GpCRC

Gastroparesis
Clinical Research Consortium

Pilot Study of the Safety, Feasibility and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

Standard Operating Procedures

Part I: Clinical Center Operations

31 March 2011

GLUMIT-DG SOP Part I: Clinical Center Operations

Contents

1. Design overview. . . . 1
   - 1.1. Design synopsis. . . . 2
   - 1.2. Data collection schedule. . . . 6
   - 1.3. Whole blood draw schedule. . . . 7

2. Eligibility and enrollment. . . . 8
   - 2.1. Inclusion and exclusion criteria. . . . 9
   - 2.2. Run-in period. . . . 10
   - 2.3. Calculation of Gastroparesis Cardinal Symptom Index (GCSI) 11
   - 2.4. Guidelines for repeat determinations of eligibility. . . . 12
   - 2.5. Co-enrollment in Gastroparesis Registry. . . . 13
   - 2.6. Enrollment and eligibility checking. . . . 14

3. Certification. . . . 15
   - 3.1. Certification overview of GLUMIT-DG. . . . 16
   - 3.2. Clinical center certification. . . . 17
   - 3.3. Personnel certification 18

4. Human subjects. . . . 19
   - 4.1. Background. . . . 20
   - 4.2. Institutional Review Board process. . . . 21
   - 4.3. Consent administration. . . . 22
   - 4.4. Time considerations for obtaining consent. . . . 23
   - 4.5. Consent handling. . . . 24
   - 4.6. Informing participants of changes to consent statement after enrollment. . . . 25
   - 4.7. HIPAA considerations. . . . 26

5. Study visits. . . . 27
   - 5.1. Overview of visit schedule. . . . 28
   - 5.2. Visits, data forms, and procedures. . . . 32
   - 5.3. Guide for screening visits. . . . 34
   - 5.4. Guide for run-in visits with insulin pump training. . . . 36
   - 5.5. Visit window: enrollment and follow-up. . . . 37
   - 5.6. Interim (unscheduled) visits or telephone contacts. . . . 38

6. Study procedures. . . . 39
   - 6.1. Assignment of study identifiers. . . . 40
   - 6.2. Screening Contact Log (SL Form). . . . 41

6.3. Upper Endoscopy Documentation (EG form).. 42
6.4. Gastric Emptying Scintigraphy Documentation (GE form). 43
6.5. Electrogastrogram water load and caloric satiety testing (WL and ST form). 45
6.6. Baseline Medical History (BH form). 58
6.7. Follow-up Medical History (FH form). 59
6.8. Physical Examination (PE form).. 60
6.9. Height and weight measurements. 62
6.10. Waist and hip circumference measurement. 63
6.11. Neuropathy foot exam.. 65
6.12. Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (GD form).. 68
6.13. Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) (UG form). 69
6.14. Laboratory Results (LR form).. 70
6.15. Plasma Collection for Biosample Repository (BP form). 71
6.16. Training Documentation (TD Form).. 77
6.17. Adverse Event Reporting (IE form). 78
6.18. Procedures for downloading medtronic CGMS iPro data. 82
6.19. Procedures for Carelink downloading of data. 90
6.20. Procedures for Re-screen in GLUMIT-DG (RC form).. 99
6.21. Procedures for Missed or Incomplete Visits (MV form). 100
6.22. Procedures for patients lost to follow-up. 101
6.23. Procedures for mortality closeout (DR form).. 102
6.24. Medical management of patients. 103
6.25. Study Closeout (CO form). 107

7. Forms management.. 108
7.1. Clinical center ID codes. 109
7.2. Patient identifiers. 110
7.3. Visit ID code.. 111
7.4. General guidelines for forms completion. 112
7.5. Instruction box. 113
7.6. Form skips, stops, caution ineligibility symbols.. 114
7.7. Headers and footers.. 115
7.8. Key fields. 116
7.9. Missing data. 117
7.10. Administrative sign off. 118
7.11. Handling forms. 119
7.12. Data rounding rules.. 120
7.13. Data audits and edits.. 121

8. Quality assurance. 122
8.1. Site visits.. 123
8.2. Performance monitoring. 126
8.3. Data quality surveillance.. 127

GLUMIT-DG SOP Part I: Clinical Center Operations

1. Design overview

1.1. Design synopsis. 2
1.2. Data collection schedule. 6
1.3. Whole blood draw schedule. 7

1.1. Design synopsis

Title

- Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous **Glu**cose **M**onitoring and **I**nsulin Pump **T**herapy in **D**iabetic **G**astroparesis (GLUMIT-DG)

Sponsor

- NIDDK

Type of study

- Multicenter, uncontrolled, open label treatment
- Safety and feasibility

Objective

- To assess the safety, feasibility, and potential (uncontrolled) efficacy of real-time continuous glucose monitoring (RT-CGM) as an adjunct to self monitoring blood glucose (SMBG) in guiding insulin pump therapy to improve glycemic control for treatment of type 1 or type 2 diabetic patients with gastroparesis

Population

- Patients aged 18 - 70 years old at registration with mild to moderate symptoms of gastroparesis for at least one year and a diagnosis of type 1 or type 2 diabetes mellitus for at least 2 years.

Study duration – per patient

- A minimum of 4 weeks and up to 16 weeks of screening and baseline assessments prior to enrollment
- 24 weeks of open label treatment and follow-up after enrollment
- Length of recruitment: 12 months

Sample size and statistical analysis of primary outcome

- A total of 40 patients will be enrolled in this pilot study
- Rationale for sample size
  - Primary safety outcome: weekly frequency of mild, moderate, or severe hypoglycemic episodes by discrete One Touch® Ultra meter glucose values and/or a reference blood glucose level if the subject is seen in a hospital (emergency room)
  - Assumed mean weekly mild, moderate, or severe hypoglycemic episodes by discrete glucose values: 0.6
  - Assumed SD for weekly mild, moderate, or severe hypoglycemic episodes by discrete glucose values: 0.8
  - Assumed intra-class correlation between baseline and on-treatment weekly mild,

moderate, or severe hypoglycemic episodes by discrete glucose values: 0.6
- Estimated variance of change from baseline (a minimum of 4 weeks up to 16 weeks) to on-treatment (24 weeks) mean weekly mild, moderate, or severe hypoglycemic episodes (estimated from SD and intraclass correlation, accounting for 3:1 ratio of on-treatment to baseline period lengths): 0.41
- Type I error: 0.05 (1-sided for equivalence)
- Power: 0.9
- Expected percent increase from baseline in mean weekly mild, moderate, or severe hypoglycemic episodes during the treatment period with RT-CGM while using the glucose pump: 0%
- Equivalence limit (maximum percent increase in mean weekly mild, moderate, or severe hypoglycemic episodes): 35% (0.6 vs. 0.81 episodes per week)
- Method for sample size calculation: One sample test for equivalence (Chow, Shao and Wang, Sample Size Calculations In Clinical Research, Taylor & Francis, NY, 2003: p. 52-53)
- Software: Centre for Clinical Trials, Chinese University of Hong Kong -- http://www.cct.cuhk.edu.hk/stat/mean/osm_equivalence.htm
- Calculated sample size: N = 37

Number of clinical centers
- 7 (two lead clinics and 5 additional clinical sites added later)

Inclusion criteria
- Age 18 - 70 years old at registration
- Type 1 or Type 2 diabetes mellitus for at least 2 years
- Symptoms of gastroparesis (nausea, vomiting, early satiety, bloating, fullness, discomfort) for at least 1 year prior to registration with a Gastroparesis Cardinal Symptom Index (GCSI) score of $\geq$ 18
- Delayed gastric emptying on gastric scintigraphy within 1 year of registration, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
- Hemoglobin A1c of at least 8.0% at registration with current therapy indicating the need for insulin therapy. Individuals already receiving diabetes therapy via an insulin pump will be eligible for study participation if, in the opinion of the investigators, he/she may acquire additional benefit from continuous glucose monitoring that might improve glycemic control
- Normal upper endoscopy within 1 year of registration
- No clinical or imaging evidence of obstruction
- Successful mastering of use of RT-CGM during the run-in period

Exclusion criteria
- Prior gastric surgery including fundoplication

- Other systemic disease potentially causative of gastrointestinal symptoms
- Acute or chronic renal insufficiency with creatinine >1.5 mg/dL
- Current psychiatric disease or eating disorder
- Pregnancy
- Any other condition which, in the opinion of the investigators, would impede compliance or hinder completion of the study

Outcome measures

- ***Primary:*** The primary outcome measure is defined as the frequency and extent of mild or moderate hypoglycemic episodes (defined as a capillary glucose level less than 70 mg/dL documented by the home glucose meter and/or a reference blood glucose level if the subject is seen in a hospital (emergency room) setting and absolute number of severe hypoglycemic episodes recorded at the 12 and 24 week follow-up visits while subjects are using a combination of RT-CGM and insulin pump therapy.

- **Secondary outcome measures** will be defined to address the following:
  Effects of RT-CGM and insulin pump therapy on:
  - Hemoglobin A1c at baseline, 12, and 24 week follow-up visits
  - Percent time of day in hypoglycemia (<70 mg/dl), euglycemia (70-180 mg/dl), or hyperglycemia (>180 mg/dl) as determined by capillary glucose measurements and in a separate analysis by RT-CGM.
  - Glycemia variability (blood glucose rate of change) based on RT-CGM readings
  - Hyperglycemia index and hypoglycemic index using capillary glucose measurements in one analysis and RT-CGM in a separate analysis.
  - Gastroparesis patient-related outcome measures using the GCSI, PAGI-SYM and PAGI-QOL scores at baseline, 12, and 24 week follow-up visits
  - Maximal volume of water and Ensure consumed during satiety tests at baseline, 12, and 24 week follow-up visits
  - Percent tachygastria, bradygastria and normal 3 cycles per minute (cpm) activity during electrogastrogram (EGG) and satiety testing at baseline, 12, and 24 week follow-up visits
  - Vagal cholinergic and sympathetic adrenergic functions at baseline, 12, and 24 week follow-up visits

Recruitment

- 20 type 1 and 20 type 2 diabetics with gastroparesis will be enrolled at 7 clinical centers
- 12 month period
- Enrollment of 10 patients at the Wake Forest University clinical center
- Enrollment of 5 patients per clinical center expected at the remaining 6 clinical centers

Duration of open label treatment and follow-up

- 24 weeks

1.1. Design synopsis

Visit schedule

- Screening into the study: enrollment should occur within 16 weeks of registration
  - During the baseline assessment, prospective participants will learn how to use an iPro sensor to obtain retrospective CGM data
  - If subjects are successful in using the iPro, they will receive training in RT-CGM and in insulin infusion pump therapy. They will be taught how to use the trend analysis from RT-CGM as adjunctive information to home glucose monitoring measurements in making insulin dose decisions.
- Run-in visits:
  - At least 4 visits to receive training on use of an insulin pump in conjunction with RT-CGM.
- Treatment and follow-up phase
  - Every 4 weeks after enrollment throughout the 24 week open label treatment study

Safety monitoring

- The NIDDK-appointed DSMB will perform interim monitoring of the accumulating GLUMIT-DG study data for patient safety and potential (uncontrolled) efficacy according to the Data and Safety Monitoring Plan (DSMP) for the GLUMIT-DG study

1.2. Data collection schedule

	Screening, run-in, and enrollment visits			Follow-up visits Weeks from enrollment					
Assessment/Procedure	**s1**	**s2**	**R***	**4**	**8**	**12**	**16**	**20**	**24**
Consent	X	.	. .	.	.	.	.	.	.
Gastric emptying scintigraphy review	X	.	. .	.	.	.	.	.	.
Upper endoscopy results review	X	.	. .	.	.	.	.	.	.
Baseline medical history	X	.	. .	.	.	.	.	.	.
Follow-up medical history	X	.	. .	X	X	X	X	X	X
Physical exam	X	.	. .	.	.	X	.	.	X
Autonomic function and ECG	X	X	. .	.	.	X	.	.	X
PAGI-QOL questionnaire	X	.	. .	.	.	X	.	.	X
PAGI-SYN questionnaire	X	.	. .	.	.	X	.	.	X
Water load and satiety test with electrogastrogram	X	X	. .	.	.	X	.	.	X
RT-CGMS training	X	X	. .	.	.	.	.	.	.
Insulin pump training with RT-CGMS	X	.	. X	.	.	.	.	.	.
Adverse event monitoring	X	X	. X	X	X	X	X	X	X
CBC, HbA1c, metabolic panel	X	.	. X†	.	.	X	.	.	X
Thyroid stimulating hormone	X	.	. .	.	.	.	.	.	.
Plasma banking	X	X	. .	.	.	X	.	.	X

***Run-in**: Four visits include training with the insulin pump and RT-CGMS to establish the baseline parameters.
†Blood draw for HbA1c only will occur at the end of the run-in period
Physical exam includes measurement of weight, vital signs (temperature, heart rate, blood pressure), general physical findings
Complete blood count (CBC): white blood cells, red blood cells, hemoglobin, hematocrit, platelets
HbA1c: Hemoglobin A1c
Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, ketonemia, calcium, blood urea nitrogen (BUN) creatinine, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin

1.3. Whole blood draw schedule

	Study visit (wk)							
Procedure	**Screening**	**4**	**8**	**12**	**16**	**20**	**24**	**Total**
Hemoglobin A1c	**10**	**.**	**.**	**5**	**.**	**.**	**5**	**20**
Complete blood count	**5**	**.**	**.**	**5**	**.**	**.**	**5**	**15**
Metabolic panel	**5**	**.**	**.**	**5**	**.**	**.**	**5**	**15**
Thyroid stimulating hormone	**5**	**.**	**.**	**.**	**.**	**.**	**.**	**5**
Blood for plasma banking	**10**	**.**	**.**	**10**	**.**	**.**	**10**	**30**
Total (in mL)	**35**	**.**	**.**	**25**	**.**	**.**	**25**	**85**

Complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets

Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, blood urea nitrogen (BUN) creatinine, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin

2. Eligibility and enrollment

2.1. Inclusion and exclusion criteria. 9
2.2. Run-in period. 10
2.3. Calculation of Gastroparesis Cardinal Symptom Index (GCSI) 11
2.4. Guidelines for repeat determinations of eligibility. 12
2.5. Co-enrollment in Gastroparesis Registry. 13
2.6. Enrollment and eligibility checking. 14

2.1. Inclusion and exclusion criteria

Patients with mild to moderate symptoms of gastroparesis, and have been previously diagnosed with diabetes, will be studied. Patients should not have idiopathic or post-surgical gastroparesis etiologies and must satisfy the following inclusion criteria:

1. Age 18 – 70 years old at registration
2 Type 1 or type 2 diabetes mellitus for at least 2 years
3. Symptoms of gastroparesis (nausea, vomiting, early satiety, bloating fullness, discomfort) for at least 1 year prior to registration with a Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 18
4. Delayed gastric emptying on gastric emptying scintigraphy within 1 year of registration, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
5. Hemoglobin Alc of at least 8.0% at registration with current therapy (insulin and/or oral hypoglycemic agents). This level of HbA1c indicates the need to advance treatment and makes the patient a candidate for insulin treatment (for those using oral agents only or optimization of insulin therapy). Individuals already receiving diabetes therapy via an insulin pump will be eligible for participation, if in the opinion of investigators, he/she may acquire additional benefit from RT-CGM that might improve glycemic control
6. Normal upper endoscopy within 1 year of registration
7. No clinical or imaging evidence of obstruction
8. Successful use of the RT-CGM during the screening period
9. Access to a computer running windows and with internet capabilities

Exclusion criteria

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

1. Prior gastric surgery including fundoplication
2. Other systemic diseases potentially causative of gastrointestinal symptoms
3. Acute or chronic renal insufficiency with creatinine >1.5 mg/dL
4. Current psychiatric disease or eating disorder
5. Pregnancy
6. Any other condition which in the opinion of the investigators would impede compliance or hinder completion of the study

2.2. Run-in period

Prior to enrollment into the GLUMIT-DG study, patients will undergo up to 8-weeks of a run-in phase in which they will learn to operate an insulin pump coupled with the MiniLink™ REAL-Time Transmitter Continuous Glucose Monitoring System (RT-CGM). At the end of the run-in phase, patients must show competency with operating the MiniMed Paradigm Insulin Pump and RT-CGM to be eligible for participation in the GLUMIT-DG study. Specifically, a patient must be able to check blood glucose levels with the RT-CGM, as an adjunct to the traditional finger stick method at least 4 times daily. In addition, patients must be able to manage the insulin pump which includes making adjustments to insulin dosing according to standards provided by the GLUMIT-DG study physician and diabetes educator. Patients must also be able to electronically transfer data from the RT-CGM via their home computer to the GLUMIT-DG study staff. Once a patient has shown the ability to complete all of these tasks and has confirmed their consent to participate, they may enroll into the GLUMIT-DG study.

2.3. Calculation of Gastroparesis Cardinal Symptom Index (GCSI)

Gastroparesis Cardinal Symptom Index (GCSI) score for gastrointestinal symptoms will be calculated using the GLUMIT-DG data collection form GD - 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 ≥18 during screening to be eligible for enrollment into the GLUMIT-DG study.

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 rescreened at a later time as follows:

- Age <18 years – the participant may be re-screened after his or her 18th birthday
- Unwilling to participate – the participant may be rescreened after 3 months at the discretion of the investigator
- Unable to complete gastric emptying scinitigraphy – the test may be repeated and the participant may be rescreened when clinically indicated
- Symptoms of gastroparesis with a Gastroparesis Cardinal Symptom index (GCSI) of less than 18 - the participant may be rescreened at the discretion of the investigator.
- Symptoms of gastroparesis for less than 1 year duration - the participant may be rescreened when 1 year of gastroparesis symptoms is reached
- Unable to complete the use of the RT-CGM and use of the insulin pump - the participant may repeat RT-CGM and insulin pump use one additional time to continue screening
- Hemoglobin A1c levels of at least 8.0% at time of registration - the participants HbA1c levels may be repeated to allow for registration
- Acute or chronic renal insufficiency with creatinine >1.5 mg/dL - the participants creatinine levels may be repeated after treatment to allow for registration
- Length of diabetes history - the participant may be rescreened after having a diagnosis of type 1 or type 2 diabetes for at least 2 years

2.5. Co-enrollment in Gastroparesis Registry

- When a Gastroparesis Registry (GpR) participant is enrolled into the GLUMIT-DG study, the visit schedule and requirements of the study take precedence over the requirements for the Registry. Registry requirements are suspended for the duration of the participant's time in the treatment study. The GpR Closeout Form (CO) should be completed to suspend the Registry visits while the patient is enrolled in the GLUMIT-DG study.

Patient enrolled in GpR who now wants to screen for GLUMIT-DG

- Whenever possible, the clinical center should wait at least 8 weeks after enrollment in the GpR before registering the patient in GLUMIT-DG. The rationales for this are: (1) we want complete, fresh data in GLUMIT-DG, and a patient is more likely to be willing to complete forms and procedures if there has been a noticeable duration since he/she completed forms for the GpR; and (2) to encourage patients who are likely GLUMIT-DG candidates to enter directly into GLUMIT-DG.
- Have the patient sign the GLUMIT-DG consent form
- Complete and key the GLUMIT-DG RG form but do NOT issue a new patient ID number and code
- Blood for biosample repository
  - Whole blood must be collected for plasma banking at the biosample repository even if plasma and serum were already banked for the GpR regardless of the time between enrollment in the GpR and registration in GLUMIT-DG
- Lab results reported on the GpR Laboratory Results (LR) form may be used on the GLUMIT-DG LR form if they were obtained within the 16 week time window specified on the GLUMIT-DG LR form. An additional blood draw to obtain and thyroid stimulating hormone levels may be necessary.
- All interviews and patient questionnaires (baseline history, quality of life, and gastroparesis symptoms) must be completed anew for GLUMIT-DG
- The physical exam (PE) form must be completed anew for GLUMIT-DG
- If the patient is enrolled in GLUMIT-DG, complete the GpR Closeout (CO) form to suspend the patient's participation in the GpR. You do not need to complete the Missed or Incomplete Visit (MV) form for the missed GpR follow-up visits. The patient remains enrolled in the GpR while participating in GLUMIT-DG, but the patient is not subject to completion of GpR visits; have the patient complete GLUMIT-DG follow-up visits and forms

2.6. Enrollment and eligibility checking

Enrollment steps

- Complete collection of all required screening data and key all screening data forms within 16 weeks of registration date
- Ensure the patient has completed the required RT-CGM and insulin pump training and are competent with using the devices
- Run electronic check on eligibility (i.e., run the Enrollment Task and resolve any missing items or ineligibility conditions)
- Run the Enrollment Task and confirm that you want to enroll the patient "now"; this task will officially enroll the patient in GLUMIT-DG and the materials needed for follow-up will be generated (i.e., labels, visit time windows)

Overriding eligibility criteria

- Requests overriding eligibility criteria must be made in writing (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 request must come from the principal investigator of the clinical center.
- 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.

Enrollment date

- The date the clinical center runs the Enrollment Task and confirms that the patient is to be enrolled "now"
- The "time zero" for reckoning the time windows specified on the patient's GLUMIT-DG visit time window guide.

3. Certification

3.1. Certification overview of GLUMIT-DG. 16
3.2. Clinical center certification. 17
3.3. Personnel certification 18

3.1. Certification overview of GLUMIT-DG

What is certification?

- It is an internal (i.e., related to the study) procedure designed to identify the staff responsible for specific data items or 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:
  - GLUMIT-DG study staff
  - Each clinical center
- Certification for the GLUMIT-DG study 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
- More than one staff member may be certified for a role and it is recommended that more than one staff member be certified for a role

Why do we require it?

- Primary purpose is to help assure consistent conduct of the study over time, within and across clinical centers. The conduct of procedures should be similar across patients and in serial testing of the same patient over the duration of follow-up.
- Study procedures may vary from the usual practice of a participating clinical center, but it is important that methods be carried out in the same manner within and across clinical centers.
- 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 GLUMIT-DG study.
- It provides a mechanism for tracking who collected key data items or made key decisions.
- The certification process may help a clinical center prepare for study activities by presenting the training, facility, and equipment needs in an organized fashion and requiring acquisition or completion of these items before study specific activities may begin.

GLUMIT-DG certification

- Certification requirements for GLUMIT-DG will be issued through notification of each clinical center by a numbered Policy and Procedure Memorandum (PPM).

3.2. Clinical center certification

General comments

- Each clinical center participating in the GLUMIT-DG study must be certified
- Completion of the Clinical Center Certification (CC) form will be required
- IRB approval for the GLUMIT-DG study protocol and consent is required

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 GLUMIT-DG study – provide a checklist of what needs to be in place before patient activities begin

Requirements for certification of a clinical center

- Outline of recruitment plan including the process identifying patients with diabetic gastroparesis, and obtaining consent
- Plan for study device storage and management
- Outline of procedures for gastric emptying, electrogastrogram, and satiety tests
- Checklist of facilities, equipment, and supplies for the GLUMIT-DG study, including the storage of patient reports and forms
- Acknowledge possession of protocol, standard operating procedures, manuals and other documents pertaining to GLUMIT-DG
- Assurances that the study participants protected health information will be kept confidential and that the identifiable information linking the participants will not be transmitted to the DCC
- All study staff must be certified and at least one person must be certified for each role; however, a person may be certified for multiple roles
- Obtain IRB approval of the most current GLUMIT-DG study protocol and consent document
- Receive written notice of approval (e-mail) from the Data Coordinating Center

3.3. Personnel certification

Staff functions requiring certification

- Clinical Coordinator
- Diabetes Educator
- Study Physician
- Diabetologist or endocrinologist
- Data Entry Technician

Requirements

- Everyone
  - Read the GLUMIT-DG study protocol and SOP I: Clinical Center Operations
  - Complete the Knowledge Assessment (KA) form; this is a written general knowledge assessment about the GLUMIT-DG study (open book)
  - Complete the Personnel Certification (PC) form; this form identifies the roles applied for and provides an assurance of data confidentiality and integrity
- Additional requirements for Study Physician
  - Study Physician must be an MD
- Additional requirements for Data Entry Technician
  - Complete the Data Entry Certification/Decertification Request (DC) form
  - 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

- Send required materials to the DCC
- The DCC will send written notice of approval for certification or pending certification
- Each staff member will be issued a Personnel Identification Number (PIN)

Staff PINs

- Each 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

4. Human subjects

4.1. Background. 20
4.2. Institutional Review Board process. 21
4.3. Consent administration.. 22
4.4. Time considerations for obtaining consent. 23
4.5. Consent handling. 24
4.6. Informing participants of changes to consent statement after enrollment. 25
4.7. HIPAA considerations. 26

4.1. Background

Consent for participation in the GLUMIT-DG study must be completed before screening for the study may begin. The patient must consent to procedures offered to and performed on him/her for screening, as well as to the follow-up visits which the patient will face in the future.

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 GLUMIT-DG study consent process has two major stages:

- The patient is asked to consent to screening and enrollment into the GLUMIT-DG study
- 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 Registration (RG) form. At the end of the screening process, the patient is asked to re-affirm their consent on the Enrollment (EN) form

4.2. Institutional Review Board process

A template consent statement has been prepared for the GLUMIT-DG study:

- Consent for screening and enrollment into GLUMIT-DG

Clinical centers are expected to use this template consent in their submissions to their Institutional Review Boards (IRBs) for approval to participate in GLUMIT-DG. Each clinic must send copies of the consent statements to be used in their clinic, stamped with their IRB's seal, to the Data Coordinating Center prior to initiating patient activities in GLUMIT-DG. Data Coordinating Center staff will review and compare the approved local consents to the template. Specific local additions to and editing of the template may be required at individual institutions, but deletion of material and 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 study protocol, consent form, 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 GLUMIT-DG study until the site has IRB approval for the GLUMIT-DG study 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

GLUMIT-DG consent

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

(1) A GLUMIT-DG 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) A GLUMIT-DG certified study physician (i.e., a GLUMIT-DG certified gastroenterologist or diabetologist) 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 or diabetologist is to help assure that the physician signing the consent is one who has a broad role in the study.

Generally, the consent statement should be offered to the patient to read through at least a day before his/her signature is requested. The consent will then be reviewed with the patient by the staff member designated to obtain consent; the consenter may opt to read the statement 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 GLUMIT-DG 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 GLUMIT-DG study physician or diabetologist for the physician to 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.

4.4. Time considerations for obtaining consent

- The **GLUMIT-DG 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 of this consent is required prior to sending the patient for any GLUMIT-DG diagnostic tests. A check for signature of this consent statement occurs on the Registration (RG) form.

- A patient may be given the consent statement to review prior to the initiation of the screening visit to meet patient needs with respect to review 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 GLUMIT-DG staff member. The consents may be mailed to the patient prior to the screening visit. Whatever timing is used by a clinic, the patient should be allowed enough time to reflect about the proposed GLUMIT-DG study procedures, pose questions, and consult with other individuals that he/she considers relevant to their participation in the GLUMIT-DG study. Patients may request and should be given time to "think it over" at home and come back at a later time.

4.5. Consent handling

- The signed consent statement is an important legal documents. The signed statement should be kept in the patient's GLUMIT-DG clinical center file together with his/her other GLUMIT-DG forms and documents. These forms are not part of the individual's institutional medical record, but part of his/her GLUMIT-DG study record. Consent statements will be examined during site visits.

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

- The GLUMIT-DG 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. If the patient refuses any part, the patient may not enroll in the GLUMIT-DG study.

4.6. Informing participants of changes to consent statement after enrollment

As new data become available during the conduct of the GLUMIT-DG study, the consent statement may need to be changed to reflect the current assessment of risks and benefits to participants in the study.

Procedures for dissemination of the revisions of the consent statement from the DCC

- Changes deemed necessary will be made to the prototype consent statements
- Revisions of the prototype consent statements will be distributed to clinical centers 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. HIPAA considerations

GLUMIT-DG study clinical center 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 GLUMIT-DG study should have access to these records. However, these records could be reviewed to make sure that the study is being done as it should. People who may see medical records or supporting 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) or the National Institutes of Health (NIH)

Each clinical center should take steps to protect patient privacy. Only 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. Any information linking the patient ID number and code should not be transmitted to the DCC or anyone else outside the insitution.

People outside the clinical center who will receive GLUMIT-DG study 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 GLUMIT-DG study data for performance and safety
- 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 GLUMIT-DG data. Patient identity will not be disclosed in any reports or publications resulting from the study. The use of the GLUMIT-DG study data must be approved by the GpCRC Steering Committee and by the research ethics committee at your institution.
- The Jaeb center will receive CGMS and insulin pump data and transfer it to a database

Patient agreement to enter the GLUMIT-DG study 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 GLUMIT-DG study.

5. Study visits

5.1. Overview of visit schedule. 28
5.2. Visits, data forms, and procedures. 32
5.4. Guide for run-in visits with insulin pump training. 36
5.5. Visit window: enrollment and follow-up. 37
5.6. Interim (unscheduled) visits or telephone contacts. 38

GLUMIT-DG SOP Part I: Clinical Center Operations

5.1. Overview of visit schedule

The patient-related activities of the GLUMIT-DG study can be divided into 3 phases:

- Screening to determine eligibility and receive training on the use of an iPro which is a CGM used for retrospective analysis of CGM results. While wearing the device the subject is blinded to their sensor glucose values. This period is so that the subjects can demonstrate a willingness to wear a sensor, gain proficiency in inserting a sensor, and provide the study baseline data of their CGM readings (retrospectively). This will occur over 2-8 weeks and include 2 visits for gastric related testing as well as iPro training. To progress in the study the subject will need to have at least 216 hours of iPro readings.
- Initiation of insulin pump training and training in the use of real-time CGM (4 visits over a minimum of 2 weeks up to a maximum of 8 weeks).
- Study treatment to assess the safety of using RT-CGM as an adjunct to SMBG-guided insulin pump therapy over 24 weeks (6 visits).

The screening phase may be conducted over 2 or more visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit. CGMS training may begin at the earliest screening visit, which is most feasible.

Screening (must be completed within 16 weeks of registration date)

The patient should be in a fasting state (no food or drink except up to 120 mL of water after midnight the night before) for this visit. The patient will sign the GLUMIT-DG consent at or prior to screening visit 1 and will undergo a history and physical examination to identify other illness and contraindications for participation such as already exhibiting good diabetes control. Anthropomorphic assessments (body weight [kg], body height [m], body mass index [BMI], waist circumference [cm], hip circumference [cm], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected and recorded. During this visit, 5 mL of blood will be drawn to measure patients hemoglobin Alc level to determine if it is at least 8% or higher, which is an eligibility criteria for this study. Additional laboratory tests that need to be obtained as part of screening or recorded from chart review include: complete blood count (CBC): white blood cells, red blood cells, hemoglobin, and platelets; a comprehensive metabolic panel and thyroid stimulating hormone (TSH). The Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL) and the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) questionnaires will also be completed. At a clinic visit as early as possible during the screening phase, patients will be seen by a diabetes educator to undergo training on measuring their blood glucose levels using the; Pro CGM.

Patients will return to the clinical center in a fasting state (no food or drink except up to 120 mL of water after midnight the night before) to continue with study procedures and baseline data collection for electrogastrography (EGG) with caloric and non-caloric satiety testing, electrocardiogram (ECG), and autonomic function testing. Patients will have their blood glucose level measured using a finger stick method to ensure their blood glucose is less than 270 mg/dL. Once confirmation is made that the patient's blood glucose level is less than 270 mg/dL, a EGG testing will be performed, as outlined in SOP I, section 6.5.

5.1. Overview of visit schedule

5.1. Overview of visit schedule

Run-in with insulin pump training

After successful completion of iPRO training, patients will return for four weekly visits, for a minimum of two weeks up to an 8-week learning period to receive training on the usage of an insulin pump coupled with RT-CGM.

- **Run-in visit 1:** Participants will receive instruction on use of the RT-CGM, including the uploading of the data using the CareLink system as well as instructions on glycemia managementusing their SMBG which will be supplemented with the trend identification using the RT-CGM. The RT-CGM has a feature known as "REAL-Time Alarms" which will be set to warn patients when their glucose levels are very low or very high. The hypoglycemic alarm threshold will be set at 80 mg/dL and the hyperglycemic alarm threshold will be set at 240 mg/dL. The low glucose snooze will be set between 15-20 minutes to allow time to observe the effect of treatment for the hypoglycemia, and the high glucose snooze will be set to 1-2 hours to allow time to observe the effects of a corrective dose of insulin. They will be taught how to calibrate their RTCGM using 2-4 glucose readings each day, obtained when there is a low rate of glucose change, as indicated by an absence of rate of change arrows. The subjects will be instructed to not make any insulin dose decisions based on the RT-CGM glucose reading without obtaining a blood glucose measurement using their glucose meter. Insulin doses may be modified based on the glucose rate of change, as was done during the JDRF15 and STAR 116 and STAR 317 trials. (See package insert for instructions for use of CGM)
- **Run-in visit 2:** This visit should be planned within a week after the first run-in visit. Patients will be taught insulin infusion pump mechanics and will be started on an insulin pump filled with saline. The purpose of filling the pump with saline is to ensure that the patient can tolerate wearing it before it is filled with insulin.
- **Run-in visit 3:** Patients will stop previous diabetes treatment and insulin administration with the pump will be initiated according to predetermined insulin dose parameters. For those patients who entered the study using an insulin pump, parameters will be adjusted as per their meter blood glucose readings using their RT-CGM readings as adjunctive information. Carbohydrate to insulin ratios, insulin sensitivity, insulin on board (3 to 5 hours), and glycemic targets will be established by the study staff. Patients will be instructed to only use the bolus wizard feature of the pump when delivering insulin doses for meals to ensure the proper amount of insulin is delivered. Due to the presence of gastroparesis, meal boluses for control of postprandial hyperglycemia combination meal boluses using a standard bolus and square wave bolus may be utilized with adjustments made based on post prandial glucose trends. This approach is aimed at minimizing a mismatch in insulin bolus administration and nutrient absorption due to delayed and possibly erratic gastric emptying. In addition to intensive education on glycemic control, participants will be instructed in depth on symptoms and signs of hypoglycemia and steps to correct it without caloric over replacement to avoid rebound hyperglycemia.

- **Run-in visit 4:** Patients will review their RT- CGM results and receive additional education on glycemia management. They will also be taught how to use glucose trends as displayed by the RT-CGM as adjunctive information to their SMBG to modify their insulin doses and to ingest carbohydrates if the RT-CGM identifies a risk of hypoglycemia, if it is confirmed by a meter glucose reading. In addition, blood will be drawn to measure their hemoglobin Alc level.

Enrollment

- en: Enrollment into the GLUMIT-DG study may occur once a patient has met all the eligibility criteria and has shown the ability to master insulin pump therapy and glucose monitoring with CGMS. Once a patient has shown the ability to complete all of these tasks and has confirmed consent to participate, he/she may enroll into the GLUMIT-DG study.

Follow-up visits

Patients will return for follow-up visits, once every 4 weeks over a 24-week period after enrollment. During these visits, patients will meet with the diabetes educator and have their insulin pump parameters (basal rate, carbohydrate to insulin ratio for meals, etc.) adjusted according to blood glucose readings from patients self-monitoring blood glucose (SMBG) levels and trends observed from the RT-CGM. For follow-up visits, at 12 and 24 weeks, the following additional procedures will take place:

- f012: Patients will have 10 mL of blood drawn for plasma banking, EGG, and autonomic function with ECG will take place. Patients will also complete the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) questionnaires. Any unanticipated adverse events will be reviewed with the patient and recorded on the Interim Event Report (IE) form.

- f024: The same testing procedures completed at f012 will be done at the f24 visit.

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Screening		*The patient should be in a fasting state for this visit.*
	RG	Registration (document consent, sociodemographics, assign IDs)
	PL	Patient location (patient contact information)
	PE	Physical examination
	BH	Baseline medical history
	EG	Upper endoscopy documentation
	GE	Gastric emptying scintigraphy documentation
	LR	Laboratory results
	GD	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
	UG	Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
	RC	Re-screen in GLUMIT-DG
	BP	Blood processing for plasma
	WL	Electrogastrogram and water load satiety test
	ST	Electrogastrogram and satiety Test

The screening phase may be conducted over 3 or more visits. The visit schedule is a guide for the centers and allows flexibility in completion of study procedures, however, enrollment of a patient will only occur if the data system shows that the patient is eligible, has signed the consent statement, and has had al required screening forms keyed into the data system. Participants will also be trained on how to use a computer to send data gathered by the RT-CGM and insulins pump to their study physician and diabetes educator.

Run-in visits		*The patient will be seen by a diabetes educator for instruction on using the RT-CGM and insulin pump*
	EN	GLUMIT-DG enrollment form will be completed during the last run-in visit
	PL	Patient location (update as needed)
	TD	Training Documentation

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Follow-up phase		
4 week follow-up visit		
f04, f08	FH	Follow-up medical history
f16, f20	IE	Interim event
	PL	Patient location (update as needed)
12 week follow-up visit		*The patient should be in a fasting state for this follow-up visit.*
f012	FH	Follow-up medical history
	PE	Physical examination
	GD	PAGI-SYM questionnaire
	UG	PAGI-QOL questionnaire
	BP	Blood processing for plasma
	LR	Laboratory results for CBC, HbA1c, and metabolic panel are required at the f12 visit
	AF	Autonomic function assessment
	ST	Electrogastrogram and satiety test
	WL	Electrogastrogram and water load satiety test
	PL	Patient location (update as needed)
24 week follow-up visit		*The patient should be in a fasting state for this follow-up visit.*
f024	FH	Follow-up medical history
	PE	Physical examination
	GD	PAGI-SYM questionnaire
	UG	PAGI-QOL questionnaire
	BP	Blood processing for plasma
	LR	Laboratory results for CBC, HbA1c, and metabolic panel are required at the f12 visit
	CO	GLUMIT-DG closeout
	AF	Autonomic function assessment
	WL	Electrogastrogram and water load satiety test
	ST	Electrogastrogram and satiety test
	PL	Update so study results can be mailed at a later date
	IE	Interim Event

5.3. Guide for screening visits

The screening visits may be conducted over 3 or more visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit to meet their needs. This visit guide allows flexibility in completion of screening procedures, however, enrollment into the GLUMIT-DG study will only occur if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening and run-in forms keyed to the data system.

Procedures

- Obtain signed consent for the GLUMT-DG study (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, anthropometric measurements, and neuropathy foot exam (height, weight, waist circumference, hip circumference, temperature, blood pressure, resting radial pulse, and respiratory rate)
  - Interview for baseline medical history (responses may be modified or expanded upon chart review)
  - Laboratory testing (CBC, HbA1c, metabolic panel, thyroid stimulating hormone)
  - Collect blood for plasma banking (1 tube)
  - Upper endoscopy results documentation
  - Gastric emptying scintigraphy results documentation
    - Questionnaires regarding gastroparesis symptom severity and quality of life
- Initiate RT-CGM training with diabetes educator
- Complete autonomic function with ECG testing
- Complete EGG with satiety test
  - Check patients blood glucose level to confirm that it is <270 mg/dL
- If patient appears eligible at the close of the initial visit
  - Schedule patient for subsequent visits to complete
  - Schedule patient for any needed tests

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
  - EG Upper Endoscopy Documentation
  - GE Gastric Emptying Scintigraphy Documentation
  - LR Laboratory Results (completion of all laboratory test results required during screening: CBC, HbA1c, metabolic panel, thyroid stimulating hormone)

5.3. Guide for screening visits

- BP Blood Processing for Plasma
- GD Patient Assessment of Upper Gastrointestional Disorders Symptom Severity Index (PAGI-SYM)
- UG Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QOL)
- ST Electrogastrogram and satiety test

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 GLUMIT-DG study chart for patient and file the completed forms
- Process blood to plasma aliquots for banking; store in local freezer at -70°
- Key data collection forms

5.4. Guide for run-in visits with insulin pump training

The run-in visits with insulin pump training may be conducted over 4 or more visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit to meet their needs. The last run-in visit should include enrollment into the GLUMIT-DG study for the convenience of the participant.

Before the patient arrives for the visit

- Abstract data from patient's medical records as needed
- Prepare the computer which will be used for teaching patients to send RT-CGM and insulin pump data to the clinical center (run-in visit 1)
- Prepare insulin pump and saline (run-in visit 2)
- Confirm eligibility with respect to successful completion of the RT-CGM training and whatever data have been keyed

Procedures

- Continue RT-CGM training including use of the "REAL-Time Alarms" (run-in visit 1)
- Review instructions for uploading insulin pump and RT-CGM data to the Carelink system
- Explain insulin pump mechanics and fill pump with saline (run-in visit 2)
- Begin insulin administration using predetermined insulin dose parameters (run-in visit 3)
- Explain the use of glucose trends displayed by the RT-CGM to modify insulin doses (run-in visit 4)
- Draw blood to measure hemoglobin A1c
- Explain to the patient that you will electronically confirm eligibility after keying the enrollment form

Data collection forms (form abbreviation)

- Forms completed for all patients
  - TD - Training Documentation
  - EN - Enrollment

Forms for clinical center use only

- Check for updates to Patient Location (PL)

After the patient leaves the clinical center

- Key data collection forms

Comment

- Use the visit window guide generated after enrollment to schedule the first follow-up visit and prepare forms that will be used at the f04 visit. The f04 visit may not be scheduled soon than 4 weeks (28 days) after enrollment.

5.5. Visit window: enrollment and follow-up

- **Enrollment** must occur within 16 weeks (112 days) of registration date
- **f04**: window runs from week 3 through 5 weeks, ideal date is 4 weeks (28 days) after enrollment date
- **f08**: window runs from (5 weeks+1 day) through 9 weeks, must be at least 4 week after f04; ideal date is 8 weeks (56 days) after enrollment date
- **f12**: window runs from (9 weeks+1 day) through 13 weeks, must be at least 4 week after f08; ideal date is 12 weeks (84 days) after enrollment date
- **f16**: window runs from (13 weeks+1 day) through 17 weeks, must be at least 4 week after f12; ideal date is 16 weeks (112 days) after enrollment date
- **f20**: window runs from (17 weeks+1day) through 21 weeks, must be at least 4 week after f016; ideal date is 20 weeks (140 days) after enrollment date
- **f24**: window runs from (21 weeks+1day) through 25 weeks, must be at least 4 week after f020; ideal date is 24 weeks (168 days) after enrollment

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 collection forms are not required at interim visits. However, if lab results are available or procedures such as endoscopy or scintigraphy are performed, then the corresponding data forms (LR, EG, GE) should be completed using visit code 'n'.

- If gastroparesis or diabetes symptom exacerbation occurs for a GLUMIT-DG patient between scheduled GLUMIT-DG visits, complete the Interim Event Report (IE) form; the visit code for the form will be 'n'. 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, 'n' for the second event, etc.

6. Study procedures

6.1. Assignment of study identifiers. . . . 40
6.2. Screening Contact Log (SL Form). . . . 41
6.3. Upper Endoscopy Documentation (EG form). . . . 42
6.4. Gastric Emptying Scintigraphy Documentation (GE form). . . . 43
6.5. Electrogastrogram water load and caloric satiety testing (WL and ST form). . . . 45
6.6. Baseline Medical History (BH form). . . . 58
6.7. Follow-up Medical History (FH form). . . . 59
6.8. Physical Examination (PE form). . . . 60
6.9. Height and weight measurements. . . . 62
6.10. Waist and hip circumference measurement. . . . 63
6.11. Neuropathy foot exam. . . . 65
6.12. Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (GD form). . . . 68
6.13. Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) (UG form). . . . 69
6.14. Laboratory Results (LR form). . . . 70
6.15. Plasma Collection for Biosample Repository (BP form). . . . 71
6.16. Training Documentation (TD Form). . . . 77
6.17. Adverse Event Reporting (IE form). . . . 78
6.18. Procedures for downloading medtronic CGMS iPro data. . . . 82
6.19. Procedures for Carelink downloading of data. . . . 90
6.20. Procedures for Re-screen in GLUMIT-DG (RC form). . . . 99
6.21. Procedures for Missed or Incomplete Visits (MV form). . . . 100
6.22. Procedures for patients lost to follow-up. . . . 101
6.23. Procedures for mortality closeout (DR form). . . . 102
6.24. Medical management of patients. . . . 103
6.25. Study Closeout (CO form). . . . 107

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

By whom

- Clinical Coordinator

Procedures

- Complete the GLUMIT-DG 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
- 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 GLUMIT-DG 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 GLUMIT-DG, including patients already enrolled in the Gastroparesis Registry

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 GLUMIT-DG

When

- Record prospective participants contacted regarding enrollment 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-k 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 (10 patients contacted) 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 GLUMIT-DG files along with other study forms

6.3. Upper Endoscopy Documentation (EG form)

Purpose

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

When

- Screening visit (the upper gastrointestinal endoscopy must have been performed within 1 year 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
- A copy of the available reports should be attached to the form

6.4. 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). The meal is adopted from the multi-center study using a low fat meal by Tougas et al.

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 some 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 how much 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%). 1 minute of anterior and 1 minute of posterior measurements will be taken. Subsequent images are taken at least 1, 2, and

4 hours after meal ingestion. It would be helpful to obtain these images at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after meal ingestion. This may help improve the test. The times of the images should be recorded.

In the time between images, subjects can be sitting, standing, or walking but should remain in close proximity to the nuclear medicine section.

Documentation

Purpose

- To record results from gastric emptying scintigraphy to determine eligibility

When

- Screening visit (the gastric emptying scintigraphy must have been performed at a GLUMIT-DG clinical center within 1 year prior to registration)
- As needed during follow-up

Procedure

- Any necessary information not contained in the report (amount of meal consumed) should be gathered from the patient during or immediately after the test
- Study Physician completes the form using the gastric emptying scintigraphy report

6.5. Electrogastrogram water load and caloric satiety testing (WL and ST form)

Pre-test procedures for water load satiety testing

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 water load satiety test. If the patient normally takes insulin, they will be asked to take only half of their normal long-acting insulin.

The EGG will be performed using 3CPM equipment. For each EGG study, the clinical center needs to have:

- A bottle of spring water refrigerated at 4 degrees C for each patient
- A cup that has a 150 mL measured mark
- 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 water load 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. Patients may take their usual medications with a small amount of water (up to 4 oz) up to two hours prior to the study, but should refrain from coffee, tea, or juice. After arriving to the clinic, the patient's blood glucose level must be checked to ensure it is less than 270 mg/dL. If the patient's blood glucose level is greater than 270 mg/dL the EGG and water load satiety test must be rescheduled for another day.

The patient should be given the opportunity to use the bathroom. Take the bottled water 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:

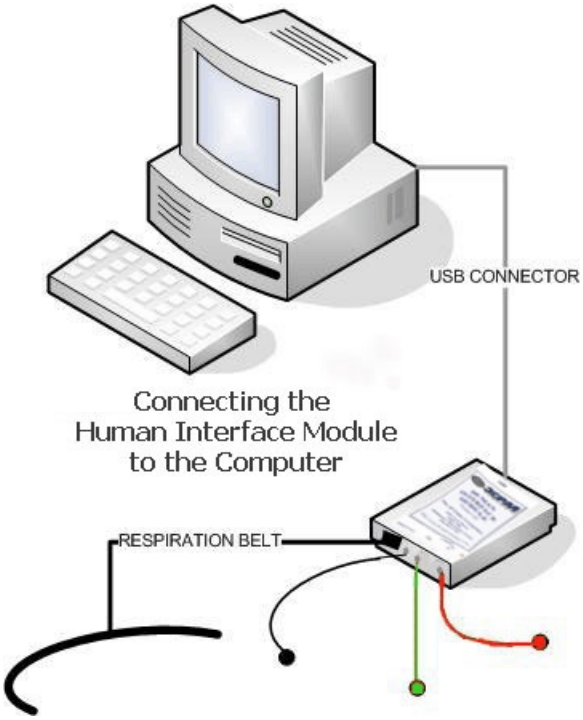
Technique for skin preparation and electrode placement

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.

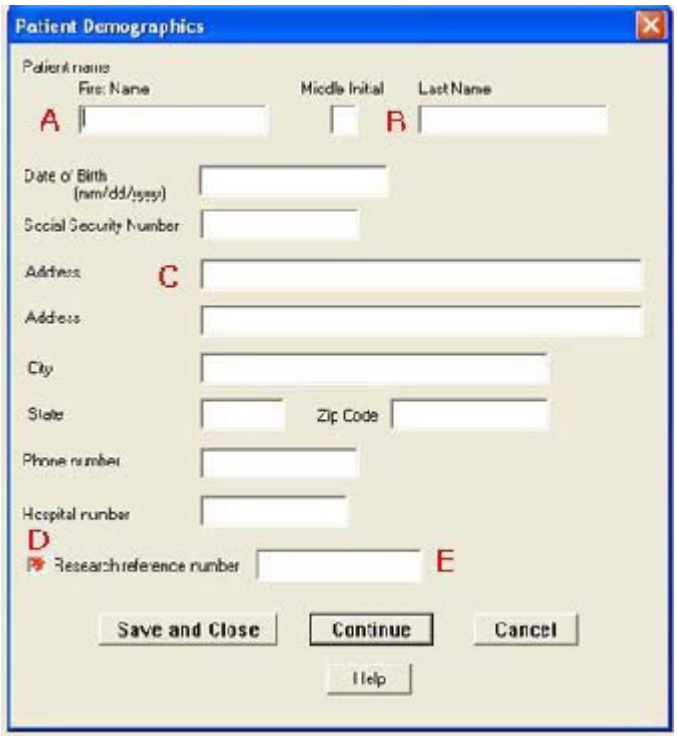
   You may elect to start a study for a new patient in one of two ways:
   - Select the icon for a new file, from the toolbar just under the top menu.
   - Select File from the top menu, then select ***New Study***, and then select ***New Patient***.

De-identifying patient data:

– For EGG recordings in the GLUMIT-DG study, 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 demographics for GLUMIT-DG research study 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 visit code(i.e., zzzs1; zzzf12)
C. Enter the study name in the **Address** field (i.e., GLUMIT-DG 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 visit code (i.e., 9000-zzzf12 for the f12 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 bottled spring water 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 Water Load Satiety Test (WL) 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 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 water consumed in this box.

Satiety test

Patients will begin the Water Load Satiety Test. For this, subjects will sit up. During the test,

subjects will drink bottled spring water for a 5 minute period until they feel "**completely full**." The patient's symptoms are recorded at 10, 20, and 30 minutes after ingestion of the bottled spring water and the total volume consumed will be recorded on page 3 of the WL form.

Instructions to patients for Satiety Test are as follows:

"You will be given a cup of bottled spring water to drink for 5 minutes until you feel completely full. You will have up to 5 minutes to drink the cup of bottled spring water. You may use all of this time, if needed. After you finish, 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 bottled spring water. This is not a test to see how much you can drink, but simply to have you drink until you feel completely full."

- The total volume of bottled spring water consumed (WL form page 3) 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 water load satiety period (after the drink is completed). The respiratory belt should be checked to verify it is snug.

Starting the EGG study recording (post water load satiety testing)

Once you have entered the amount of bottled spring water 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 0-10 minute period, you will have the subject complete a symptoms score sheet (WL form page 4). **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 11-20 minute postprandial period, you will have the subject complete a symptoms score sheet (WL form page 5). At the end of the 21-30 minute postprandial period, you will have the subject complete a symptoms score sheet (WL form page 6). 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:

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 (bottled spring water). You can do this by using one of the 4 following methods.

1. Select the 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 0-10), 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 10 minute period by making the Start Period 0.0 and the End Period 10.0 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 11-20) and third post-stimulation period (minutes 21-30). **Do not select more than 10 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 10 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 3***) is used for selecting the period length for the remaining 21-30 minute period for selecting good minutes. Use the EGG report to complete page 7-8 of the WL form.

Electrogastrogram and Satiety Test (WL form)

The Electrogastrogram and Water Load Satiety Test (WL) form is used to document symptoms and results of the water load satiety test and electrogastrogram in GLUMIT-DG study participants.

- Complete the WL form during screening and at follow-up visit f12 and f24.
- Have the patient respond to symptom evaluations on pages 2, 4 and 5 by marking a vertical line in each of the visual analog scales on pages 2, 4, 5, and 6. The scales are 100 mm in length and 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 9, 10, 14, 15, and 16.
- Using the EGG report, complete section **E. EGG data**
- The Study Physician and Clinical Coordinator should complete section **F. Administrative information**

Best practices when performing the EGG:

- When selecting minutes: choose whole minutes only; choose **at least 4** consecutive good minutes, up to 10 minutes. Do not select more than 10 minutes for any period.
- Attach a copy of the EGG report to the WL form. Save the raw digital EGG data to a USB flash drive.
- 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 "GLUMIT-DG Exported Data", then create individual subfolders each time you export a group of patient EGG files. This will organize and archive exported GLUMIT-DG patient data to a specific folder in a way that the data may be tracked and documented.

6.5. Electrogastrogram water load and caloric satiety testing

For quality assurance purposes, each clinical center must forward their first two GLUMIT-DG 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 in NORIG for instructions as they also apply to the GLUMIT-DG study), do not enter any patient demographics when prompted. Enter the 4-digit patient ID number under First Name and the 3-letter patient codein 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 "GLUMIT-DG 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@wfubmc.edu), Dr. Kenneth Koch (kkoch@wfubmc.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

Pre-test procedures for caloric satiety testing

The patient should fast for two hours after the water load satiety test is completed. 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 at 4 degrees C 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

6.5. Electrogastrogram water load and caloric satiety testing

Test protocol

Refer to the water load satiety testing for instruction on the following:

- Equipment set-up
- De-identifying patient data
- Equipment test
- Recording of EGG and respiratory signals

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 at 10, 20, 30 and 60 minutes after ingestion of Ensure® and the total volume of Ensure® consumed will be recorded on page 3 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 4 of the ST form. The total volume of Ensure® consumed (ST form page 3) 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 60 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 60 minute post satiety

EGG recording.

- A continuous 60 minute EGG recording is then obtained.

- At the end of the 0-10 minute period, you will have the subject complete a symptoms score sheet (ST form page 4). **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 11-20 minute postprandial period, you will have the subject complete a symptoms score sheet (ST form page 5). At the end of the 21-30 minute postprandial period, you will have the subject complete a symptoms score sheet (ST form page 6). At the end of the 60 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:

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 the 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 0-10), by setting the ***Start minute*** and ***End minute***.

6.5. Electrogastrogram water load and caloric satiety testing

NOTICE: The first post stimulation period includes all the minutes of the study (0.0 Start Minute and 60.0 End minute). You will change this and select the length of the first 0 to 10 minute period by making the Start Period 0.0 and the End Period 10.0 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 11-20). **Do not select more than 10 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 10 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 stimulation periods 21-30, 31-40, 41-50 and 50-60 and for selecting good minutes. Use the EGG report to complete pages 8-9 of the ST form.

Electrogastrogram and Satiety Test (ST form)

The Electrogastrogram and Caloric Satiety Test (ST) form is used to document symptoms and results of the satiety test and electrogastrogram in GLUMIT-DG study participants.

- Complete the ST form during screening and at follow-up visit f12 and f24.
- Have the patient respond to symptom evaluations on pages 2, 4, 5, 6 and 7 by marking a vertical line in each of the visual analog scales on pages 2, 4, 5, 6, and 7. The scales are 100 mm in length and 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 9, 10, 14, 15, and 16.
- Using the EGG report, complete section **E. EGG data**
- The Study Physician and Clinical Coordinator should complete section **F. Administrative information**

For best practices when performing the EGG and exporting the EGG files, refer to the water load satiety testing at the beginning of this section.

6.6. Baseline Medical History (BH form)

Who

- Complete for all GLUMIT-DG patients
- Study Physician and Clinical Coordinator sign the form

What

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

When

- Screening visit

How

- Mix of interview data and data obtained by chart review
- Other 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

6.7. Follow-up Medical History (FH form)

Who

- Complete for all GLUMIT-DG patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries/reviews
  - Change in patient's symptoms
  - Medical history diagnoses and procedures since the last visit
  - Medication use since the last visit

When

- Visits f04, f08, f12, f16, f20, and f24

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

6.8. Physical Examination (PE form)

Who

- All GLUMIT-DG patients

What

- Vital signs
  - Temperature
  - Blood pressure
  - Resting radial pulse
  - Respiratory rate
- System review
  - Chest and lungs
  - Oropharynx
  - Trachea
  - Thyroid
  - Heart
  - Abdomen
  - Abdomen abnormality
  - Liver and spleen
  - Nervous system
  - Pupil reflexes
  - Eye fundus
  - Extraocular movement
  - Dentition
  - Lymph nodes
- Anthropometry
  - Height
  - Weight
  - Waist circumference
  - Hip circumference
- Electrocardiogram and autonomic function assessment
- Neuropathy foot exam

When

- Screening, f12, and f24

6.8. Physical examination (PE form)

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 $36); it is manufactured by Country Technology Inc: 608-735-4718
- See the sections that follow which detail the protocol 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 or blouse or surgical gown), shorts, socks and 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
- Two measurements are recorded
- 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 or blouse or surgical gown), shorts, socks and 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)
- Remove the tape, retract the tape, and repeat the procedure
- 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

6.10. Waist and hip circumference measurement

Hips 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)
- 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)
- Remove the tape and repeat the procedure

6.11. Neuropathy foot exam

As part of the physical examination, a specialized foot examination will be used to identify the presence and/or development of diabetic peripheral neuropathy. This examination has been adopted from the Michigan Neuropathy Screening Instrument. The examination has 5 parts: appearance of foot, ulceration, ankle reflexes, and vibration perception at great toe and 10-gram filament. Each foot is examined and scored separately. Note: if a participant has had an amputation, indicate this on the form and skip the examination.

The Clinical Examination

APPEARANCE OF FOOT (Foot Inspection): The feet are inspected for evidence of excessively dry skin, callus formation, fissures, frank ulceration, or deformities. Deformities would include flat feet, hammertoes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal head, medial convexity (Charcot foot), and amputation. Indicate on the form whether the foot appears abnormal or normal.

ULCERATION: On the Physical Exam (PE) form, indicate whether ulcers were absent or present on the clinical examination.

ANKLE REFLEXES (Muscle Stretch Reflexes): The ankle reflexes will be examined using an appropriate reflex hammer (e.g., Tromner or Babinski (European), or Queen's Square or almost anything except a very light Taylor's (tomahawk) because the ankle jerk is difficult to elicit with them). The ankle reflexes should be elicited in the sitting position, with the foot dependent and patient relaxed. For the reflex, the foot should be passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles Tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the participant is asked to perform the Jendrassic Maneuver (i.e., locking the fingers together and pulling). Reflexes elicited with the Jendrassic Maneuver alone are designated as present with reinforcement. If the reflex is absent, even with Jendrassic Maneuver, the reflex is designated as absent.

VIBRATION PERCEPTION AT GREAT TOE (Vibration Sensation): Vibration sensation should be performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork place over the dorsum of the great toe on the bony prominent of the DIP joint. The participant (with eyes closed) is asked to indicate when he/she can no longer sense the vibration from the vibrating tuning fork.

In general, the examiner should be able to feel vibration from the hand-held tuning fork for 5 seconds longer on his/her distal forefinger than a normal participant can at the great toe (i.e., examiner's DIP joint of the first finger versus the participant's toe). If the examiner feels vibration for 10 or more seconds on her/her finger, then vibration is considered decreased. The test should be given when the tuning fork is not vibrating to be certain the participant is responding to vibration and not to pressure or some other clue.

Vibration is scored: present if the examiner senses the vibration on his/her finger for < 10 seconds; reduced if sensed for 10 or more seconds, and absent if no vibration is detected.

10 GRAM FILAMENT (Semmes-Weinstein Monofilament Examination): For this examination, the foot should not be supported (no standing). The filament must be 5.07 and should be initially pre-stressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly (for < 1 second) with an even pressure. When the filament bends the force of 10 grams has been applied. The patient, whose eyes are closed, is asked to respond 'yes' if he or shoe feels the filament. This is done ten times on each big toe. If there are 8 or more correct responses (out of 10 applications), this is considered present; 1-7 correct responses is considered reduced sensation; no correct responses is considered absent.

Scoring the Neuropathy Screening Instrument.

For each foot separately, scores would be as follow:

Appearance of Foot: Normal=0 Abnormal=1

Ulceration: Absent=0 Present=1

Ankle Reflexes: Present=0 Present with Reinforcement=0.5 Absent=1

Vibration Perception: Present=0 Reduced=0.5 Absent=1

10-gram Filament: 8-10 Correct=0 1-7 Correct=0.5 None Correct=1

Calculate scores for each foot separately. There are a possible 5 points per foot.

Interpretation of Scores (Cross-sectionally and Longitudinally)

6.12 Neuropathy foot exam

The following scores (out of a possible 10) from the clinical examination would denote presence/absence of neuropathy:

0 to 2 No Neuropathy

2.5 to 10 Neuropathic

Every increase over time of at least 1 point denotes progression of neuropathy.

Recommended Instruments
Reflex Hammers:
Tromner Hammers $62.20 (estimate)
SSR Inc.
PO Box 537
Oyster Bay, NY 11711

Other Hammers:
Babinski (Euopean), Queen's Square
Tuning forks (128 Hz.) $11.40 (estimate)
Monofilament:
The monofilament must be 5.07 (eliciting 10 grams of pressure)
Center for Specialized Diabetic Foot Care
405 Hayden Street
PO Box 373

Belzoni, MS 39038
(800) 543-9055
$10.00 each (estimate)

Connecticut Bioinstruments Inc.
39-B Mill Plain Road
Danbury, CT 06811
(800) 336-1935
$10.00 each (estimate)

Smith & Nephew, Inc.
PO Box 1005
Germantown, WI 53022
(800) 558-8633
$19.99 each (estimate)

6.12. Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (GD form)

What

- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (GD form)

Purpose

- To obtain the patient's views of the severity of his/her gastroparesis symptoms

When

- Screening visit
- Follow-up visits f12 and f24

Procedure

- Clinical Coordinator should complete Part A of each form and apply labels to subsequent pages as needed before giving the form to the patient to complete
- Self administered
- Clinical Coordinator should check returned forms for completeness before the patient leaves the clinical center

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6.13. Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) (UG form)

What

- Patient health questionnaire is a 15-item patient reported measure (UG form)

Purpose

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

When

- Screening visit
- Follow-up visits f12 and f24

Procedure

- Clinical Coordinator should complete Part A and apply labels to page 2 before giving the form to the patient to complete
- Self administered for patients
- Clinical Coordinator should check returned form for completeness before the patient leaves the clinical center

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6.14. Laboratory Results (LR form)

Who

- All GLUMIT-DG patients

What

- Form LR covers assessments collected during screening
  - Complete blood count
  - Hemoglobin A1c
  - Metabolic panel
  - Thyroid stimulating hormone (TSH)

When

- All laboratory test results are required at the screening visit
- Complete blood count, Hemoglobin A1c and metabolic panel are required at f12 and f24
- When laboratory results are available during follow-up

Instructions for form LR

- The measures on form LR are intended to be obtained by chart review, both at screening and during follow-up; the time window for each type of assessment is specified on the form
- During screening, if the chart review tests are out of the 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

6.15. Plasma Collection for Biosample Repository (BP form)

Purpose

- Collection of whole blood from GLUMIT-DG patients for plasma banking
- Separation of plasma at clinical center: up to ten - fourteen 0.5 mL aliquots of plasma are to be obtained 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

Forms / Materials

- BP - Blood Processing for Plasma
- MACO Labels for heparin (green top) tube and BP form
- Blue labels - choose one of the cryovial label sets provided by the DCC
- Barcode scanner
- SS - Specimen Shipment log
- NIDDK Biosample Repository shipper

When

- Screening visit
- Follow-up visits f12 and f24
- Batch shipments: Monthly

By whom

- Phlebotomist
- Clinical Coordinator

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 @ $41.49

- 10-14 or more 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
  - Model/product number: Model #CV200-2
  - Vendor contact information:

1) Cryogenic Storage Systems and Supplies
   243 Lawyers Road, NW
   Vienna, VA 22180
   703-319-8247
   877-738-8247
   703-938-9351 (fax)

2) Corning External Thread Cryogenic Vials
   Catalog # 430659
   50 per pack, 500pk/case: $204.17
   Telephone: 1-800-492-1110

3) Fisher
   1-800-766-7000
   Catalog #10-500-26

Labels

- Preprinted MACO labels for whole blood collection tubes (10 mL heparin tube for Form BP) – *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
- Barcode scanner (provided by the DCC)

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

- Patient instructed to fast 8 hours prior to blood draw
- Collect whole blood into one pre-labeled 10 mL heparin (green top; Becton-Dickinson #367874) tube for plasma
- Blood for plasma to be centrifuged, aliquoted, and frozen within one hour
- If sample appears to have hemolyzed; do not aliquot. Re-draw blood.
- Collect blood into heparin (green top; Becton-Dickinson) tube. Ensure that heparin tubes have not expired. (*check that date shown above "Exp" in lower right corner of label is later than current month*)
- 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

Blood Processing for Plasma (BP) form

- Complete the Blood Processing for Plasma (BP) form
- Affix MACO labels for the plasma to the BP form
- Affix aliquot 00 cryovial label to the BP form

Applying labels to cryovials

- Attach the blue plasma label to the vial when the vials are at room temperature
- 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)

Barcode Scanners

- Plug the scanner to the USB port on your computer
- Open your template Excel file (filename GpCRC_Site6xx_shipdate.xls) and replace the x with the last two digits for your clinical center's site ID and replace ship date with the date of shipment
- Place the cursor in the first cell under Barcode number
- Hold the scanner approximately 4-8 inches from the cryovial barcode you wish to scan. (The scanner will emit a red light as it searches for the barcode and will emit a beep and a green dot when the barcode has been successfully read.)
- The scanner automatically enters the barcode into the proper field and immediately goes to the next cell
- Scan all the cryovials you are shipping to the NIDDK Biosample Repository into the Excel spreadsheet
- Place the cryovials back in the freezer or pack in shipper with dry ice to prevent thawing
- For each cryovial barcode scanned, enter the following in the corresponding column of your Excel file: Site ID-Patient ID numbers, the 3 letter patient code, the date the sample was collected (mm/dd/yy format) and the specimen type (P = plasma). The volume should be a standard 0.5 and the unit of measure will always be milliliters
- Save the Excel spreadsheet with the correct ship date at the end of the file name (Click on File then click on Save As) and print 2 copies

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 cell. 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 (Form SS) stapled to the Excel spreadsheet of scanned cryovials 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:" block
- Affix the repository address label to the side of the box in the "Consignee:" block
- 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
- Ship specimens in the STP 320 Saf T Pak shipper (provided by the NIDDK Biosample Repository); each shipper can accommodate aliquots for 8 patients, depending on the number of aliquots obtained for each patient (maximum capacity of each shipper is 230 aliquots)
- Complete the Specimen Shipment Log (Form SS), staple to the corresponding Excel spreadsheet of scanned cryovials and enclose a copy with each shipment of specimens.
- Keep a notebook of all original completed Specimen Shipment Logs (Form SS) stapled with the corresponding Excel spreadsheet of scanned cryovials so that you have a record of all shipments to the Biosample Repository
- Email the Excel spreadsheet to the Biosample Repository at bio- niddkrespository@thermofisher.com with the Fed Ex tracking number in the subject line of the email. This email will ensure that you receive a replacement shipper.

6.15. Plasma Collection for Biosample Repository (BP form)

- Notify the Biosample Repository of the shipment via fax (301-515-4049) or email bio- niddkrespository@thermofisher.com)on the day the package is picked up by Federal Express. Include the tracking number in the notification

6.16. Training Documentation (TD Form)

Purpose

- To document the dates patients began wearing the iPRO CGM, MiniLink REAL-Time Transmitter CGM and Paradigm 722 Insulin pump during the screening and run-in periods.

Forms

- Complete the Training Documentation (TD) form

When

- Enrollment visit

By Whom

- Clinical Coordinator

Procedure

- Clinical coordinator should complete the TD form and key into the the GLUMIT-DG data system at the enrollment visit.

6.17. Adverse Event Reporting (IE form)

Definitions

- **Adverse event** is any untoward medical occurrence that may present itself during a research study which may or may not have a causal relationship with the treatment or study participation. 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 occurrence of anticipated problems.
- **Associated with study participation** means that there is a reasonable possibility that the event may have been caused by participation in the study.
- **Serious adverse event** A serious adverse event (SAE) is an adverse event occurring at any time during the study that results in death, life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Severe hypoglycemic and severe hyperglycemic events will be considered an SAE. Other events may also be considered an SAE if, based on medical judgement, the event jeopardized the patient to the point of requiring medical or surgical intervention to prevent the occurrence of any of the conditions for an SAE.

Reportable GLUMIT-DG events

- Any serious adverse event thought to be associated with a GLUMIT-DG procedure, such as a severe hypoglycemic or hyperglycemic event, is reportable to all clinical centers, the Data Coordinating Center, the GLUMIT-DG Serious Adverse Events Adjudication Committee (SAEAC) and the DSMB.
- For the GLUMIT-DG study, sentinel events are described as (1) deaths, (2) severe hypoglycemic occurrences, or (3) severe hyperglycemic occurrences. These events will be monitored closely as they may occur during the course of diabetes. While hypoglycemic and hyperglycemic episodes are expected to occur during GLUMIT-DG participation, the frequency of occurrences and the severity of these events will be monitored.
- Severe hypoglycemic events occur when a patient's capillary glucose falls below 50 mg/dL and the patient is incapable of self treatment, hence needing the assistance of a third party for resolution of the hypoglycemia. This type of event will be recorded on study form(s). If a patient has more than two severe hypoglycemic events (i.e., ER visit, relative, etc.) during the study, he/she will be re-evaluated with the diabetologist with an option to be placed back on the previous diabetes medications. Study staff will follow up with patients to ensure that severe hypoglycemic events were properly managed and make any necessary modifications to their treatment.

- Severe hyperglycemic events occur when a patient's capillary glucose is above 500 mg/dL as revealed on the CGMS and corroborated by a finger stick reading. The patient may be symptomatic (polyuria, polydipsia) or with concurrent illness, but capable of good communication; or the patient's symptoms may be intense, or the patient is incapable of good communication and immediate transport to emergency department may be necessary. These severe hyperglycemic events will be recorded on study case report forms.
- 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

Clinical center responsibilities regarding reportable GLUMIT-DG 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 clinical research study. These reporting requirements may be more stringent than those adopted by the GLUMIT-DG study. Regardless of what the GLUMIT-DG study requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than GLUMIT-DG, you may report events locally that you do not report to GLUMIT-DG.
- 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.
- 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 GLUMIT-DG study as follows: If an event has occurred that you judge is reportable to GLUMIT-DG, complete the Interim Event (IE) form. Key this form to the GLUMIT-DG 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 GLUMIT-DG study or study 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 (IE)

- Serious adverse events (SAE) must be reported upon discovery at the clinical center per local IRB guidelines. This may involve describing the severity of the adverse event and providing further information. The serious adverse event must be reported in the GLUMIT-DG database, using the Interim Event (IE) form, together with a memo summarizing the circumstances of the event and the current status of the patient.

- When clinical centers determine that a serious adverse event (see the GLUMIT-DG protocol section 6.4 Adverse event reporting) has occurred, this event must be reported and adjudicated according to the procedures outlined in this section. Examples of SAEs that may occur during the time that a patient is enrolled in the GLUMIT-DG study, that are of particular concern are deaths or severe hypoglycemic or severe hyperglycemic events that may or may not require immediate transport to an emergency department. Any other serious adverse events that occur will be reported and adjudicated.
- The SAEAC reviews all pertinent information surrounding the SAE gathered by the DCC from the clinical center and may request additional information, if needed, to determine the etiology of the event. A decision will be made whether a relationship exists between the SAE and participation in the GLUMIT-DG study, as part of the adjudication of the SAE. The study physicians will be removed from the adjudication process, if the SAE under review has occurred at one of their respective clinical centers. In the event that an SAEAC member cannot participate within 5 business days, the NIDDK Project Scientist (Dr. Hamilton) will designate a substitute.
- The SAEAC will make one of the following recommendations as a result of its adjudication of the SAE: (1) continue the GLUMIT-DG study without interruption, (2) suspend further enrollment (including any patients that may be in the screening process), (3) stop the study, or (4) any other recommendation that the SAEAC deems appropriate. The SAEAC recommendation, with supporting materials, will be communicated to the DSMB, the Steering Committee, and the NIDDK. Recommendations (2) or (3) will require a Steering Committee conference call to consider the process for suspending or stopping the study, with regard to patient safety. The Steering Committee will develop an action plan and rationale for either resuming or stopping the study or responding to any other recommendation that the SAEAC makes. The action plan and rationale must be reviewed by the DSMB and approved by the NIDDK prior to implementation. All clinical centers must also comply with all reporting requirements for their respective IRBs.

Local reporting requirements

- Your institution's IRB has reporting requirements of its own regarding events occurring in the course of conduct of a study. These reporting requirements may be more stringent than those adopted by the GLUMIT-DG study. Regardless of what the GLUMIT-DG study requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than the GLUMIT-DG study's, you may report events locally that you do not report to the GLUMIT-DG study.

- 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.

Reporting deaths occurring in GLUMIT-DG study participants

- As soon as a clinical center is aware of a GLUMIT-DG participant's death, the Study Physician and Clinical Coordinator should complete the Death Report (DR) form and send the DCC Center (Attn: Mika Green) the 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 6.22 for additional instructions for mortality closeout.
- The Death Report (DR) form should be keyed to the GLUMIT-DG data system.

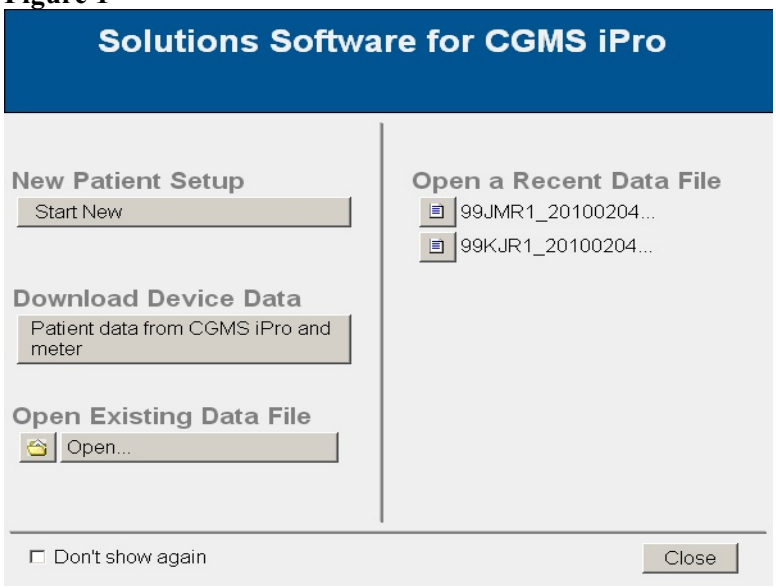
6.18. Procedures for downloading medtronic CGMS iPro data

1. **Downloading Medtronic CGMS iPro**

Below are the procedures for downloading and exporting the files using the CGMS Solutions Software for CGMS iPro.

Open the software to the main screen shown in Figure 1 and select the button “Patient data from CGMS iPro and meter”. If the main screen does not appear (ie you have previously selected to not display the screen), you can select the button on the top left menu to Download Device Data.

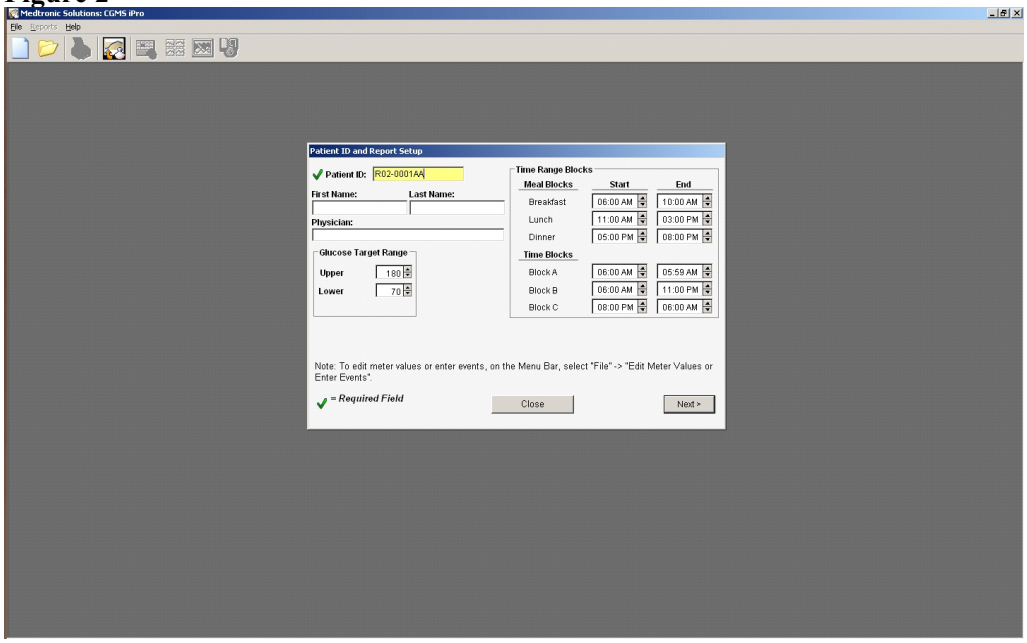
Figure 1



2. The screen in Figure 2 will appear.
   - Enter the PtID in the correct format: the letter "G" + 2-digit clinical center number* + "-" + 4 digit GpCRC subject number + 3 character GpCRC alpha code (e.g; G05-5999izv).
   - Leave the First Name, Last Name and Physician fields blank.
   - Click "Next"

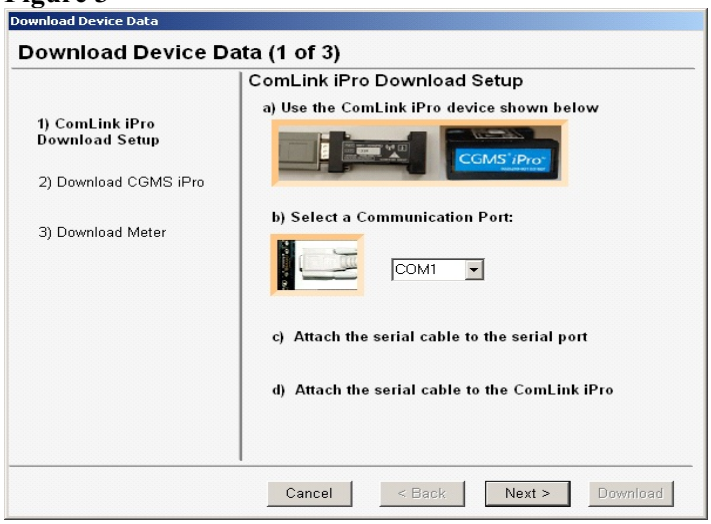
*The 2-digit clinical center numbers are as follows:
- Temple University (TU) - 01
- University of Michigan (UMI) - 02
- University of Mississippi (UMS) - 03
- Stanford University (SU) - 04
- Wake Forest University (WFU) - 05
- Texas Tech University Health Sciences (TTU) - 06
- California Pacific Medical Center (CPMC) - 07

Figure 2



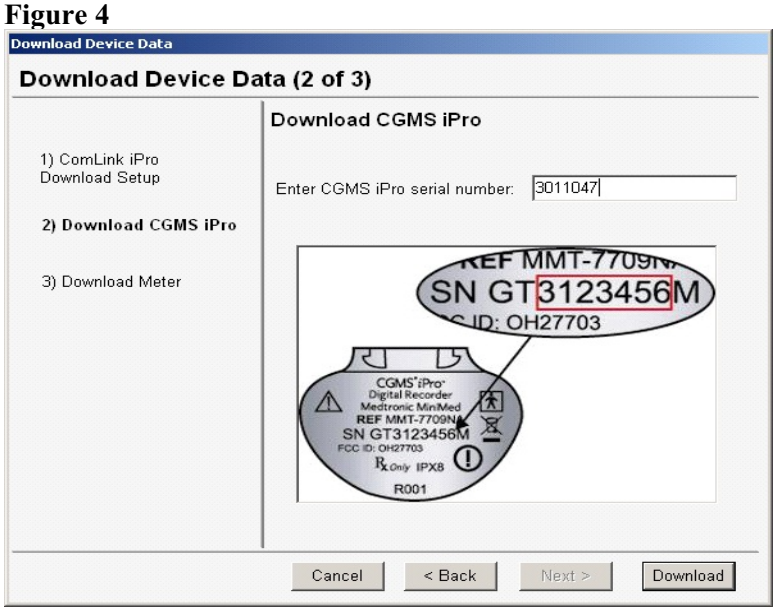
3. The screen in Figure 3 will appear.
   - Follow the instructions for connecting the ComLink iPro to the PC (NOTE: the regular ComLink cable will not work for downloading the iPro, you must have the ComLink specific for the iPro device).
   - Click "Next"

Figure 3



4. The screen in Figure 4 will appear.
   - Enter the numeric portion of the iPro serial number (on the back of the device).
   - Click "Download"

Figure 4



5. The screen in Figure 5 will appear.
   - Follow the instructions indicated and click "OK".

Figure 5

6. The screen in Figure 6 will appear while the data are being downloaded.
   - NOTE: the ComLink may need to be held very close to the iPro device during downloading.
   - When the data have been successfully downloaded, the screen in Figure 7 will appear.

Figure 6

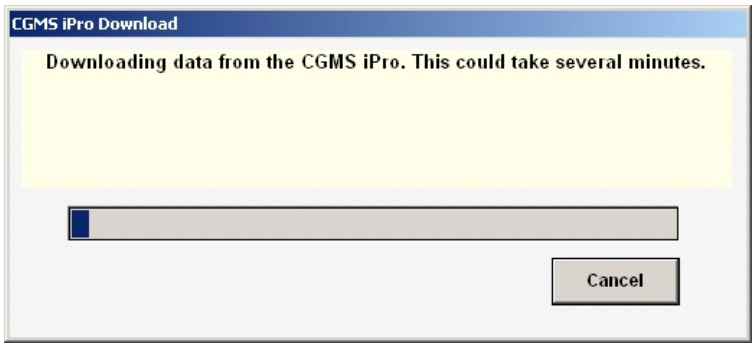
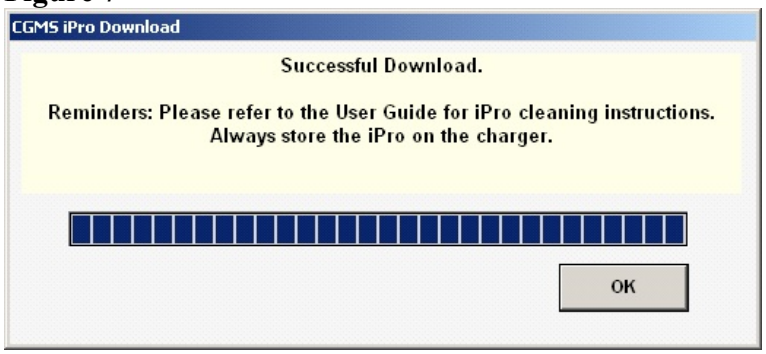


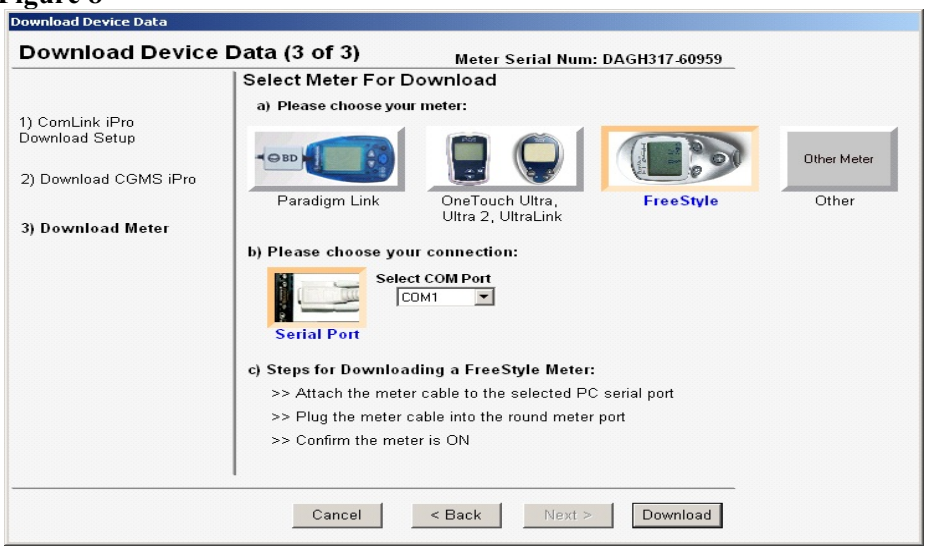
Figure 7



2. Downloading HGM Data for Retrospective Calibration

1. The screen in Figure 8 will appear for downloading the meter used by the subject during the iPro wear.
   - The only meter that can be downloaded using a USB cable for this software is the Paradigm Link meter. All other meters must use a serial cable, even if a USB cable exists for downloading that type of meter.
   - Select the type of meter and the port that the meter will be connected to for downloading.
   - Read the instructions at the bottom of the screen for downloading that type of meter and click "Download"
   - NOTE: Refer to Steps

Figure 8



2. When the meter data have been downloaded, the screen in Figure 9 will appear.
   - Click "OK" and the screen in Figure 10 will appear.
   - Click "Yes" to save the file.

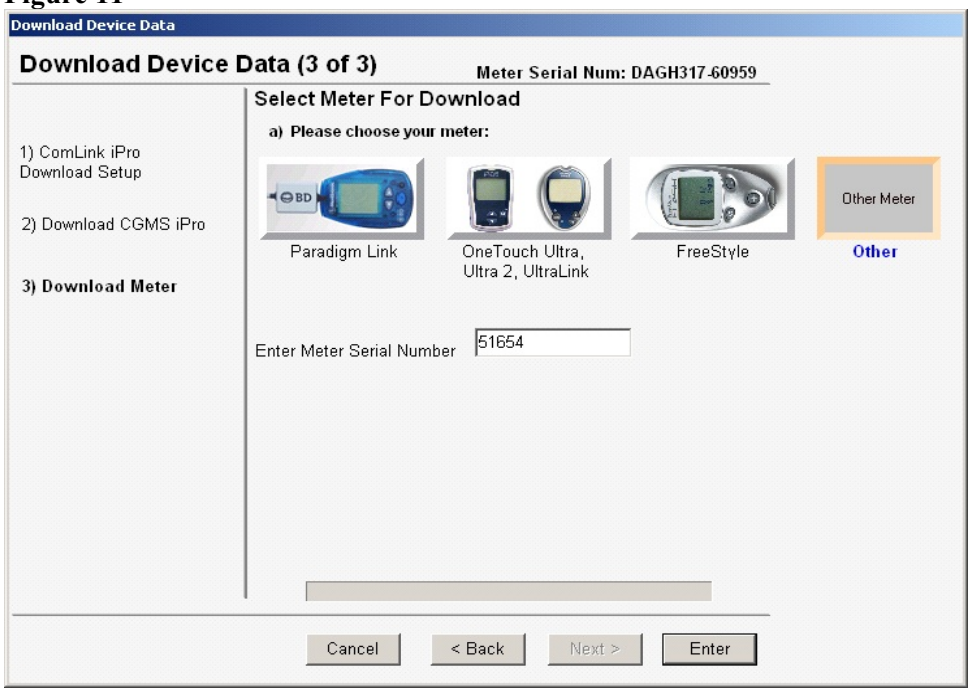
Figure 9

Figure 10

2.1 Entering HGM Data Manually

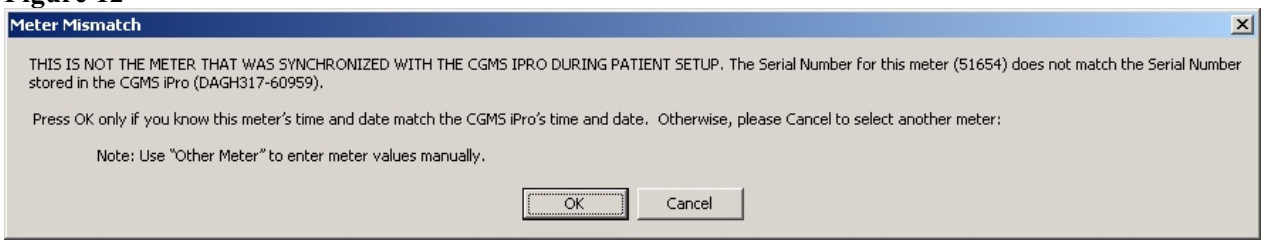
1. If the subject used a meter that is not one of the options for downloading, the meter values will need to be manually entered into the software. In this case, select "Other" and enter the serial number of the meter to be downloaded as shown in Figure 11 and click "Enter".

Figure 11



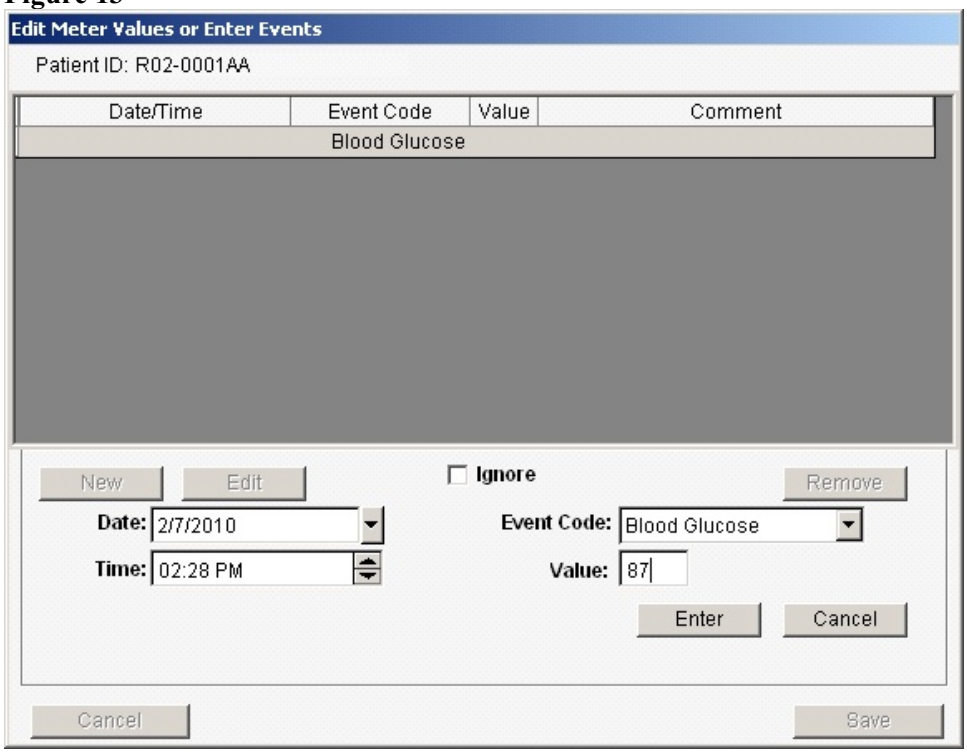
2. If the serial number entered is different than what was programmed into the software upon initiating the sensor for the subject, the message in Figure 12 will appear.

Figure 12



3. Click "OK" and the screen in Figure 13 will appear for the HGM values to be entered manually.

Figure 13



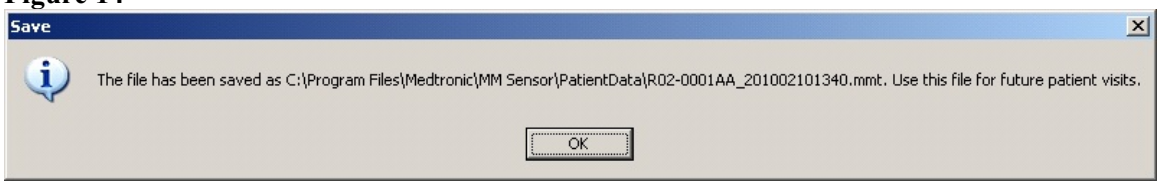
4. For each HGM reading, click "New" then enter the Date and Time and select "Blood Glucose" from the Event Code dropdown and then enter the value. Click "Enter" and the data will appear in the table and additional HGM values can be entered be following the steps again.

a. When done entering any manual HGM values, click "Save" and the data will be merged with the iPro data.

3. Finalizing Data Download

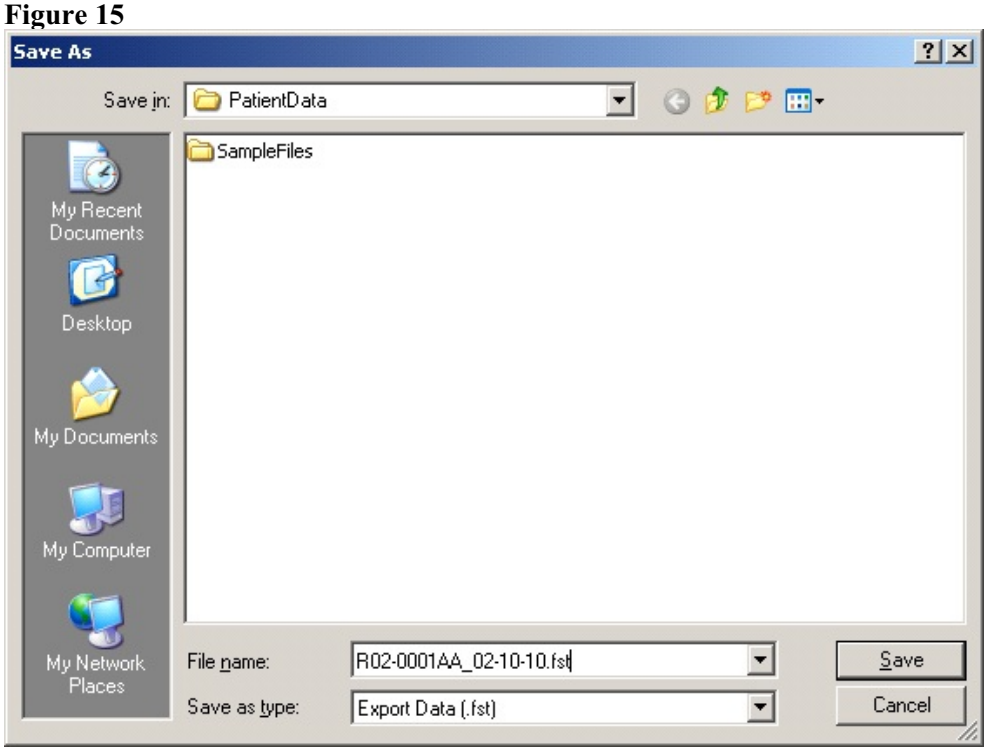
1. When the iPro data and HGM data are merged, the message in Figure 14 will appear.

Figure 14



4. Exporting Data File
1. In the upper left corner select File - Export File - Modified Sensor Data
2. The screen in Figure 15 will appear.
3. Change the Filename to be the PtID + "_" + Date of download with the file extension .fst (e.g; G05-5999izv_04-02-10).
4. Send the file as an attachment to direcnet-data@jaeb.org and indicate the PtID, Visit type (e.g; "Screening" or "scr") and CGMS iPro data in the subject line of the email

Figure 15



6.19. Procedures for Carelink downloading of data

1. **Reference Sheet for Downloading:**
   - **Guardian Clinical**
   - **Paradigm REAL-Time insulin pump system**

CareLink is a therapy management software application designed to provide a means to gather and view subject data for analysis and therapy management.
It is accessible via the Internet at URL: http://trials.minimed.com

The application will be used to upload device data, which are accessed for online reports. This reference sheet was developed as a means to quickly guide you through the requirements and processes of CareLink. **For assistance, please refer to your User Guide or contact our 24 Hour Product Helpline at 1-800-MINIMED Extension 7085.**

Systems requirements
The following is a list of systems requirements necessary to use CareLink:

Platform	Windows ® 98 or greater	
Browser	Internet Explorer® 5.5 SP2 or greater	
Applets	Supported	
IFrames	Supported	
Java Script	Enabled	
SSL	128-bit key	
Resolution	800 x 600 or greater	
Color Depth	8-bit colors or greater	
Other	Adobe Acrobat® Reader 5.0 or greater	

If you meet these requirements, you should be able to access CareLink through the following URL.

2. **Connecting devices to your computer.**
   Connect the device to the computer using either a serial cable or USB adapter. During the system upload process, detailed connection instructions are displayed, such as whether the device should be on or off.

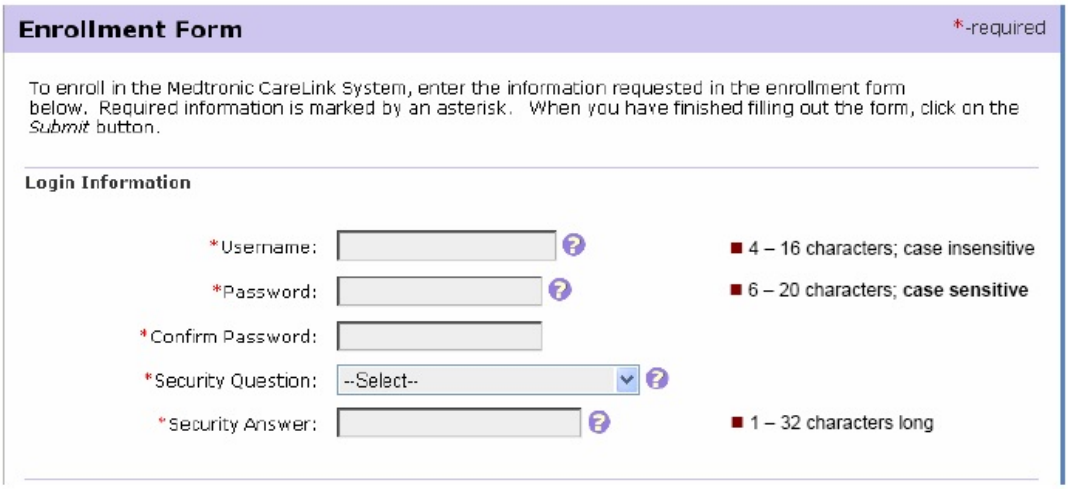
3. **Enrolling a subject (COMPLETED BY GLUMIT- DG CLINIC Connecting devices to your computer.**
   Connect the device to the computer using either a serial cable or USB adapter. During the system upload process, detailed connection instructions are displayed, such as whether the device should be on or off.

3. Enrolling a subject (COMPLETED BY GLUMIT- DG CLINIC COORDINATOR)

- Go to URL: http://trials.minimed.com
- Enrollment is restricted and must be handled by site coordinator.
- The Enrollment code should only be shared with the site coordinators.
- Each subject must be individually enrolled.
- Enrollment is accomplished by selecting the "Sign up now" button.
- Use the Enrollment Form to enroll a subject.
- Values for fields requiring special instructions are shown below.
- All of the information must be filled in, in order to proceed with enrollment.

4. COORDINATOR)

- Go to URL: http://trials.minimed.com
- Enrollment is restricted and must be handled by site coordinator.
- The Enrollment code should only be shared with the site coordinators.
- Each subject must be individually enrolled.
- Enrollment is accomplished by selecting the "Sign up now" button.
- Use the Enrollment Form to enroll a subject.
- Values for fields requiring special instructions are shown below.
- All of the information must be filled in, in order to proceed with enrollment.



6.19. Procedures for Carelink downloading of data

Login Information

- **Username:** Enter the letters GD + 2-digit clinical center number* + the last 2 numeric digits of the GpCRC 4-digit code + GpCRC 3 character alpha code (e.g., for PtID G05-5999izv you would enter GD0599izv).

*The 2-digit clinical center numbers are as follows:

- Temple University (TU) - 01
- University of Michigan (UMI) - 02
- University of Mississippi (UMS) - 03
- Stanford University (SU) - 04
- Wake Forest University (WFU) - 05
- Texas Tech University Health Sciences (TTU) - 06
- California Pacific Medical Center (CPMC) - 07

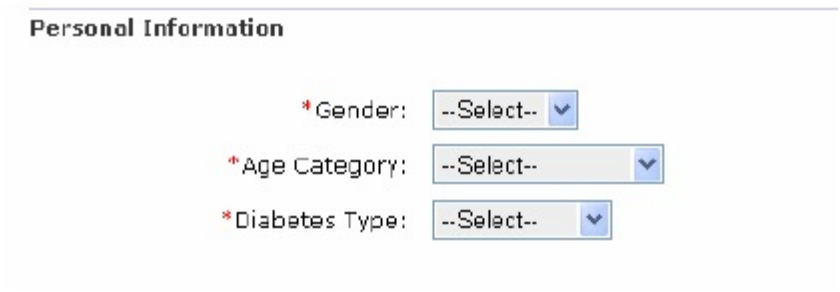
- **Password, Security Question, and Security Answer:** The clinic coordinator selects the password, security question and answer.

Physician Contact Information

- First Name is entered as the letters GD + 2-digit clinical center number + last 2 numeric digits of the GpCRC 4-digit code + GpCRC 3 character alpha code (e.g., GD0599izv)
- Last Name is entered as the clinical center code (e.g., WFU).
- Address fields will use the clinic address.
- The email address is the email address of the clinic coordinator since the "Forgot your password" feature will send an email to the address on file.

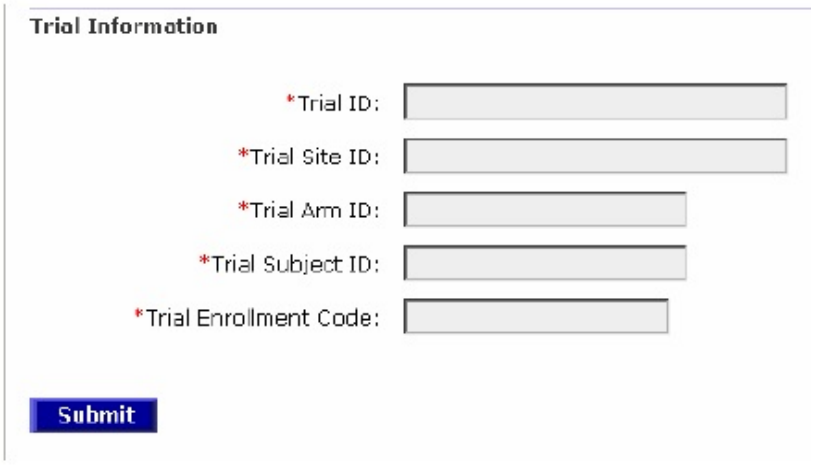
Completion of Contact Information

- **First Name**: GD + 2-digit clinical center number + last 2 numeric digits of the GpcRC 4-digit code + GpCRC 3 character alpha code (e.g., GD0599izv)
- **Middle Name or Initial**: Leave blank
- **Last Name:** Enter the Clinical Center code (e.g.,WFU)
- **Address 1:** Enter the address of the Clinical Center
- **Address 2:** This is an optional field
- **City:** Enter the city of the Clinical Center
- **State/Province:** Enter the state of the Clinical Center
- **Postal code:** Enter the postal code of the Clinical Center
- **Country**: Enter the country of the Clinical Center
- **Phone:** Enter the phone number of the Clinical Center
- **E-mail:** Enter the email address of the clinic coordinator



Personal Information:

- A selection must be made for each in order for enrollment to proceed



Trial Information

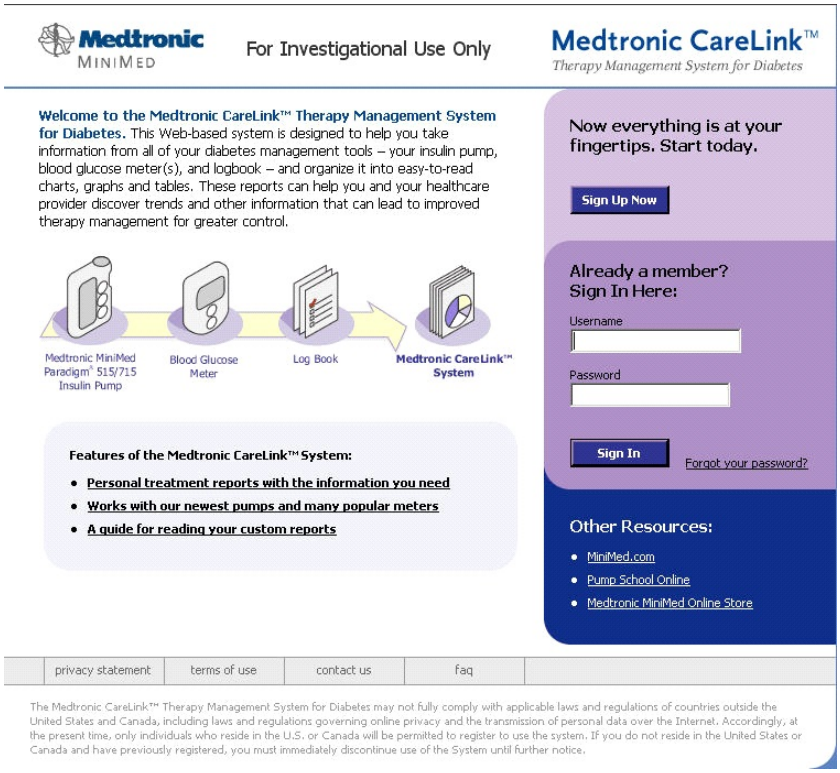
- Trial ID: Enter "DirecNetM"
- Trial Site ID: Enter Clinical Center 2-digit clinical center number (e.g; 05)
- Trial Arm ID: Enter GLUMIT-DG
- Trial Subject ID: Enter the letters GD + 2-digit clinical center number + last 2 numeric digits of the GpCRC 4-digit numeric code + GpCRC 3 character alpha code (e.g., GD0599izv)
- Trial Enrollment Code: Enter "Hesttia".

(Enrollment code is case sensitive, type as appear above)

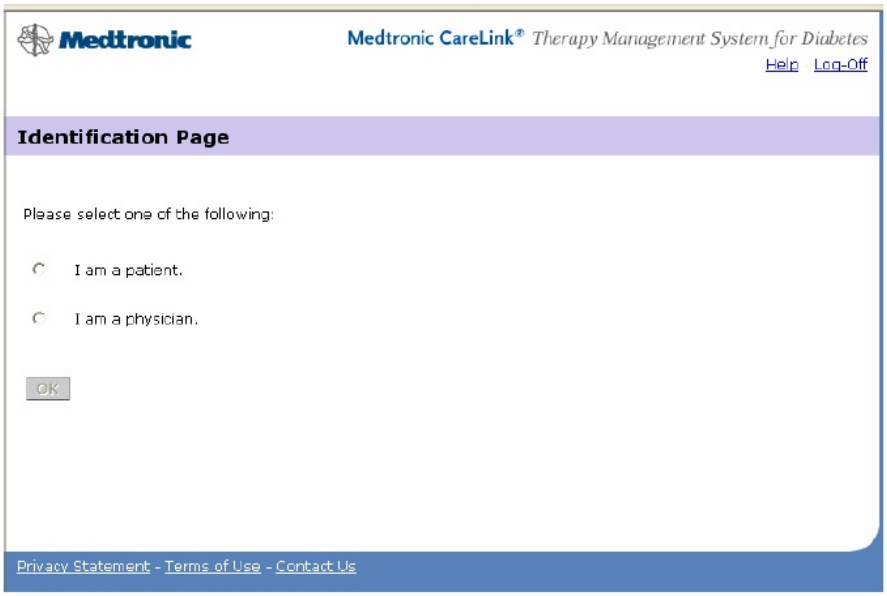
You will receive confirmation upon successful enrollment.

CHECK ALL INFORMATION BEFORE CLICKING THE 'SUBMIT' BUTTON. THE USERNAME CANNOT BE CHANGED ONCE THE SUBJECT IS ENROLLED.

5. Logging In (For downloading the device)

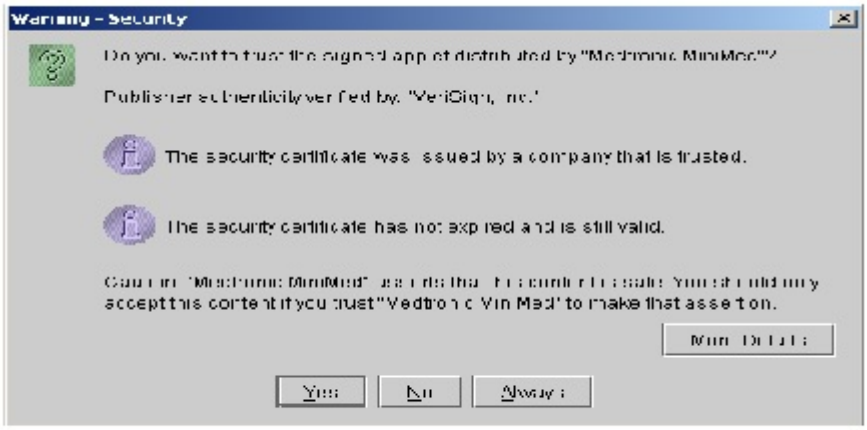


- At the Welcome Page, be sure the page reads "For Investigational Use Only."
- **Log in using Username (the letters GD + 2-clinical center number + last 2 numeric digits of the GpCRC 4-digit numeric code + GpCRC 3 character alpha code: GD0599izv) and password.**
- **Click "Sign In."** You will be routed to the Identification Page.



- Select, "I am a Physician" and OK. You will be routed to the Home Page upon successful login.
- Be sure to read the Privacy Statement and Terms of Use Agreement. It must be accepted in order to use the application.

Before the first Upload screen is displayed, the following security warning displays.



Choose Always: you can proceed with the upload. Plus, you will no longer see this warning when you select the Upload screen.

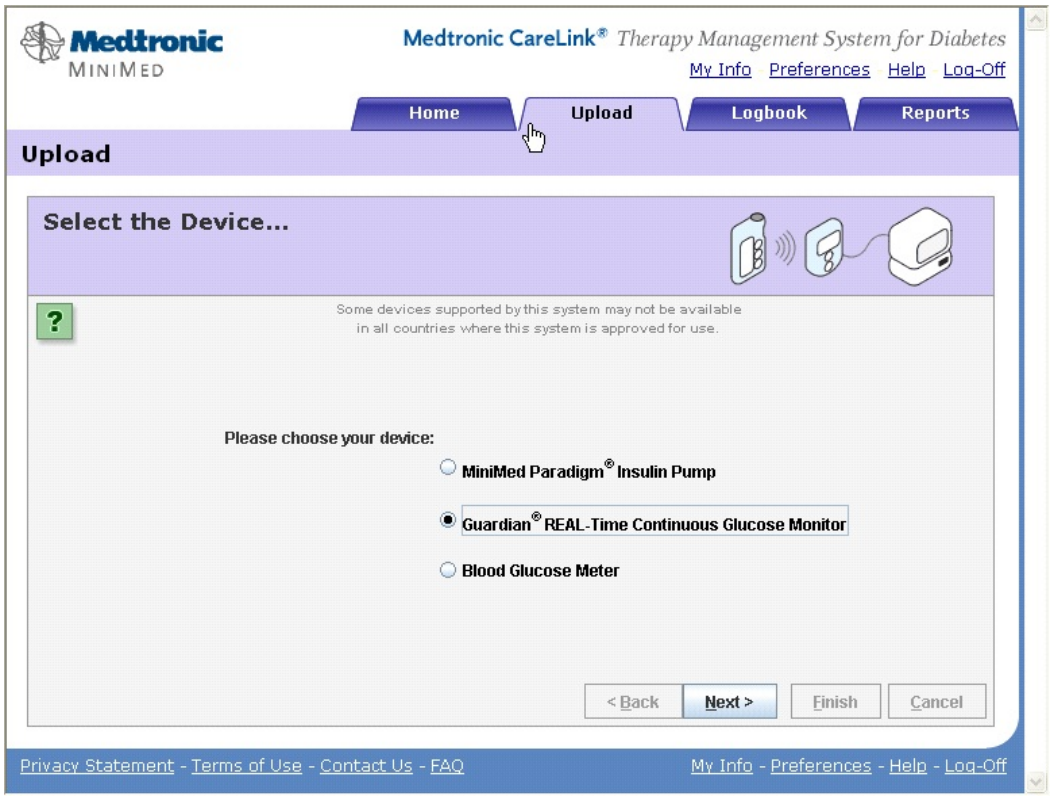
6. Uploading the device

- If you are able to view the Upload Your Device screen, your computer is equipped with the appropriate requirements to upload your device.
- NOTE: The system will detect your computer's settings and prompt you to download files that are missing. Please follow the instructions on your screen to complete the download process. Please contact our Product Helpline at (800) MiniMed Extension 7085 if you experience any difficulty.

WARNING: a bolus or temp basal is being delivered, allow it to finish before uploading the

CAUTION: The pump will be in SUSPEND mode during an upload. Make sure the pump is taken out of SUSPEND mode when the upload is complete.

- Select appropriate device (Minimed Paradigm Insulin Pump for those in the intense group or Guardian Real-Time Continuous Glucose Monitor for the blinded device for those in the standard care group) for upload
- Follow instructions to upload the device.



7. Viewing data

- Select the Report tab.
- Follow instructions in **Report Screen** to generate and view reports.
- Subjects can be instructed to save the PDF reports and email them to the clinic coordinator prior to each scheduled phone call.
- To learn more information about viewing the individual reports and "batch reporting", please click on "Understanding My Reports."

Please be sure to refer to your User Guide or contact our 24 Hour Product Help Line at 800-MiniMed Extension 7085 for questions or details.

8. Clearing the Data on the Guardian Clinical

Once the download from the Guardian Clinical has been received by the Coordinating Center, the data will be reviewed by Coordinating Center staff to verify that the data are acceptable and will notify the clinic coordinator when the device can be cleared to use with another subject. The Guardian Clinical must be cleared before it is given to another subject.

To clear the Guardian Clinical:
From the Home Screen

6.19. Procedures for Carelink downloading of data

- Press ACT to get to the main menu
- Select utilities
- Select user settings
- Hold the shift key (far left arrow) and press ACT at the same time
- You will see "save settings" highlighted
- Scan or arrow down to "clear all user info"
- Press ACT
- You will get a message asking if you really want to clear the system
- Press ACT to accept
- It will ask a second time if you really want to clear the system
- Press ACT to accept

You can press escape to get out of the menu and back to the home screen. RESET will appear in the home screen if the device has truly been cleared.

6.20. Procedures for Re-screen in GLUMIT-DG (RC form)

Purpose:

- To rescreen a patient who was previously found to be ineligible for GLUMIT-DG due to a temporary ineligibility.

When

- Screening visit.

By whom

- Clinical Coordinator.

Procedures for rescreening a patient

- Complete the RC form for a patient who was previously found to be ineligible for GLUMIT-DG due to a temporary ineligibility and who now wants to rescreen for GLUMIT-DG.
- The patient must complete all GLUMIT-DG screening data collection anew.
- All previously keyed GLUMIT-DG screening forms should be deleted from the data system except the RG form.
- Update sections B, C, D, and G of the original RG form and update the keyed record (you cannot delete the RG form).
- The RC form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 112-day screening window is reckoned from).
- Plasma must be collected anew. New screening phase tube and questionnaire labels will be available for printing upon keying this form.

6.21. Procedures for Missed or Incomplete Visits (MV form)

Purpose

- Record data about missed or incomplete visits

Form

- Missed or Incomplete Visit (MV) form

When

- At close of a visit window for any missed follow-up visit or for any follow-up visit with specific 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

6.22. 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

6.23. Procedures for mortality closeout (DR form)

Purpose

- Record participant death

Forms

- Complete the Death Report (DR) form

By whom

- Study Physician and Clinical Coordinator

Procedures for reporting a death

- As soon as a clinical center is aware of a GLUMIT-DG study participant's death, the Study Physician and Clinical Coordinator should complete the Death Report (DR) form and send the DCC (Attn: Mika Green) the following:
  - A narrative description of the event including hospitalization information as applicable
  - A copy of your report to your (IRB), as applicable.
- The Death Report (DR) form should be keyed to the GLUMIT-DG data system.

6.24. Medical management of patients

Purpose

- To ensure all GLUMIT-DG patients receive the same management of common safety concerns and to provide guidance for the management of hypoglycemic and hyperglycemic events.

A standardized management plan for the most common safety concerns related to insulin pump therapy and continuous glucose monitoring system side effects as well as management of hypoglycemic and hyperglycemic occurences are outlined below:

Safety concerns related to insulin pump therapy and continuous glucose monitoring system:

Patients in this study will use the One Touch® finger stick meter as well as the RT-CGM MiniLink™ REAL-Time Transmitter. Because these devices will be inserted subcutaneously, there is a risk for the patient to develop an infection. The two plastic needles that will be used for the RT-CGM and the insulin pump also carry an infection risk. However, with proper technique and good care, the infection risk is small. If patients notice any discoloration of the skin or signs of inflammation (redness, swelling, pain), they will be required to contact the study investigator immediately. Patients may need treatment with antibiotics, if indicated. The needles may also cause hematomas (the needles may pierce small vessels and blood may leak). Hematomas return to normal unless the areas become infected. Very rarely, some people are allergic to the glue or the material used to secure the plastic needle to the skin; there may also be itching, redness and swelling. If this reaction occurs, medication administration may be necessary.

Safety concerns related to incidence and management of hypoglycemic and hyperglycemic episodes:

Diabetic patients with gastroparesis run the risk of developing hypoglycemic or hyperglycemic episodes. In the event that a hypoglycemic or hyperglycemic episode should occur, appropriate treatment measures will be taken to resolve the event.

HYPOGLYCEMIA

Mild hypoglycemic episodes

For a **hypoglycemic event** to be considered mild, the capillary glucose will be below 70 mg/dL and equal or above 50 mg/dL as revealed on the CGMS corroborated by a finger stick reading and the patient is fully capable of self treatment without the need of third party assistance. Mild

hypoglycemia may be symptomatic or asymptomatic. The protocol for treatment of mild hypoglycemic episodes are:

1. If the glucose value is below 50 - 70 mg/dL, it should be treated by ingestion of 15-20 grams of carbohydrates (e.g. 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non-diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice).
2. Blood glucose should be self-tested 15-20 minutes after ingestion of carbohydrates and therapy will be repeated as above, as needed. Cycle should be repeated until glucose level is 80 mg/dL or above.
3. Once episode is resolved, if no meal is scheduled the next 2 hours, a mixed nutrient snack, including a carbohydrate, protein, and fat will be ingested right after the initial therapy and after resolution of episode to prevent another episode.

Moderate hypoglycemic episode

For a hypoglycemic event to be considered moderate, the capillary glucose will be below 50 mg/dL as revealed on the CGMS and corroborated by a finger stick reading and the patient is fully capable of self-treatment, without the need of third party assistance. The protocol for treatment of moderate hypoglycemia is:

1. If blood glucose level is less than 50 mg/dL, the patient should ingest 30 grams of carbohydrates (e.g., 6-8 glucose tablets).
2. Blood glucose will be tested 15-20 minutes after ingestion of carbohydrate and therapy will be repeated as above, as needed and repeated until glucose level is 80 mg/dL or above.
3. Once the episode is resolved, if a meal is not scheduled within the next 2 hours, a mixed nutrient snack, including carbohydrate, protein, and fat should be ingested right after resolution of episode to prevent another episode.

Severe hypoglycemic episodes

If the capillary glucose level is below 50 mg/dL, as revealed on the CGMS and corroborated by a finger stick reading and the patient is incapable of self-treatment, hence in need of assistance from a third party (friend, relative, paramedic), the following treatment protocol will be followed:

<u>For patients that are conscious and cooperative:</u>

1. Turn patient on side and administer 1 mg of glucagon (intramuscular, subcutaneous, or intravenous) using the provided kit.

2. Check finger stick in 10 minutes.
3. If consciousness and cooperation are fully restored and finger stick glucose value is above 80 mg/dL provide with 20 grams of sugar (e.g. 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non-diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice and check glucose level again in 20 minutes.
4. If finger stick is partially restored >60-80 but patient remains conscious and fully cooperative provide with another 20 grams of carbohydrate and repeat cycle until finger tick is >80 and stable.
5. If finger stick is NOT above 60 in the 10 min check, call 911 and if patient still cooperative offer 20 grams of carbohydrate, repeat cycle until paramedics arrive.

For patients that are unconscious or neurologically impaired:

1. Turn patient on side and administer 1 mg of glucagon (intramuscular, subcutaneous, or intravenous) using the provided kit.
2. Call paramedics or 911 (if haven't already done so).
3. Check finger stick in 10 minutes.
4. If consciousness and cooperation are fully restored and finger stick glucose value is above 80 mg/dL and paramedics have NOT arrived, provide with 20 grams of sugar (e.g. 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non-diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice and check glucose level again in 10 minutes and provide with a mixed nutrient drink. Check finger stick reading every 10 minutes until paramedics arrive.

HYPERGLYCEMIA

Mild hyperglycemia episodes

For a **hyperglycemic event** to be considered mild, the capillary glucose will exceed 180 mg/dL up to 300 mg/dL as revealed on the CGMS and corroborated by a finger stick reading, the following treatment protocol has been established:

1. The pump settings have been set up to provide extra amounts of insulin as "boluses" based on target for glycemia and estimated insulin sensitivity index (so called correction factor) as well as estimated residual insulin from previous boluses (proprietary calculation of Medtronic).

Moderate hyperglycemia episodes

For a hyperglycemia event to be considered moderate, the capillary glucose will exceed 300 mg/dL up to 500 mg/dL is revealed on the CGMS and corroborated by a finger stick reading. The treatment protocol should be followed:

1. If patients are symptomatic or mildly symptomatic, they will be requested to contact the diabetes educator or diabetologist and decisions will be made via the telephone (self adjustment, a visit to the study doctor, emergency department visit) based on individual circumstances.
2. Patients with type 1 diabetes, will be required to test themselves for ketones using the ketone-meters provided to them. If the ketonemia is equal or greater than 0.6 mm/L, the patient will be requested to change the infusion set of the pump and additional insulin may be provided with injections to avoid further progression into ketoacidosis.
3. If the glycemia and ketonemia worsen, the patient will be requested to visit the emergency department.

Severe hyperglycemia episodes

For a **hyperglycemic event** to be considered severe, the capillary glucose will exceed 500 mg/dL as revealed on the CGMS and corroborated by a finger stick reading. The following treatment protocol will be followed:

1. If patient is symptomatic (polyuria, polydipsia) or with concurrent illness, but capable of good communication, a phone contact to diabetologist is mandatory who will make the decision regarding a visit to see the study doctor or emergency department visit.
2. If symptoms are intense, or the patient is incapable of good communication, immediate transport to emergency department should precede the phone contact.

6.25. Study Closeout (CO form)

Purpose

• To close out a patient's participation in the GLUMIT-DG study and document the patient's consent to join
or re-enter the Gastroparesis Registry

Form

• Closeout (CO) form

When

• The Closeout form should be completed at the f24 visit (or at the close of the f24 visit window) for all patients enrolled in the GLUMIT-DG study.

By whom:

• Clinical coordinator

Instructions

• Ask the patient if he/she consents to re-entering or enrolling in the Gastroparesis Registry

• Patients willing to re-enter or join the Gastroparesis Registry should sign the most recent version of the Gastroparesis Registry informed consent approved by your IRB (follow your institutional IRB guidelines for re-consenting participants previously enrolled in the Gastroparesis Registry).

• Each consenting patient should be scheduled for a Gastroparesis Registry follow-up visit approximately 16 weeks after the date of their GLUMIT-DG f24 visit. For patients previously enrolled in the Gastroparesis Registry, consult the patient's Gastroparesis Registry visit schedule (time windows guide) generated at their enrollment and schedule the Gastroparesis Registry visit that is open 16 weeks from the date of their GLUMIT-DG f24 visit.

• For patients who were not previously enrolled in the Gastroparesis Registry, a new visit schedule (time windows guide) will be automatically generated when the GLUMIT-DG Closeout form (CO) is keyed into the web based data management system database. The new visit schedule will use the GLUMIT-DG enrollment date as the effective date of enrollment into the Gastroparesis Registry. Schedule the participant approximately 16 weeks from their GLUMIT-DG visit for their next Gastroparesis Registry follow-up visit.

• For GLUMIT-DG participants who decline to participate in the Gastroparesis Registry; inform them that the study results will be available to them sometime after the close of the GLUMIT-DG study.

7. Forms management

7.1. Clinical center ID codes. 109
7.2. Patient identifiers. 110
7.3. Visit ID code. 111
7.4. General guidelines for forms completion. 112
7.5. Instruction box. 113
7.6. Form skips, stops, caution ineligibility symbols. 114
7.7. Headers and footers. 115
7.8. Key fields. 116
7.9. Missing data. 117
7.10. Administrative sign off. 118
7.11. Handling forms. 119
7.12. Data rounding rules. 120
7.13. Data audits and edits. 121

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

Stanford University	SU
• California Pacific Medical Center (CPMC) is a satellite of Stanford University and will use SU's alphabetic and numeric ID's	
Temple University	TU
Texas Tech University	TTU
University of Michigan	UMI
University of Mississippi	UMS
University of Wake Forest	WFU

Numeric site IDs

- The NIDDK Biosample Repository uses numeric ID's 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

Stanford University	613
Temple University	610
Texas Tech University	637
University of Michigan	611
University of Mississippi	612
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

Stanford University	SU	4001	-	4999
• California Pacific Medical Center (CPMC) is a satellite of SU and will use SU's range of patient ID's				
Temple University	TU	1001	-	1999
Texas Tech University	TTU	6001	-	6999
University of Michigan	UMI	2001	-	2999
University of Mississippi	UMS	3001	-	3999
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 3 character alpha-numeric code
- Determined by purpose of visit and timing with respect to visit windows
- Visit ID codes
  - s Screening, baseline data collection
  - en enrollment
  - f04 4 weeks follow-up visit
  - f08 8 weeks follow-up visit
  - f12 12 weeks follow-up visit
  - f16 16 weeks follow-up visit
  - f20 20 weeks follow-up visit
  - f24 24 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 a screening visit would be completed and keyed as "s1").
- 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.

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:

GLUMIT-DG 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: GLUMIT-DG 3

- 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 GLUMIT-DG data collection forms that require the Physician's signature, the signature is the assurance as the clinical center's principal investigator, that 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 GpR forms or performs the procedures, but does require assumption of responsibility signified by signing the NORIG 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 can print master copies from the website or data system and then photocopy as needed or print as needed from the website or data system – 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
- If a master copy gets frayed or faded, print a new master — always use clear copies for reproduction masters.

Form storage

- Forms for patients registered but not enrolled in the GLUMIT-DG study should be kept in a single folder or binder in a locked room in a locked cabinet.
- Each patient who is enrolled in the GLUMIT-DG study 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 GLUMIT-DG study documents for the patient – consents, forms, appointment schedule, labels, enrollment 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 GLUMIT-DG study, apply the rounding rule only at the last step, when required to record a quantity on the GLUMIT-DG study 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 periodic data audits as a quality control measure
- Audits may be done by mail or on-site
- During an audit, the forms will be reviewed to see if they were completed and keyed correctly; the forms will also be checked against the source documents to be sure that values were transcribed correctly.

Source documents include but are not limited to:

- Gastric emptying scintigraphy reports
- Gastric emptying breath test reports
- Upper endoscopy reports
- Gastric imaging study reports
- Laboratory test result reports
- Electrogastrophy reports
- Medical records for archival information
- 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 periodically
- The data edits check for consistency and questionable values in the database.

Changes resulting from audits or edits

- Changes made to the forms as a result of an audit or an edit should be marked "per audit" or "per edit" and should be dated and initialed.

8. Quality assurance

8.1. Site visits. 123
8.2. Performance monitoring. 126
8.3. Data quality surveillance. 127

8.1. Site visits

Purpose

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

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

- IRB communications organized with original approval letters, revision approvals, annual renewals, 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 GLUMIT-DG study 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 other resource centers associated with the GpCRC 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

- GLUMIT-DG study documents
  - Directory
  - SOPs
  - Forms Book
  - PPMs
  - Protocol
  - Consent forms

- 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 GLUMIT-DG forms and their source documents:
    - laboratory test results
    - gastric emptying report and scintigraphy on CD if available
    - upper endoscopy report
    - gastric emptying breath test report
    - electrogastrogram reports
    - CGMS data

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

- Protocol performance
  - Protocol deviations

- 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 CC.
  - 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 enrollment reports that will provide a count of participants enrolled at each clinical center

- On approximately 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 GLUMIT-DG 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, the timeliness of data entry, and protocol deviations. 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 enrolled
  - 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. The clinical center must respond to each edit on the listing, make appropriate changes to the forms and database, compute documentation of each change, 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.

8.3. Data quality surveillance

Forms audits

On a periodic (approximately 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 7 days
- The DCC will generate a summary report of the audit discrepancies by clinical center to be distributed to all GLUMIT-DG centers
- Discrepancy rates over time by clinical center are reported to the Steering Committee

GpCRC

Gastroparesis
Clinical Research Consortium

Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

Standard Operating Procedures

Part IV: Standard of Care for Patients with Diabetic Gastroparesis

18 October 2010

GLUMIT-DG SOP IV Standard of Care

Contents

1. Introduction.. 1
2. Patients with diabetic gastroparesis. 2
3. Treatment of hypoglycemic and hyperglycemic events. 5
4. Follow-up visits. 9
5. Dietary and nutritional recommendations.. 10
6. References.. 16

GLUMIT-DG SOP IV Standard of Care

1. Introduction

The purpose of this document is to articulate 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 diabetic gastroparesis who are enrolled in the Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG) Study. The standard of care manual was developed so that patients with diabetic gastroparesis will be evaluated uniformly during their open-label treatment in the GLUMIT-DG study. Once patients are in the GLUMIT-DG study, 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 variability for treatment and outcomes. In addition, the standard of care manual is developed to delineate the tests and procedures used for routine clinical care of patients with diabetic gastroparesis. The standard of care manual was developed by expert opinion as expressed by prior documents by the American Gastroenterological Association[2,3], American Diabetes Association[5,6], and the American Motility Society[4] and refined by the consensus of investigators of the GpCRC. Every effort will be made to adhere to the standard of care manual for each patient.

2. Patients with diabetic gastroparesis

Each patient will be evaluated for diabetic gastroparesis based on the following:

1. Symptoms of gastroparesis (nausea, vomiting, early satiety, bloating fullness, discomfort) for at least 1 year .
2. Diagnosis of Type 1 or Type 2 diabetes mellitus for at least 2 years.
3. Hemoglobin A1c of at least 8.0%.
4. Gastric emptying scintigraphy using a 4 hour low fat Egg Beaters meal as described by Tougas et al 2000[1]. Delayed gastric emptying on gastric emptying scintigraphy is defined as >60% retention at 2 hours or >10% retention at 4 hours. General practice is to try to stop medications known to delay or accelerate gastric emptying for 3 days prior to the gastric emptying test.
5. Normal upper endoscopy (retained gastric food is permitted)- reports taken upon Registry enrollment can be used if performed in last year; subjects not enrolled in the Registry will have to undergo upper endoscopy as part of routine clinical care prior to enrollment into GLUMIT-DG study.
6. Exclusion of gastrointestinal obstruction – generally performed with a careful history and physical examination, laboratory testing, radiographic evaluation, and upper endoscopy.

Although there are general guidelines for the evaluation of patients with gastroparesis[2,3,4], the exact evaluation of a patient may differ depending on the individual case characteristics.

Initial evaluation of a patient with diabetic gastroparesis

History

Longstanding diabetes mellitus: diagnosed Type 1 or Type 2 diabetes mellitus in which current hemoglobin A1c value is at least 8.0%.

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, poor glycemic control in diabetics

Complications of diabetes mellitus: a) retinopathy b) cardiovascular disease c) peripheral neuropathy d) nephropathy (serum creatinine must be <1.5mg/dL)

Assessment of nutritional status

Dietary intolerance

Other disorders and surgeries – especially those that might relate to symptoms of gastroparesis (e.g. collagen vascular disease, endocrine diseases such as hypothyroidism, peptic ulcer surgery, fundoplication, surgeries involving gastric nerve plexi – as for neurofibromatosis)

Symptoms or diagnosis of overlap syndromes: migraine headaches, fibromyalgia, interstitial cystitis, endometriosis, depression.
Other medical problems
Prior surgeries
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

Physical examination

Vital Signs: blood pressure, pulse, temperature, weight, height, body mass index (BMI)
Abdominal examination: visible distention, tympany, succussion splash, tenderness, organomegaly

Laboratory tests

Thyroid stimulating hormone (TSH)
Glycosylated hemoglobin (Hb A1c)
Complete blood count (CBC), including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (hgb), hematobcrit (hct), platelet count
Complete metabolic panel, including sodium, potassium, chloride, carbon dioxide, glucose, calcium, blood urea nitrogen (BUN), creatinine, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin

Endoscopy

Upper endoscopy (must have been done within 1 year prior to entering the GLUMIT-DG study). Esophageal, gastric and duodenal biopsies may be obtained by history, physical examination (associated bloating, diarrhea, or family history of celiac disease), or laboratory findings (unexplained microcytic anemia)

Nuclear medicine

Gastric emptying scintigraphy (solid phase - % retention at 0, 0.5, 1, 2, 3, 4 hrs). Must have been done at a GpCRC clinical center within 1 year prior to enrollment. Required standardized test meal outlined in GLUMIT-DG SOP Part I: Clinical Center Operations, section Gastric Emptying Scintigraphy.

Standard Therapy of Diabetic Gastroparesis

- Patients will have adjustments of initial pharmacological therapy made if deemed necessary.
- Patients will have an appointment with a diabetes educator to review and reinforce principals of medical, and nutritional therapy for diabetes.
- A baseline diabetic gastroparetic instruction sheet will be given to the patients with suggestions to follow. Additional treatments for refractory symptoms or if pain is a dominant symptom may include the use of tricyclic anti-depressants or analgesic medications. Occasionally newer agents (duloxetine Hcl (Cymbalta) or pregabalin (Lyrica)) are tried on an off label basis.
- Patients with more severe manifestations of diabetic gastroparesis, such as refractory vomiting, pronounced dehydration, or chaotic glucose control, might require hospitalization, intravenous hydration, nasogastric suction to decompress the stomach, or intravenous administration of antiemetic and prokinetic agents.
- Consideration of surgically or endoscopically placed enteral tubes for feeding 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.

Nutritional Counseling

It is imperative that adequate nutrition be maintained during the course of this study. As part of the initial instruction by the diabetes educator, a balanced diabetic diet will be taught to each patient. At each subsequent visit, patients will be queried by the diabetes educator about their food intake. Patients will be weighed and vital signs will be obtained at each visit to confirm that malnutrition or dehydration have not occurred. Patients will be further instructed to contact the diabetes educator for any weight loss >5 pounds in any one month period during the study. Patients will be instructed to consume non-caloric liquids for lightheadedness and will be instructed to present to the diabetologist or emergency department if presyncope or syncope develop as a consequence of hypovolemia.

3. Treatment of hypoglycemic and hyperglycemic events

Management of hypoglycemic and hyperglycemic episodes:

Diabetic patients with gastroparesis run the risk of developing hypoglycemia or hyperglycemia. In the event that a hypoglycemic or hyperglycemic episode should occur, appropriate treatment measures should be taken to resolve the event.

HYPOGLYCEMIA

Mild hypoglycemic episodes

For a **hypoglycemic event** to be considered mild, the capillary glucose (SMBG) will be 50 - 70 mg/dL as confirmed by a finger stick (Ultra) reading; and the patient is fully capable of self treatment without the need of third party assistance. Mild hypoglycemia may be symptomatic or asymptomatic. The following treatment protocol for mild hypoglycemic episodes will be followed:

1. If the Ultra glucose value is 50 - 70 mg/dL, it should be treated by ingestion of 15-20 grams of carbohydrates (e.g., 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice). If the subject is in the hospital, the Ultra glucose reading will be confirmed by a laboratory glucose measurement but treatment will be in inhaled based on the Ultra reading.
2. Blood glucose should be self-tested 15-20 minutes after ingestion of carbohydrates and therapy will be repeated as above, as needed. Cycle should be repeated until glucose level is 80 mg/dL or above.
3. Once episode is resolved, if no meal is scheduled the next 2 hours, a mixed nutrient snack, including a carbohydrate, protein, and fat will be ingested right after the initial therapy and after resolution of episode to prevent another episode.

Moderate hypoglycemic episode

For a **hypoglycemic event** to be considered moderate, the capillary glucose will be below 50 mg/dL using a Ultra finger stick reading; and the patient is fully capable of self-treatment, without the need of third party assistance. The following protocol for treatment of moderate hypoglycemia will be followed:

1. If blood glucose level is less than 50 mg/dL, the patient should ingest 30 grams of carbohydrates (e.g., 6-8 glucose tablets). If the subject is in the hospital, the Ultra glucose reading will be confirmed by a laboratory glucose measurement but treatment will be in inhaled based on the Ultra reading.
2. The capillary blood glucose will be tested 15-20 minutes after ingestion of a carbohydrate and therapy will be repeated as above, as needed, and repeated until glucose level is 80 mg/dL or above.

3. Once the episode is resolved, if a meal is not scheduled within the next 2 hours, a mixed nutrient snack, including a carbohydrate, protein, and fat should be ingested right after resolution of the episode to prevent another episode.

Severe hypoglycemic episodes

If the capillary glucose level is below 50 mg/dL, by an Ultra finger stick reading; and the patient is incapable of self-treatment, hence in need of assistance from a third party (friend, relative, paramedic), the following treatment protocol will be followed:

For patients that are conscious and cooperative:

1. Turn patient on side and administer 1 mg of glucagon (intramuscular, subcutaneous, or intravenous) using the provided kit.
2. Check finger stick glucose value in 10 minutes.
3. If consciousness and cooperation are fully restored and finger stick glucose value is above 80 mg/dL, provide with 20 grams of sugar (e.g., 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice) and check glucose level again in 20 minutes.
4. If the Ultra finger stick glucose value is partially restored >60-80 mg/dL but patient remains conscious and fully cooperative, provide patient with another 20 grams of carbohydrate and repeat cycle until finger stick glucose value is >80 mg/dL and stable.
5. If finger stick glucose value is NOT above 60 mg/dL at the 10 minute check, call 911. If patient is still cooperative, offer 20 grams of carbohydrate; repeat cycle until paramedics arrive.

For patients that are unconscious or neurologically impaired and NOT in the hospital, clinic or ER:

1. Turn patient on side and administer 1 mg of glucagon (intramuscular, subcutaneous, or intravenous) using the provided kit.
2. Call paramedics or 911 (if haven't already done so).
3. Check finger stick glucose value in 10 minutes.
4. If consciousness and cooperation are fully restored and finger stick glucose value is above 80 mg/dL and paramedics have NOT arrived, provide patient with 20 grams of sugar (e.g., 4-5 glucose tablets, 5-6 Lifesavers, 4-6 oz. of a regular [non diet] soft drink, or 8 oz. low fat milk, 4 teaspoons of sugar dissolved in a liquid or juice) and check glucose level again in 10 minutes, and provide with a mixed nutrient drink. Check finger stick glucose value every 10 minutes until paramedics arrive.

Whenever possible, all hypoglycemic glucose values will be confirmed by a laboratory glucose measurements, if the patient is in a setting where a laboratory glucose measurement can be obtained.

For those patients with hypoglycemia IN a hospital setting, established protocols of the hospital will be followed including but not confined to administration of dextrose and glucogon as per the clinical judgement of the attending phsycian.

HYPERGLYCEMIA

Mild hyperglycemia episodes

For a hyperglycemic event to be considered mild, the capillary glucose will exceed 180 mg/dL up to 300 mg/dL using a Ultra finger stick reading, and there are no blood or urine ketones present and the subject is not nauseated, vomiting or having an altered sensorium. For mild hyperglycemic, the following treatment protocol will be followed:

1. The pump settings have been set up to provide extra amounts of insulin as "boluses" based on target for glycemia and estimated insulin sensitivity index (so-called correction factor) as well as estimated residual insulin from previous boluses (proprietary calculation of Medtronic). Patients will be asked to check blood sugar 1 hour following correction to access effectiveness of correction. In the event the glucose does not drop by 50 mg/dL or more in one hour, patients will be asked to use the ? wizard to determine the correction dose, but not deliver the dose, disconnect from the pump and deliver the calculated dose using a syringe or insulin pen. They will then be asked to change the insulin in the reservoir, the tubing and the infusion, and continue to monitor blood glucose hourly, til blood glucose is less than 50 mg/dL.

Moderate hyperglycemia episodes

For a hyperglycemia event to be considered moderate, the capillary glucose will exceed 300 mg/dL up to 500 mg/dL using an Ultra finger stick reading. The treatment protocol should be followed:

1. If patients are symptomatic or mildly symptomatic, they will be requested to contact the diabetes educator or diabetologist and decisions will be made via the telephone (self adjustment, a visit to the study doctor, emergency department visit) based on individual circumstances.
2. Patients with type 1 diabetes, will be required to test themselves for ketones using the ketone-meter strips provided to them. If the ketonemia is equal or greater than 0.6 mM/L, the patient will be requested to change the infusion setting of the pump and additional insulin may be provided with injections to avoid further progression into ketoacidosis.
3. If the glycemia and ketonemia worsen or the endocrinologist judges it necessary, the patient will be requested to visit the emergency department.

Severe hyperglycemia episodes

For a **hyperglycemic event** to be considered severe, the capillary glucose will exceed 500 mg/dL using an Ultra finger stick reading and/or patients may have ketones as evidenced by blood ketone test of 0.6 mmol/L or higher or large urine ketones and/or the presence of nausea, vomiting, or altered mental state. The following treatment protocol will be followed:

1. If patient is symptomatic (polyuria, polydipsia) or with concurrent illness, but capable of good communication, a phone contact to diabetologist is mandatory who will make the decision regarding a visit to see the study doctor or emergency department visit.
2. If symptoms are intense, or the patient is incapable of good communication, immediate transport to emergency department should precede the phone contact.

GLUMIT-DG SOP IV Standard of Care

4. Follow-up visits

Patients will return once every 4 weeks over a 24-week and meet with a diabetes educator to review blood glucose levels and to make necessary adjustments to insulin doses through the patients insulin pump. In addition, to enhance compliance, participants will be contacted by telephone at least once between each follow-up visit.

At the follow-up visits and the 12 and 24 week visits, in addition to reviewing blood glucose levels and making necessary adjustments to insulin doses, patients will complete questionnaires, undergo a physical exam, blood will be drawn for hemoglobin A1c testing and blood glucose levels will be checked followed by automatic nerve testing and electrogastrography (EGG) caloric and non-caloric satiety testing. Before physiological testing begins, fasting blood glucose levels will be taken and a reading of <270 mg/dL is a requirement to have physiological testing done. If the glucose level exceeds 270 mg/dL, a blood sample will be taken and sent to the lab for confirmation and supplemental insulin will be ordered by the endocrinologist or diabetes educator of the research team to decrease the blood glucose to less than 270 mg/dL. Once confirmation is made that the patients blood glucose level is less than 270 mg/dL, the electrogastrography with non-caloric satiety tests will be performed.

At each 4 week visit, if the glycemic targets are achieved (fasting glucose 70-110 mg/dL, postprandial <140 mg/dL), current treatment will be continued. If glycemic targets are not achieved, basal insulin will be added and titrated up to 0.5 u/kg/day if the patient is on three agents, or other strategies may be used.

Items for documentation

History

Review of disease course
Assessment of current symptoms - GCSI and QOL
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: Temperature, blood pressure, pulse, weight
Abdominal examination: tenderness, succession splash

Laboratory tests

Glycosylated hemoglobin (Hb A1c)
Blood glucose levels, Complete blood count, complete metabolic panel, thyroid function tests

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 diabetic 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 diabetic 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 diabetic gastroparesis seek dietary counseling with a dietician to help individualize nutrition therapy and maximize nutritional benefits.

If gastroparesis is due to diabetes, the most important goal is to achieve or maintain optimal glucose control. This is achieved more easily by frequent monitoring of blood glucose levels and self-adjustment of insulin given throughout the day. Nutritional intake is often variable due to symptoms of anorexia, early satiety, bloating and fullness and can often be inconsistent from meal to meal and day to day. Because the diabetes patient with gastroparesis is often not able to tolerate regular meals or solid foods, this can compromise glucose control and produce fluctuating glucose levels throughout the day. Also, an increase in insulin requirements often occurs because of the need to add nutritional supplements. The following guidelines may be useful to assist the patient in improving glucose control and nutritional adequacy:

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 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.

- When liquid foods are the only source of nutrition, the optimal choices would be liquids with higher quantities of nutrients, such as milk or fruit juices, rather than low-nutrient liquids such as regular sodas or soft drinks. The quantity and total amount of carbohydrate consumed, however, is more important than the source of the carbohydrate in regard to its impact on increasing blood glucose levels; therefore, the more consistent you are with the amount of carbohydrate consumed at each meal, whether in solid or liquid form, the easier it will be to maintain more stable, fewer fluctuating blood glucose levels.

- Monitor blood glucose levels before the small meal or snack is eaten and adjust insulin dose according to the blood glucose level and the anticipated amount of CHO to be eaten.

- An insulin regimen of a basal dose of insulin (NPH or a long-acting insulin such as glargine) at bedtime or in the evening and a bolus or supplemental dose of short-acting (Regular insulin) or rapid-acting insulin (Aspart or Lispro) before the meal or snack (some patients may need to do this ~ ½ hour after their meal once they are sure the meal will stay down) would be the most ideal to promote optimal glucose control.

- Eat and drink all foods and beverages while sitting up.

- Solid foods are often better tolerated earlier in the day with a switch to liquid meals later in the day.

- 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, hence 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, 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.

Patients with kidney disease but serum creatinine <1.5mg/dL need to follow additional dietary advice. The dietary restrictions will depend on 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.

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

1) 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

2) Sample meal plan for 6 semi-liquid meals

Breakfast (6 Carb choice)
- Citrus Juice (1/2 cup: 15g CHO)
- Thinned Cooked Cereal (1/2 cup cooked cereal: 19g CHO)
- Liquid Supplement or Milkshake (see suggestions) (10 oz milkshake: 32g CHO)
- Milk (1 cup: 12g CHO)
- Coffee or Tea (unsweetened: 0g CHO)
- Cream, Sugar (1 Tbsp sugar: 15g CHO)

Lunch and Dinner (6 Carb choices)
- Thinned Soup (1 cup chicken broth: 1g CHO)
- Thinned or Puréed Meat or Substitute
- Thinned Potato or Substitute (3 oz potato: 15g CHO)
- Thinned or Puréed Vegetable
- Thinned Dessert or Puréed Fruit (1/2 cup fruit: 15g CHO)
- Liquid Supplement or Milkshake (milkshake: 32g CHO)
- Milk (1 cup: 12g CHO)
- Coffee or Tea (unsweetened: 0g CHO)
- Cream, Sugar (1 Tbsp sugar: 15g CHO)
- Salt and Pepper

Snack: Mid-Morning, Afternoon, and Bedtime (1 Carb choice)
- Milk or Fruit Juice (1 cup milk, 1/2 cup juice: 15g CHO)
- Liquid Supplement or Milkshake (see suggestions)

6. References

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