterology clinical guidelines and refined by the consensus of investigators of the GpCRC. Every effort will be made to adhere to these guidelines for each patient.

APRON SOP Part IV: Standard of Care

2. Patients with gastroparesis or related disorders

Each patient will be evaluated for gastroparesis or related disorders based on the following:

1. Presence of symptoms/signs of gastroparesis for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score≥21
2. Gastric emptying scintigraphy using a 4 hour low fat Egg Beaters meal as described by Tougas et al 2000 [2]. Delayed gastric emptying using 4 hour scintigraphy is considered with gastric retention at 2 hours postprandially to be >60% or at 4 hours to be >10%. General practice is to stop medications known to delay or accelerate gastric emptying for 3 days prior to the gastric emptying test.
3. Significant nausea defined with a visual analog scale (VAS) score of ≥ 25mm on a 0 to 100 mm scale
4. Normal upper endoscopy (retained gastric food is permitted) or upper GI series to exclude gastrointestinal obstruction

Although there are general guidelines for the evaluation of patients with gastroparesis [1,3,4] or related disorders, the exact evaluation of a patient may differ depending on the individual case characteristics.

Initial evaluation of a patient with suspected gastroparesis or related disorders

History

Gastric symptoms: dominant and associated symptoms (nausea, vomiting, pain/discomfort, early satiety, fullness, bloating), duration, frequency, onset (abrupt vs. insidious), course, precipitating/relieving factors. Nature of symptoms: cyclic vs. non-cyclic. If cyclic, are cycles regular or not.

Extragastric symptoms: Other GI symptoms (diarrhea, constipation), anorexia, weight loss, dehydration, orthostatic symptoms

History of infectious disorders with resultant chronic upper GI motility symptoms

Assessment of nutritional status

Dietary intolerance

Other disorders – especially those that might relate to symptoms of gastroparesis (e.g., collagen vascular disease, endocrine diseases such as hypothyroidism)

Symptoms or diagnosis of overlap syndromes: migraine headaches, fibromyalgia, interstitial cystitis, endometriosis, depression

Hospitalizations/emergency room visits for intractable symptoms (frequency/yr)

Other medical problems: seizures, cardiac arrhythmias, glaucoma

Family history of gastroparesis, GI motility disorders, overlap syndromes

Review of current medications

Clinical response to present and past medications given for patient's symptoms: acid suppressants, antiemetics, prokinetics, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, calcium channel blockers, analgesics

2. Patients with gastroparesis or related disorders

Physical examination

Vital Signs: blood pressure, pulse, temperature, weight, height, body mass index (BMI)

Abdominal examination: visible distention, tympany, succussion splash, tenderness, organomegaly

Electrocardiogram

Laboratory tests

Glycosylated hemoglobin (HbA1c) for patients with diabetes

Complete blood count (CBC): white blood cell count, red blood cell count, hemoglobin, hematocrit and platelet count

Complete metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and alkaline phosphatase

Endoscopy

Upper endoscopy (must have been done within 2 years prior to registration in APRON) Esophageal, gastric, and duodenal biopsies may be obtained if indicated by history, physical examination (associated bloating, diarrhea, or family history of celiac disease), or laboratory findings (unexplained microcytic anemia)

Radiology

Abdominal obstruction series, if suggested by history (profound pain, bloating, or vomiting) or physical examination (distention, tympany)

Abdominal right-upper quadrant ultrasound to rule out gallbladder, liver, and pancreatic disease, if suggested by history, physical examination (RUQ pain or tenderness), or laboratory findings (elevated liver chemistries)

Nuclear medicine

Gastric emptying scintigraphy (Solid phase - percent retention at 0, 0.5, 1, 2, 3, 4 hours). Must have been done within 2 years prior to registration. Required standardized test meal and test procedures are outlined in APRON SOP Part I: Clinical Center Operations.

Other tests which may be obtained

Electrogastrogram with nutrient bar meal or water load

Antroduodenal manometry (to exclude associated small intestinal dysmotility)

Small bowel radiographic examination (to exclude mechanical lesions of the small intestine): Small bowel follow-through, enteroclysis, computer tomographic enterography

Small intestinal transit testing: Scintigraphy, small intestinal barium series, lactulose breath testing

Hydrogen breath testing (to exclude small intestinal bacterial overgrowth)
Sitzmarker study, in patients with lower bowel complaints
Anal manometry and/or anal EMG, balloon evacuation
Urodynamic evaluation, in patients with urinary symptoms
Wireless motility capsule testing

Psychometric and quality of life measures, including

Gastrointestinal Symptom Rating Scale (GSRS)
Health Related Quality of Life Questionnaire (SF-36)
Gastroparesis Cardinal Symptom Index (GCSI)
Brief Pain Inventory (BPI) focusing on abdominal pain
Beck Depression Inventory (BDI-II)
Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
Patient Health Questionnaire (PHQ-15)
State Trait Anxiety Inventory (STAI)

Autonomic testing

Standard cholinergic and adrenergic or 24 hour Holter for heart rate variability, giving an assessment of high and low frequency power

Treatment

- The general principles for treatment of gastroparesis are to (1) correct fluid, electrolyte, and nutritional deficiencies, (2) identify and rectify the underlying cause of gastroparesis if possible, and (3) reduce symptoms [5].
- The patient's medication list should be reviewed to eliminate drugs that might exacerbate the underlying dysmotility disorder or prevent the beneficial actions of a prokinetic agent.
- Diabetes patients should strive for reasonable glycemic control to minimize any inhibitory effects of hyperglycemia on gastric emptying [1].
- Primary treatment of gastroparesis includes dietary manipulation and the administration of antiemetic and/or prokinetic therapies.
- Additional treatments for refractory symptoms or a dominant symptom of pain may include the use of tricyclic antidepressants and/or analgesic medications. Occasionally newer agents (Cymbalta or Lyrica) are tried on an off label basis.
- For relatively mild disease, dietary modifications and intermittent administration of a low-dose antiemetic or prokinetic agent may provide satisfactory control of symptoms.
- Patients with more severe manifestations of gastroparesis, such as refractory vomiting or pronounced dehydration might require hospitalization, intravenous hydration, nasogastric suction to decompress the stomach, and/or intravenous administration of antiemetic and prokinetic agents.
- Consideration of surgically or endoscopically placed enteral tubes for feeding and/or venting.
- Surgical options (gastric electrical stimulation, jejunostomy placement) are considered for persistently refractory cases.
- Other medications can be given for related overlap symptoms, such as for migraine headaches.

2. Patients with gastroparesis or related disorders

- Oral intake is preferred for nutrition and hydration. Dietary counseling should be available to patients regarding meal size, frequency, and composition. [1].

3. Patients with chronic unexplained nausea and vomiting

Nausea and vomiting are debilitating symptoms for patients and can be challenging problems in diagnosis and management for physicians. If a specific diagnosis can be made, and if that specific medical or surgical disease or disorder is treated properly, then the associated nausea and vomiting oftentimes is eradicated. On the other hand, many patients have thorough evaluations, the standard diagnoses are excluded, and the nausea persists for more than 1 month. These patients have chronic unexplained nausea and vomiting or CUNV.

Differential Diagnosis

The differential diagnosis of nausea and vomiting is extensive and includes a broad range of pathologic and physiologic conditions affecting the gastrointestinal tract, the peritoneal cavity, and the CNS as well as endocrine and metabolic functions.

Mechanical Obstruction
- Stomach, duodenum
- Small bowel, colon
- Hepatobiliary disease
- Pancreatic duct disease

Peptic disease
- Esophagus--GERD
- Stomach--gastritis, ulcer, H. pylori
- Duodenum--duodenitis, ulcer

Peritoneal irritation (peritonitis, cancer, irradiation)

Carcinoma
- Gastric, ovarian
- Hypemephroma
- Paraneoplastic syndrome

Metabolic--hormonal
- Diabetes mellitus
- Uremia, hypercalcemia
- Addison's disease
- Hyperthyroidism, hypothyroidism
- Pregnancy, progesterone/estrogen

Drugs
- Levodopa, digitalis, phenytoin, cardiac anti-arrhythmias, NSAIDs, antibiotics, chemotherapy agents, morphine, nicotine, progesterone, estrogen

Ischemic gastroparesis

Postoperative
- Vagotomy
- Partial/total gastrectomy
- Fundoplication, fundic resection

Intestinal pseudo-obstruction (visceral neuropathy/myopathy)
- Scleroderma, amyloidosis
- Idiopathic

CNS disease
- Migraine
- Infections
- Tumors
- Complex partial seizures
- Vestibular nerve-brain stem lesions
- Parkinson's disease

Psychologic/psychiatric disorders
- Anorexia nervosa
- Bulimia nervosa
- Rumination, psychogenic nausea (vomiting)

Idiopathic nausea and vomiting
- With gastroparesis (idiopathic)
- Without gastroparesis
- Gastric dysrhythmias
- Cyclic Vomiting Syndrome

APRON SOP Part IV: Standard of Care

In order to treat chronic unexplained nausea and vomiting appropriately, standard diagnostic tests are performed to exclude common diseases and disorders that can be treated with specific therapies. However, in the absence of a specific diagnosis, gastric neuromuscular disorders should be considered and diagnosed in patients with unexplained nausea and vomiting symptoms [10]. Patients with chronic nausea and vomiting want to know why they have these symptoms. The following provides explanation of their condition and recommendations towards alleviating their disorder.

Diet and Lifestyle Modifications

- If gastroparesis has been found, then the function of the stomach as a muscle to perform the work of stomach emptying should be explained. Patients with a "weak" gastroparetic stomach should understand why they cannot eat solid foods in the way they used to eat.
- If a gastric dysrhythmia is present, patients should be told that they have a dysrhythmia, a disturbance of electrical rhythmicity of the stomach. The dysrhythmias may have a role in their nausea, much like cardiac dysrhythmias have a role in palpitations or vague discomforts in the chest. By describing the pathophysiologic events that have been found, the physician can help the patient form realistic goals for therapies. The patients will also have a better understanding of the diet counseling and drugs selected for treatment of their symptoms.
- For patients with meal-related symptoms, dietary counseling is extremely important as a therapeutic approach.
- The goal is to decrease the workload of the dysfunctional stomach by proper food selections to decrease meal-related symptoms. A three-step "gastroparesis" diet (see below) is very helpful in counseling these patients in their choices of foods to ingest.
- Fresh fruits and vegetables contain fibrous materials that are difficult to empty from the dysfunctional stomach. Therefore, such foods should be limited. A multivitamin should be taken each day.
- Gastric neuromuscular disorders are frequently chronic conditions, and symptoms wax and wane due to intercurrent viral infections, the use of antibiotics, or hormonal changes during the menstrual cycle. During these setbacks, patients may have to shift down from Step 3 to Step 1 (see three-step diet on next page) for several days. During this time, they are instructed to ingest a sports drink, bouillon, or broths to avoid dehydration. Visits to the emergency room may be necessary for intravenous fluid therapy. As they begin to feel better, they advance their diet once again.
- If the patient's weight or proper hydration cannot be supported with oral caloric intake provided by the gastroparesis diet, a jejunostomy tube may have to be provided for enteral feeding to maintain weight. Successful jejunal feedings also reduce the continual pressure on the patient to take food by mouth.

- Sometimes a PIC line is used for peripheral hyperalimentation if it is anticipated that the acute gastric dysfunction may persist for a number of weeks and that additional nutritional support will be needed. In these cases, the patient's stomach function is expected to improve with time. For example, diabetic patients with nausea, vomiting, and weight loss may receive this mode of nutritional supplementation during hospitalization.
- Central hyperalimentation is rarely needed in patients with gastroparesis and should be avoided if at all possible.
- Central hyperalimentation is used if the patient cannot tolerate any foods by mouth and nutritional parameters indicate the need for parenteral nutrition. In these patients, small bowel dysmotility and intolerance of enteral formulations prevents enteral feedings. Complications with line sepsis in patients with central hyperalimentation lines are almost inevitable.

Three-step diet for patients with nausea and vomiting

Step 1: Sports drink and bouillon

Diet: Patients with severe nausea and vomiting should sip small volumes of salty liquids such as sports drinks or bouillon in order to avoid dehydration. These liquids include salt and sugar in addition to water. Any liquid to be ingested should have some caloric content. A one-a-day vitamin should be taken.

Goal: To ingest 1000 to 1500 cc per day in multiple servings, e.g., 12 4-oz servings over the course of 12 to 14 hours. 1 to 2 oz at a time may be sipped to reach approximately 4 oz per hour.

Avoid: Citrus drinks of all kinds, since the citric acid may cause stomach upset.

Step 2: Soups

Diet: If sports drinks and bouillon are tolerated, the diet may be advanced to include a variety of soups with noodles, rice, or crackers. Peanut butter, cheese, and crackers may be tolerated in small amounts. Caramels or other chewy confections may be tried. These foods should be given in at least six divided meals per day. A one-a-day vitamin should be taken.

Goal: To ingest approximately 1500 calories per day. Patients who can accomplish this will avoid dehydration and will hopefully ingest enough calories to maintain their weight. In many patients, maintenance of their present weight, not weight gain, is the realistic goal.

Avoid: Creamy, milk-based liquids, since fat delays gastric emptying.

Step 3: Starches, chicken, and fish

Diet: Starches such as noodles, pastas, potatoes, and rice are easily mixed and emptied by the stomach. Soups, mashed or baked potatoes, pasta dishes, rice, baked chicken breast, and fish are usually well-tolerated sources of carbohydrates and proteins. These solids should also be ingested in six divided meals per day. A one-a-day vitamin should be taken.

Goal: To find a diet of common foods that the patient finds interesting, satisfying, and that evoke minimal nausea/vomiting symptoms. As the patient learns what liquids and solids are tolerated, the variety and number of foods that can be enjoyed will increase.

Avoid: Fatty foods that delay gastric emptying, and red meats and fresh vegetables, which require considerable trituration. Avoid pulpy fibrous foods like celery, cabbage, and orange pulp, which form bezoars.

Pharmacologic Treatment

Gastroprokinetic drugs such as metoclopramide, cisapride, and erythromycin are given to enhance gastric contractility. These drugs have also been shown to improve gastric dysrhythmias and symptoms of nausea and vomiting [6, 7, 8]. Some element of acid sensitivity of the stomach and/or the esophageal mucosa (i.e., GERD) may contribute to nausea and vague epigastric distress in these patients. In some patients with nausea, occult GERD is the predominant pathophysiological mechanism of the nausea [9]. Therefore, trials of H2-receptor blockers or proton pump inhibitors are usually warranted.

Generic (Trade) Name	Standard Dosage	Contraindications/Side Effects
Metoclopramid (Reglan)	10-25mg oral, 20-30 min before meals and bedtime	increaesd extra-pyramidal side effects, restlessness, and depression
Cisapride (Propulsid)	5mg 4 times daily oral	cardiac dysrhythmias
Erythromycin	50-250mg oral or IV	abdominal cramps and diarrhea
Domperidone (Motilin)	10-20mg 4 times daily oral	increase prolactin levels, galactorrhea, or breast tenderness in 5%
Prochlorperazine (Compazine)	5-10mg 3 times daily	spastic torticollis, dystonia, hypertentsion
Amitryptyline (Elavil) Nortriptyline (Pamelor)	50 mg at bedtime 25-50 mg at bedtime	mild anticholinergic effects
Droperidol (Inapsine)	2.5-5 mg IV or IM	sedative properties
Ondansetron (Zofran)	6-16 mg IV	

4. Follow-up visits

Patients will be seen every two weeks for a total of 6 weeks by the gastroenterologist to evaluate changes in clinical course, symptoms, and possible side effects. These follow-up visits will include an interim medical history, review of symptoms, updated medication list, physical examination, diagnostic tests, and discussion of adherence to the study drug regimen as well as standard of care recommendations.

Items for documentation

History

Review of disease course
Assessment of current symptoms
Assessment of nutritional status
Other disorders and surgeries
Review of current medications
Response to any treatment given since last visit
Psychosocial history – document any changes

Physical examination

Vital Signs: blood pressure, pulse, temperature, weight, height, body mass index (BMI)
Optional: orthostatic vital signs
Abdominal examination: tenderness, succussion splash

Laboratory tests

Complete blood count, complete metabolic panel
Optional: Erythrocyte sedimentation rate, amylase/lipase C-reactive protein, urinalysis
Optional: Abdominal obstruction series
Optional: thyroid function tests

Treatment considerations

Discuss test procedures to be done such as the electrogastrogram and discuss the use of daily medications as well as rescue medications for nausea, vomiting, and pain that are allowed during the trial. Consider additional treatment with hydration, nutrition, antiemetic agents, prokinetic agents, analgesic agents, botulinum toxin, and gastric electric stimulation if needed. Consider home intravenous (IV) medications if symptoms are particularly severe and/or cyclic.

5. Dietary and nutritional recommendations

Gastroparesis, or paralysis of the stomach, refers to a stomach that empties slowly. Gastroparesis is characterized by symptoms from the delayed emptying of food, namely bloating, nausea, vomiting, or feeling full after eating only a small amount of food. Gastroparesis can occur as a result of several conditions, especially in people with diabetes. However, in many individuals with gastroparesis, the cause of the disorder is not known. It is more common in women and can have a major impact on quality of life.

The general principles for treating gastroparesis involve several strategies. First, attempts are made to correct fluid and nutritional deficiencies that may have occurred from chronic nausea and vomiting and/or the inability to eat normally. Second, treatments are given for the unpleasant symptoms that accompany gastroparesis. Third, the underlying cause of gastroparesis, such as diabetes, is treated. The treatment of patients with gastroparesis generally relies on dietary modifications, glycemic control medications that enhance gastric emptying, and medications that reduce nausea and vomiting.

A number of dietary recommendations have been developed based on the understanding of normal stomach emptying of different types of foods. These dietary recommendations are likely to be of greatest benefit to those with mild to moderate disease, but are also tried in patients with more severe gastroparesis to complement other medical treatments. It is recommended that anyone with gastroparesis seek dietary counseling with a dietician to help individualize nutrition therapy and maximize nutritional benefits.

Basic dietary guidelines:

- Small, frequent meals. Reducing the meal size reduces the distention of the stomach from the meal. By eating smaller meals, patients may not feel as full or bloated and the stomach may empty faster. With the reduction in meal size, increasing the number of meals to 4-6 per day is needed to maintain adequate nutritional intake.
- Avoid foods high in fat. Fat can delay emptying of the stomach. Eating less fat-containing foods will decrease the amount of time food stays in the stomach. However, fat-containing liquids, such as milkshakes, may be tolerated and provide needed calories.
- A diet low in fiber is suggested. Fiber delays gastric emptying. In addition, fiber may bind together and cause a blockage of the stomach, called a bezoar, in some patients. Examples of high fiber foods that should be avoided include oranges, berries, green beans, potato peels, apples, sauerkraut, and Brussel sprouts. Fiber supplements for treatment of constipation should also be discontinued if possible.

- Chew food well before swallowing. Patients should avoid foods that may not easily be chewed such as broccoli, corn, popcorn, nuts, and seeds. Solid food in the stomach does not empty well. Dental problems, such as missing or broken teeth, may lead to poorly chewed food; this may add to the problem of inadequate breakdown of food into smaller particles in the stomach for passage into the small intestine for absorption.
- A daily multivitamin/mineral supplement can be taken if dietary intake is inadequate.

If these measures are ineffective, the patient may be advised to consume the bulk of their meals as semi-solids or liquids, such as puréed foods or soups. Stomach emptying of liquids is often normal in patients with gastroparesis. Calorie-containing drinks, such as Hawaiian Punch or Hi-C, provide fluid and calories and are better than water alone. Some options while on a liquid diet include milk, instant breakfast, milkshakes, yogurt, puddings, custard, cereals, and smoothies. To meet the nutritional needs of patients, it may be necessary to supplement the diet with a liquid nutrient preparation that is low in fiber such as Ensure, Boost, or even baby foods. Blenderized foods prepared by the patient may also be used as a liquid nutrient source. Any food can be blenderized; solid foods will need to be thinned with some type of liquid, such as broth, milk, juice, or water.

There are quite a few medications that can delay stomach emptying. Check if any of the medications the patient is taking could be slowing down the stomach emptying.

For patients with diabetic gastroparesis, an important goal is to achieve or maintain good glucose control. This is achieved more easily by frequent monitoring of blood sugar levels and adjustment of insulin. Keeping the blood sugar under control may help stomach emptying. Consult the endocrinologist if the patient's blood sugar runs > 200 mg/dL on a regular basis.

Patients with kidney disease and serum creatinine <1.5mg/dL need to follow additional dietary advice. The dietary restrictions will depend on the nephrologist's assessment. Adequate protein is needed for nourishment, but too much may increase a waste product called urea that kidneys may not be able to get rid of. High sodium (salt) intake can increase blood pressure and fluid retention. Restriction of potassium varies depending on the stage of kidney disease. Generally, one should avoid high potassium foods such as bananas, oranges, kiwi, leafy greens, and broccoli. Kidneys may not be able to remove phosphorous from the blood. High phosphorous foods include dried beans, peas, nuts, and liver.

Patients with chronic symptoms of gastroparesis, despite these attempts at dietary intervention and medication, may develop dehydration and malnutrition. Occasionally, patients need an alternative method to obtain fluid and nutrition. This might involve delivering fluids and nutrients directly into the small intestine, bypassing the stomach, using a jejunostomy tube. In severe cases, intravenous fluids and nutrition may need to be provided.

5. Dietary and nutritional recommendations

Summary tables of basic dietary guidelines

Table 1: Dietary Recommendations for Gastroparesis

- Eat smaller, more frequent meals
- Eat less fatty foods
- Avoid fiber
- Avoid foods that cannot be chewed well

Table 2: Additional dietary recommendations for gastroparesis

- Liquid nutrients are better tolerated over solid food
- Good glucose control in patients with diabetes (aim for blood glucose < 180 mg/dL)
- Avoid medications that can delay stomach emptying such as:
  - Aluminum-containing antacids (Amphojel)
  - Narcotic pain medications (Percocet, Tylenol #3, Tylox, Oxycontin, and others)
  - Anticholinergic agent (Bentyl, Levsin, Elavil, and others)
  - Bulk-forming agents (Metamucil, Perdiem, Fibercon, and others)

Table 3: Foods that are encouraged

- Breads, cereals, crackers, ground or pureed meats
- Vegetables – cooked and, if necessary, blenderized/strained (avoid raw vegetables)
- Fruits – cooked and, if necessary, blenderized/strained (avoid raw fruits)
- Juices, beverages, milk products, if tolerated

Table 4: High fiber foods that should be avoided in gastroparesis

- Fruits – apples, berries, coconuts, figs, oranges, persimmons,
- Vegetables – Brussel sprouts, green beans, green peas, lettuce, potato peels, sauerkraut
- Bran/whole grain cereals
- Nuts and seeds
- Legumes/dried beans – baked beans, lentils, soy beans

5. Dietary and nutritional recommendations

A sample diet for patients with gastroparesis: sample meal plan for 6 small meals

Breakfast	1 cup cream of wheat cereal ½ cup skim milk ½ cup grape juice 1 scrambled egg
Snack	10 ounces of instant breakfast with skim milk
Lunch	½ cup vegetable soup ½ turkey sandwich ½ cup applesauce ½ cup milk 1 tablespoon mayonnaise
Snack	10 ounces banana shake made with l plain or vanilla yogurt, milk, and sugar
Dinner	2-3 ounces baked chicken or fish ½ cup mashed potatoes 1 teaspoon margarine ½ cup spinach ½ cup milk ½ cup fruit cocktail
Snack	½ cup pudding, custard, or gelatin

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