GDM2 Study

"Comparison of Two Screening Strategies for Gestational Diabetes"

NIH Grant #: 1R01HD079647-01A1
PittPRO ID: STUDY19070199
ClinicalTrials.gov Identifier: NCT02309138

Manual of Procedures

Version V – December 1, 2019

Principal Investigator: Esa M. Davis, MD, MPH
University of Pittsburgh

GDM2 Study Manual of Procedures, Version V: Table of Contents

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AE	Adverse Event
BMI	Body Mass Index
BPA	(Epic) Best Practice Alert
CLB	(UPMC) Clinical Laboratory Building
Co-I	Co-Investigator
CRHC	Center for Research on Health Care
CRHC-DC	Center for Research on Health Care – Data Center
CSSD	Computing Services and Systems Development
CTRC	Clinical and Translational Research Center
CTSI	Clinical and Translational Science Institute
DM	Diabetes Mellitus
DOB	Date of Birth
DSMB	Data Safety Monitoring Board (*a.k.a.* IDSMB)
EBL	Estimated Blood Loss
ED	Emergency Department
EDC	Estimated Date of Confinement
EHR	Electronic Health Record (*a.k.a.* EMR)
EMR	Electronic Medical Record (*a.k.a.* EHR)
eSYSDM	Electronic System for Data Management
GA	Gestational Age
GDM	Gestational Diabetes Mellitus
GSPH	Graduate School of Public Health
GCT	Glucose Challenge Test
hsCRP	High-sensitivity C-reactive Peptide
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
ICD	Informed Consent Document
IDSMB	Institutional Data Safety Monitoring Board (*a.k.a.* DSMB)
IRB	Institutional Review Board
LDR	Labor and Delivery Room
LGA	Large for Gestational Age
LMP	Last Menstrual Period
LTFU	Lost to Follow-Up
MFM	Maternal-Fetal Medicine
MRN	Medical Record Number
MWH	Magee-Womens Hospital

MWRI	Magee-Womens Research Institute
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
OB	Obstetrician/Obstetrics
OGTT	Oral Glucose Tolerance Test
OSPU	Obstetric Specimen Procurement Unit
PI	Principal Investigator
R3	Health Research Records Request
RA	Research Assistant
RC	Research Coordinator
SAE	Serious Adverse Event
SGA	Small for Gestational Age
TOLAC	Trial of Labor After C-section
UPMC	University of Pittsburgh Medical Center

Study Investigators and Responsibilities

GDM2 Principal Investigator

Principal Investigator: Esa M. Davis, MD, MPH

University of Pittsburgh School of Medicine
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-692-4843
Email: emd55@pitt.edu

Dr. Esa Davis, Associate Professor of Medicine, Clinical and Translational Science, is a family medicine physician. She will be responsible for supervision of all aspects of the research project, including conceptualization, protocol implantation, data analyses and interpretation, data safety monitoring, and publication and dissemination. She will ensure the ethical conduct of the study, which includes protecting human participants' rights, safety, and welfare; protocol compliance; and adherence to institutional, state, and federal regulars and guidance. She will comply with the financial and administrative policies and regulations associated with the award, overall fiscal management of the project, and conflict of interest disclosure.

GDM2 Co-Investigators

Co-Investigator/Site Principal Investigator: Hyagriv Simhan, MD, MSCR

Magee-Womens Hospital
Division of Maternal-Fetal Medicine
300 Halket Street
Pittsburgh, PA 15213
Phone: 412-641-4222 or 412-641-6361
Email: hsimhan@mwri.magee.edu

Dr. Hyagriv Simhan, Professor, Director of Division of Maternal-Fetal Medicine and Executive Vice Chair of Obstetrical Services at Magee-Womens Hospital (MWH) has expertise in conducting clinical trials in pregnancy through the Maternal-Fetal Medicine network and will be actively involved in study implementation within MWH obstetrical clinics, data analyses and interpretation, and manuscript preparation. He will provide supervision of adverse events and clinical input when needed, He will participate in research team and data safety monitoring meetings. He will be responsible for making important study-related decisions in compliances with the ethical conduct and regulatory requirements of the study.

Co-Investigator: Christina Scifres, MD

Indiana University
Division of Maternal-Fetal Medicine
550 N. University Boulevard
UH 2440
Indianapolis, IN 46202
Phone: 317-948-4103
Email: cmscifre@iu.edu

Dr. Christina Scifres, Associate Professor of Obstetrics and Gynecology and a specialist in maternal-fetal medicine, is a co-principal investigator on this research study. She was instrumental in the success of the pilot study and has been key in the conception and implementation of the current trial. She will provide clinical perspective and assist with the implementation of study procedures, and she will contribute to data analyses and interpretation of findings, publications, and presentations. She will participate in research team and data safety monitoring meetings. She will be responsible for making important study-related decisions in

compliance with the ethical conduct and regulatory requirements of the study and will assist in the management and leadership of this trial.

Co-Investigator: Patrick Catalano, MD

Tufts University
Department of Obstetrics and Gynecology
800 Washington Street
Box 394
Boston, MA 02111
Phone: 617-636-4187
Email: pcatalano@tuftsmedicalcenter.org

Dr. Patrick Catalano, Professor and Vice Chair of Obstetrics and Gynecology and a specialist in maternal-fetal medicine, is a co-investigator on this research study. He will provide supervision and input on collection, analyses, and interpretation of the metabolic lab profiles at Visit 2 (randomization) and Visit 3 (12-months postpartum). He will participate in research team meetings, data analyses and interpretation of findings, manuscript writing and dissemination to the IADPSG and the National Institutes of Health (NIH) Gestational Diabetes Mellitus (GDM) consensus committee.

Co-Investigator and Study Biostatistician: Kaleab Z. Abebe, PhD

University of Pittsburgh
Center for Research on Health Care – Data Center
200 Meyran Avenue, Suite 300
Pittsburgh, PA 15213
Phone: 412-246-6931
Email: kza3@pitt.edu

Dr. Kaleab Abebe, Associate Professor of Medicine, Biostatistics, and Clinical and Translational Science, will be responsible for supervising all aspects of data management and statistical analyses. He will work with CRHC-DC data managers and systems analysts to implement an online data management application, as well as oversee randomization and data safety monitoring. He will be responsible for generating monthly reports for the study team and quarterly reports for the Data Safety Monitoring Board (DSMB) and Institutional Review Board

(IRB). Dr. Abebe will oversee the primary statistical analysis of the current study and will work with the study team to disseminate the results through reports, abstracts, and manuscripts.

Co-Investigator: Tina Costacou, PhD

University of Pittsburgh
Diabetes and Lipid Research Clinic
3512 Fifth Avenue
Pittsburgh, PA 15213
Phone: 412-383-2062
Email: costacout@edc.pitt.edu

Dr. Tina Costacou, Assistant Professor of Epidemiology, is a nutrition and diabetes epidemiologist. For this project, Dr. Costacou will provide input on diabetes measures and trial design. She will participate in research team meetings and provide input on recruitment, enrollment, and longitudinal retention, assist with problem-solving any issues that arise with study implementation, data analyses and interpretation, and assist with manuscripts. She will assist in making important study-related decisions in compliance with the scientific and ethical conduct of the study.

Co-Investigator: Nancy Day, PhD, MPH

University of Pittsburgh
Department of Psychiatry
3811 O'Hara Street
Pittsburgh, PA 15213
Phone: 412-681-3482
Email: nday@pitt.edu

Dr. Nancy Day, Professor of Psychiatry, Epidemiology, and Pediatrics, will assist in making important study-related decisions in compliance with the scientific and ethical conduct of the study. She will provide input on study aims, design, and measurement of variables. She will provide her expertise in observational design, measurement, managing follow-up and attrition, and analyses. Dr. Day will be involved in research team meetings to discuss study-related issues, data analyses, and interpretation and manuscript writing.

Co-Investigator: Lisa Bodnar, PhD, MPH, RD

University of Pittsburgh
Graduate School of Public Health
130 DeSoto Street
A742 Crabtree Hall
Pittsburgh, PA 15261
Phone: 412-624-9032
Email: bodnar@edc.pitt.edu

Dr. Lisa Bodnar, Associate Professor of Epidemiology, Obstetrics and Gynecology, and Psychiatry, is a registered dietitian and licensed nutritionist. Dr. Bodnar is a nutritional epidemiologist in the field of reproductive health. She will supervise the dietary recalls of participants at Visit 2 (baseline) and Visit 3 (12-months postpartum), as well as the infant feeding assessments. She will train the research study staff to administer the 24-hour Dietary Recalls for these visits. She will also participate in data analysis and interpretation of this variable. Dr. Bodnar will be involved in research team meetings to discuss study-related issues, data analyses, and interpretation and manuscript writing.

GDM2 Study Personnel and Responsibilities

GDM2 Principal Study Staff

Research Assistant: Alison Decker, BA

University of Pittsburgh
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-647-0246
Email: deckerap@upmc.edu

Alison Decker will work with the study investigators and other staff in implementing this study. Study staff duties will include: scheduling appointments, completing phone assessments, and maintaining regular contact with study participants; run study visits and complete blood draws and study laboratory procedures; data collection and entry; maintain quality control for data correctness and completeness; update participants' electronic medical records as needed; supervision of student workers; and coordination with ancillary studies. Study staff will monitor adverse events, serious adverse events, and protocol deviations, and report such events to the investigators in a timely manner. She will also maintain the staff calendar and work assignments, monitor study invoices, and act as the study's IDSMB coordinator.

Research Assistant: Kathleen (Ly) Meeder, MPH, CHES

University of Pittsburgh
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-692-4312
Email: lyk@upmc.edu

Kathleen Meeder will work with the study investigators and other staff in implementing this study. Study staff duties will include: scheduling appointments, completing phone assessments, and maintaining regular contact with study participants; run study visits and complete blood draws and study laboratory procedures; data collection and entry; maintain quality control for data correctness and completeness; update participants' electronic medical records as needed; supervision of student workers; and coordination with ancillary studies. Study staff will monitor

adverse events, serious adverse events, and protocol deviations, and report such events to the investigators in a timely manner. She will also prepare materials for and run weekly staff meetings and biannual co-investigator meetings, monitor dietary recalls and the ASA24 backend, create study newsletters for participants and providers, and act as the study's recruitment lead and IRB coordinator.

Research Assistant: Steven Orris, BS

University of Pittsburgh
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-647-1468
Email: orrissr@upmc.edu

Steven Orris will work with the study investigators and other staff in implementing this study. Study staff duties will include: scheduling appointments, completing phone assessments, and maintaining regular contact with study participants; run study visits and complete blood draws and study laboratory procedures; data collection and entry; maintain quality control for data correctness and completeness; update participants' electronic medical records as needed; supervision of student workers; and coordination with ancillary studies. Study staff will monitor adverse events, serious adverse events, and protocol deviations, and report such events to the investigators in a timely manner. He will act as the study's delivery/postpartum time point lead, responsible for maintaining an accurate list of participants expected to deliver soon, and act as the study's liaison with the Obstetric Specimen Procurement Unit at MWH. He will also be the study's laboratory liaison at the UPMC Clinical Laboratory Building and Magee-Womens Research Institute, responsible for creating laboratory procedures and materials, creating specimen storage maps, and transporting specimens between labs for long-term storage at MWRI.

GDM2 Clinical Team

Magee-Womens Hospital Clinical and Translational Research Center Administrator: Cindy Schatzman, RN

Magee-Womens Hospital
Clinical and Translational Research Center
300 Halket Street, Suite 5500
Pittsburgh, PA 15213
Phone: 412-641-6111
Email: schatzmancl@mail.magee.edu

Cindy Schatzman, RN, will support the study by providing specified services at the Magee-Womens Hospital Clinical and Translational Research Center (MWH CTRC), including glucose testing, phlebotomy, and nursing care for study participants.

UPMC Automated Testing Laboratory Director: Octavia Peck-Palmer, PhD

UPMC Clinical Laboratory Building
3047 Euler Way, Room 3014
Pittsburgh, PA 15213
Office Telephone: 412-578-9489
Email: palmerom@upmc.edu

Dr. Octavia Palmer, Associate Professor of Pathology and Medical Director of the Automated Testing Laboratories at UPMC Presbyterian, will supervise sample processing and analysis of blood samples at the UPMC Clinical Laboratory Building.

UPMC Special Chemistry and Immunoserology Laboratory Manager: Mary Jane Horenzy

UPMC Clinical Laboratory Building
Department of Special Chemistry
3047 Euler Way, Room 4025
Pittsburgh, PA 15213
Phone: 412-647-3769
Email: horenzymj@upmc.edu

Mary Jane Horenzy, laboratory manager at the UPMC Special Chemistry and Immunoserology laboratories, will oversee the analysis of the A1c and insulin specimens.

Magee-Womens Research Institute Lab Liaison: Sharon Price

204 Craft Avenue
Pittsburgh, PA 15213
Phone: 412-641-6148

Sharon Price is the GDM2 Study's liaison at the Magee-Womens Research Institute (MWRI), where all banked specimens from the study will be stored.

Obstetric Specimen Procurement Unit Liaison: Lindsay Stewart

Magee-Womens Hospital
Obstetric Specimen Procurement Unit
300 Halket Street
Pittsburgh, PA 15213
Phone: 412-354-4077
Email: stewartl4@upmc.edu

Lindsay Stewart is the GDM2 Study's liaison with the Obstetric Specimen Procurement Unit (OSPU) at MWH. The OSPU team will identify study participants at delivery and collect cord blood specimens for c-peptide analyses. The OSPU team will process and store specimens until they are transferred from MWH to MWRI.

GDM2 Data Center Staff

Data Center Information Systems Manager: Timothy Bragg

University of Pittsburgh
Center for Research on Health Care – Data Center
200 Meyran Avenue, Suite 200
Pittsburgh, PA 15213
Phone: 412-692-4898
Email: braggtj@upmc.edu

Timothy Bragg is the GDM2 Study's Information Systems Manager and is responsible for data management and supervision of Charlene Xie, the study's Data Systems Analyst.

Data Center Data Systems Analyst: Charlene Xie, MSIS

University of Pittsburgh
Center for Research on Health Care – Data Center
200 Meyran Avenue, Suite 200
Pittsburgh, PA 15213
Phone: 412-246-6926
Email: xiecx@upmc.edu

Charlene Xie is responsible for designing and developing the study's database. She is responsible for data management procedures, including the data flow and procedures for data entry, error identification, and correction quality control.

Data Center Data Analyst: Diane Comer

University of Pittsburgh
Center for Research on Health Care – Data Center
200 Meyran Avenue, Suite 200
Pittsburgh, PA 15213
Phone: 412-692-4896
Email: dianecomer@pitt.edu

Diane Comer is responsible for assisting Dr. Abebe with the study's data analysis.

GDM2 Regulatory Staff

University of Pittsburgh Institutional Review Board: Lisa DeSantes, BS, CIP

University of Pittsburgh Institutional Review Board
3500 Fifth Avenue
Hieber Building, Main Office, Suite 106
Pittsburgh, PA 15213
Phone: 412-383-1488
Email: lisa.desantes@pitt.edu

Lisa DeSantes has reviewed and approved the GDM2 Study protocol and is responsible for reviewing study modifications, unexpected problems, and serious adverse events reportable to the Institutional Review Board (IRB). She will also answer questions related to University of Pittsburgh IRB guidelines and procedures.

Clinical and Translational Science Institute, Data Safety and Monitoring Board Coordinators: Susan Sandusky and Samantha Hurst

University of Pittsburgh Clinical and Translational Science Institute
Forbes Tower, Suite 7057
Atwood and Sennott Streets
Pittsburgh, PA 15213

Susan Sandusky:
Phone: 412-383-1036
Email: sls127@pitt.edu

Samantha Hurst:
Phone: 412-605-0264
Email: seh142@pitt.edu

Susan Sandusky and Samantha Hurst of the Clinical and Translational Science Institute (CTSI) will provide oversight of the GDM2 Study's Data Safety and Monitoring Board (DSMB), ensuring safe conduct of this clinical trial. They have assisted in the identification of DSMB members. They will schedule and attend DSMB meetings and will prepare minutes and reports for those meetings. Ms. Sandusky and Ms. Hurst will schedule and attend follow-up (and, if needed, emergency) DSMB meetings and will subsequently prepare minutes and reports.

GDM2 Administrative Staff

Center for Research on Health Care Grants Administrator: Patrick Reitz, MA

University of Pittsburgh
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-692-4858
Email: reitzpm@upmc.edu

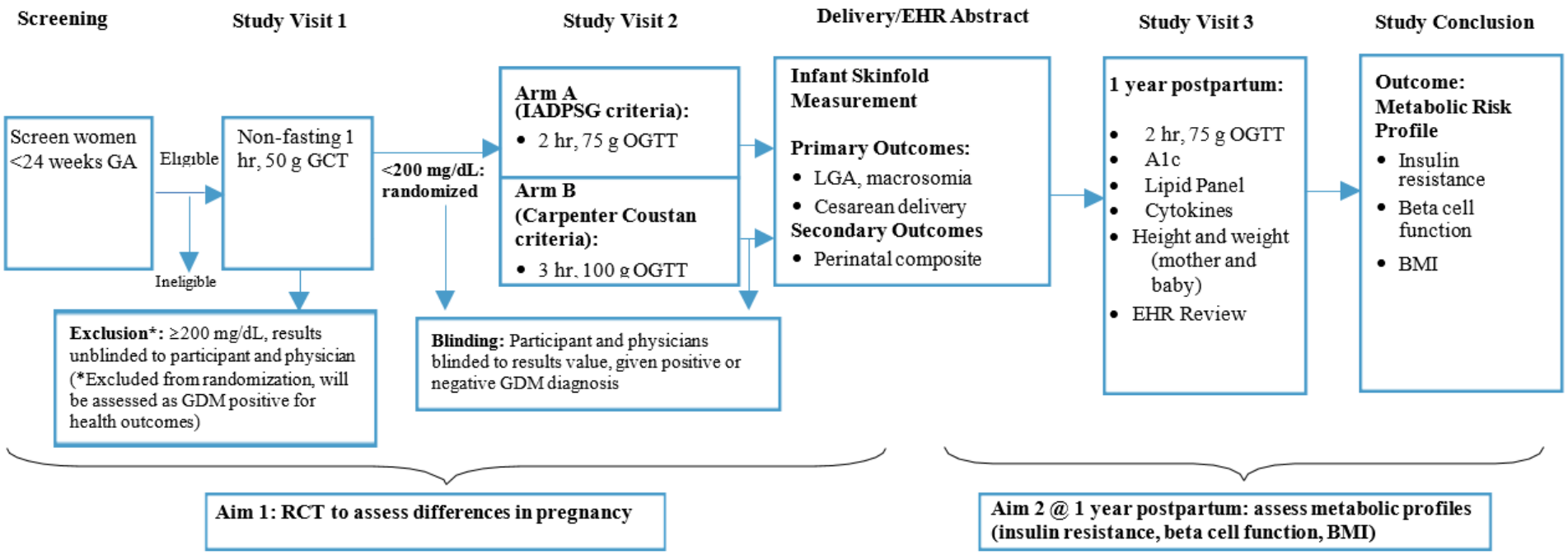
Patrick Reitz is the GDM2 Study's grant administrator and will oversee that the grant received will be properly utilized according to its conditions and responsibilities.

Administrative Coordinator: Kristee Rosen, MS

University of Pittsburgh
Center for Research on Health Care
230 McKee Place, Suite 600
Pittsburgh, PA 15213
Phone: 412-692-4853
Email: adamskj2@upmc.edu

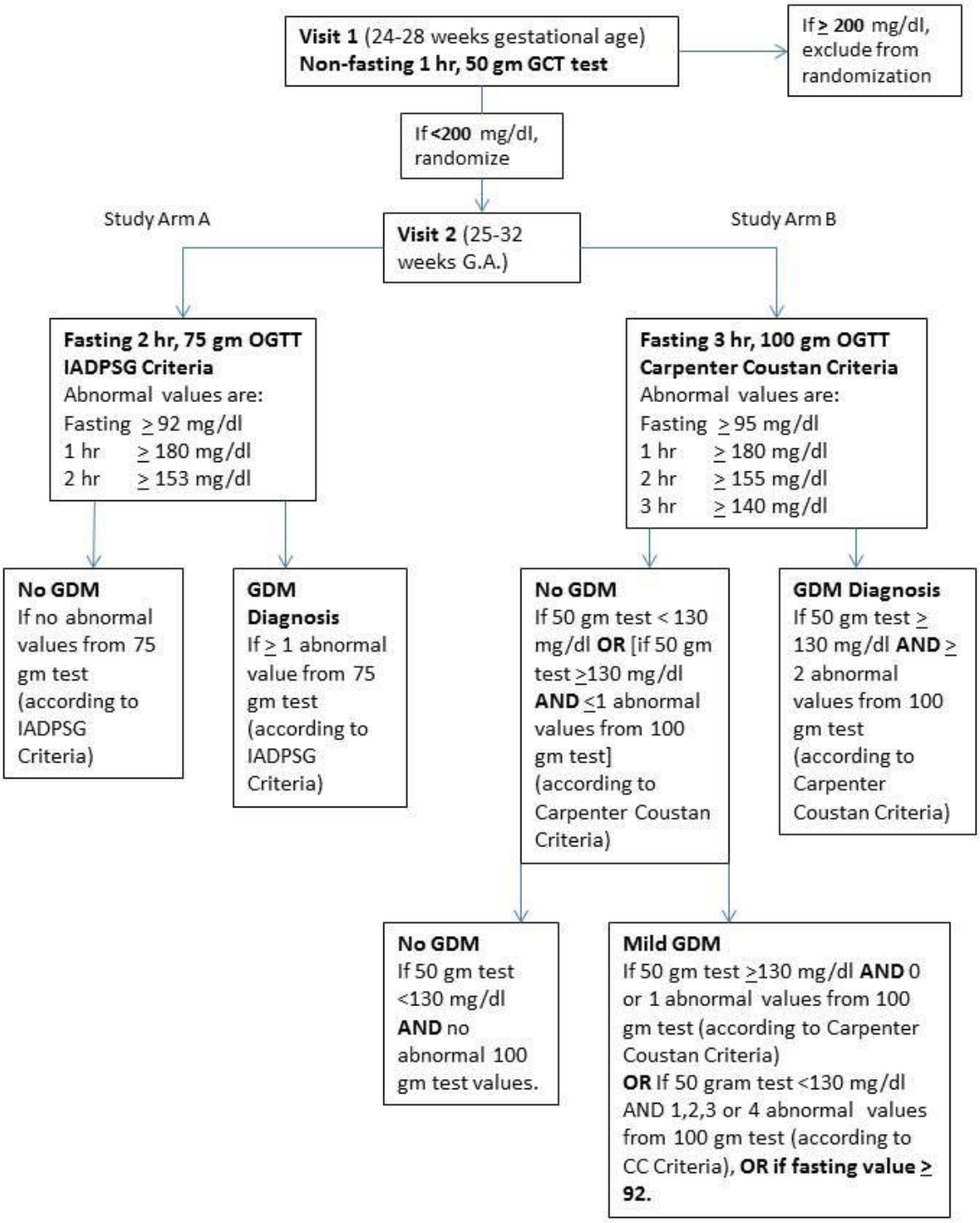
Kristee Rosen is the administrative coordinator for the Center for Research on Health Care (CRHC). She will supervise staff that will assist the study team by providing administrative support with general clerical activities, scheduling and coordinating study-related meetings, and purchasing study supplies.

Study Flow Chart and Randomization Schema



GDM2 Study Timeline (from grant)										
Study Activity/Months	1-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60
Orientation & Start-Up	x									
Finalize IRB	x									
Enrollment		x	x	x	x					
Intervention		x	x	x	x	x	x	x		
Postpartum Follow-up			x	x	x	x	x	x		
Data QA/Cleaning		x	x	x	x	x	x	x	x	
Primary & Secondary Analyses								x	x	x
Publication & Presentations								x	x	x
Study Meetings	x	x	x	x	x	x	x	x	x	x

GDM Diagnostic Criteria



GDM² Study Overview

Table 1: Overview of Data Collection and study visit

Description of Assessments	Phone Screen 18-24 weeks	Visit 1: Baseline 24-28 weeks	Visit 2: 25-32 weeks	Delivery	6-8 weeks post-partum	3 Months	6 Months	9 Months	Visit 3: 1 y post-partum	Physician Input: ongoing
Screen for Eligibility	X									
Consent										
• Verbal	X									
• Written		X								
Questionnaires										
• Pt views			X		X				X	X
• Physician views										
• Health			X						X	
• Dietary recall			X X						X X	
• Infant feeding						X	X	X		
• Health Outcomes						X	X	X		
Lab Tests										
• 50 g GCT		X								
• 2 hr or 3 hr OGTT			X						X	
• Clinical and cytokine			X						X	
• Cord Blood				X						
• Urine pregnancy									X	
Anthropometric:										
• Weight		X							X	
• Height		X							X	
• Caliper measures									X	
• Circumferences									X	
PEAPOD Assessment				X						
EHR Data Abstraction										
• Delivery Data				X						
• Diabetes rescreening rates					X				X	
• Medical and surgical history, labs, and testing		X		X[a]	X[b]				X[c]	

Recruitment Plan

The GDM2 Study's goal is to recruit 920 pregnant women between 18w0d and 28w0d gestation. Participants will be women undergoing care in the following clinics:

- Resident Outpatient Clinic – Red Unit (public)
- Resident Outpatient Clinic – Blue Unit (public)
- Resident Outpatient Clinic – Orange Unit (Midwives; public)
- Resident Outpatient Clinic – Orange Unit (public)
- Resident Outpatient Clinic – Yellow Unit (public)
- Resident Outpatient Clinic – Pink Unit (public)
- Resident Outpatient Clinic – Tan Unit (PAC; public)
- Resident Outpatient Clinic – Tan Unit (Midwives; public)
- OB/GYN Associates of Pittsburgh (private)
- Maternal-Fetal Medicine (private)
- University NIA OB/GYN Associates (private)
- Midwives at Magee (private)
- WomanCare Associates (3 clinics within MWH; private)
- Wiesenfeld-Updike (private)

We will use various recruitment methods, including physician letters, flyers, brochures, the Epic Best Practice Alert (BPA), the Pitt+Me research registry, the MWH electronic message boards, newsletters such as "UPMC Extra", and the University of Pittsburgh's "Read Green", and TrialSpark, which uses social media as a recruitment tool. Recruitment materials can be found in Appendix A.

Magee-Womens Hospital Clinic Recruitment

Provider and Staff Orientation

Before active recruitment begins, provider and staff orientation meetings will be held at the selected obstetrical clinics located at MWH. Drs. Davis and Simhan will present the protocol, explain study procedures, and ask for preferences regarding study participating and relaying results. These orientation meetings will acquaint providers and their staff with the project and will help to promote patient referrals to the study. Study staff will maintain ongoing contact with the selected clinics to keep providers and staff informed on study progress and to address any site-specific issues or problems with study implementation.

In-Clinic Recruitment

Women undergoing care in the selected obstetrical clinics will be considered for enrollment in this study. Contact cards and drop boxes will be placed in several of the selected clinics' waiting rooms. Study staff will collect these cards once a week and follow-up with potential participants by telephone or email.

Potential participants can be pre-screened (informing the individual about the study and collecting their contact information) or screened (informing the individual about the study and completing the 11-item screening questionnaire) during their regular OB visits. If study staff is on-site, clinic staff or providers can ask potential participants if they would be willing to hear about the study. With the patient's permission, study staff will present the study using the same script that is used for telephone screening. If the patient is interested, they can then be screened using the 11-item screening questionnaire. (See Appendix B.) Face-to-face screening will take place in a private area such as an exam room or consult office.

Epic Best Practice Alert

A Best Practice Alert (BPA) within the Epic outpatient record will alert providers when a potential participant is within the gestational age eligibility window and prompt them to ask if the potential participant is interested in participating in the study. If a potential participant is agreeable the BPA will be used to notify study staff, who will then contact them by phone to describe the study and screen them further for eligibility.

Additional Recruitment Methods

Posters, flyers, and brochures (see Appendix A) will be placed in exam rooms, waiting rooms, and restrooms within clinic offices, and on approved bulletin boards throughout MWH for patient self-referral, and to remind clinic staff to refer potential participants to the study. Flyers and brochures will also be distributed in public areas throughout the Pittsburgh metropolitan area, such as the WIC office in downtown. Letters and brochures are put into the new OB packets that are given to patients in the clinics.

A "featured research study" description will be including in the "UPMC Extra" email newsletter that is sent to all UPMC employees, for interested women to self-refer to the study. Similarly, the University of Pittsburgh's "Read Green" email newsletter will also be used to recruit potentially interested employees. A description of the study will be posted on CTSI's Pitt+Me research

registry website for women to self-refer. Pitt+Me also distributes emails that will advertise the study to women who may be eligible based upon demographics and/or participant-chosen health areas of interest. Pitt+Me advertises over multiple social media avenues such as Twitter and Facebook.

Another recruitment avenue through CTSI that will be utilized is the Pediatric PittNet. PittNet is a practice-based research network that works collaboratively with University of Pittsburgh researchers and pediatric primary care practices. Study advertisements will be on their website and message boards located in pediatric offices. PittNet also rotates featured research studies each month, and this study will be added to the rotation to be featured on their website and newsletter.

Digital message boards throughout the UPMC Health System will be used to advertise the study. TV screens at the following UPMC hospitals will display a PowerPoint slide with a brief description of the study and contact information for interested women.

- UPMC Magee-Womens Hospital
- UPMC Children's Hospital of Pittsburgh
- UPMC East
- UPMC McKeesport
- UPMC Mercy
- UPMC Passavant
- UPMC Presbyterian
- UPMC Shadyside
- UPMC St. Margaret

TrialSpark will be used as a recruitment source for the study. It uses advertisements on social media platforms such as Facebook and Twitter to direct interested women to fill out a pre-screening form through TrialSpark's unique GDM2 Study landing page (see Appendix A).

Screening Procedures

Eligibility Criteria

Study staff will contact patients expressing an interesting in study participation in-person or by telephone to determine eligibility. A pre-screening interview will be conducted, where the study will be explained in detail using an IRB-approved script (see Appendix A).

After explaining the study in detail, study staff will ask for verbal consent to administer the screening questionnaire (see Appendix B). Screening information will be entered directly into the study database, which will automatically determine eligibility based on the study's inclusion and exclusion criteria as follows:

Participants are **eligible** to participate if they meet the following criteria:

- Between the ages of 18-45 years of age
- A singleton pregnancy at the time of screening between the gestational ages of 18w0d-28w6d

Participants are **ineligible** to participate if they meet any of the following criteria:

- Pre-existing Type 1 or Type 2 Diabetes Mellitus
- Diabetes diagnosed <24 weeks gestational age
- Multiple gestations (e.g., twins)
- Hypertension, requiring medication
- Corticosteroid (IM, IV, or oral) use in the past 30 days
- Major fetal congenital anomaly
- Anticipated pre-term delivery because of maternal or fetal indications before 34 weeks gestational age
- Inability to complete the glucose testing before 32 weeks gestational age
- Advanced HIV
- Severe liver disease (as indicated by elevated transaminase [AST] and/or alanine transaminase [ALT] values)
- Dumping syndrome as a result of gastric bypass surgery, or other illness/surgery, that preclude them from drinking the glucola solution

Hypertension and Corticosteroid Medications

For hypertension, treatment with low-dose/baby aspirin (LDASA/BASA) is acceptable. If a participant was on hypertension medication before pregnancy but was discontinued in their first trimester, they are eligible to participate.

A participant is still eligible to enter the study if they can complete a 30-day washout period post-corticosteroid use, before completing the Visit 1 appointment within their eligibility window. If it is discovered that a participant was on corticosteroid medications within 30 days of Visit 1, they will not be withdrawn, but the medication use should be documented in the Concomitant Medication Form in the database.

Once a participant has been enrolled in the study, if they start a corticosteroid medication, study staff should try to schedule Visit 2 (or Visit 3) after a 7-day washout period has been completed. If the participant will be out of window, then staff should still schedule the study participant to complete their visit in window. At that visit, staff should document the medication use in the Concomitant Medication Form.

Hypertension medications	**Hypertension medications**	**Corticosteroids (IV, IM, oral)**
Amlodipine	Labetalol	Betamethasone
Atenolol	Lisinopril	Budesonide
Bisoprolol	Losartan	Cortisone
Carvedilol	Methyldopa	Dexamethasone
Diazide	Metoprolol	Hydrocortisone
Diltiazem	Nadolol	Methylprednisolone
Enalapril	Nifedipine	Prednisolone
Furosemide	Triamterine	Prednisone
Hydrochlorothiazide (HCTZ)	Valsartan	

Documentation of Eligibility

If study staff have questions related to a potential participant's eligibility, the option to keep the screening survey open is available in the study database, until the PI or Site PI can be consulted.

Once primary eligibility has been established, study staff will complete a recruitment form, collect the participant's contact information, and verify their gestational age (GA). At this time, the participant will be asked to give their verbal consent for study staff to enter the participant's electronic medical record (EMR) in Epic. After obtaining verbal consent, study staff will verify

gestational age in the participant's EMR, by checking the estimated date of confinement (EDC) and/or dating by ultrasound.

GA will be calculated by the database by the weeks/days from date of the screening time point to the EDC entered into the database. If GA is between 18w0d and 28w6d, the participant is eligible to undergo their 50-gram Glucose Challenge Test (GCT) between 24w0d-28w6d through the GDM2 Study. If the participant's GA is <18w0d, the participant will be placed into a "pending" category and will be re-contacted once they reach 18w0d. NOTE: If a potential participant is <14 weeks upon initial contact, they must be re-screened at 18w0d. Participants whose GA has exceeded 28w6d are ineligible and will be moved to the ineligible category within the database.

Documentation of Study Participation in the EMR or Fax

Once a participant has been screened and agreed to participate in the study, study staff will alert a participant's provider of study participation via fax or the participant's Epic EMR. (See Appendix G for Epic documentation templates.) This is important so that the provider does not order a 50 g GCT outside of the study, which would unblind the provider and participant, making the participant ineligible to participate. Different providers prefer different modes of notification. Desired mode of notification will be addressed a provider/staff orientation meetings and made known to study staff. If a participant's provider prefers fax or cannot be contacted through the Epic EMR system, a completed GDM2 cover sheet and study participation letter (see Appendix A) are to be faxed, and the originals and fax confirmation sheet retained.

Screening Time Point Forms

The following forms are to be completed at the screening time point:

- Screening Survey Form: The screening form determines eligibility according to inclusion and exclusion criteria.
- Recruitment Form: This form records the participant's OB clinic, and where and how they learned about the GDM2 Study. The form also confirms that the participant is interested in study participation and that they have given verbal consent for their EMR to be reviewed to confirm eligibility and GA. Once their EMR number is captured, it is entered into this form and automatically entered into the participant's Medical Record Number (MRN) Capture form.

- Contact Information Form: The contact form captures the participant's name, date of birth (DOB), mailing address, email, telephone number, emergency contact information, and primary care provider information.
- Gestational Age Verification Form: The participant's last menstrual period (LMP) and EDC are entered into this form, which calculates the participant's exact GA based upon the date of form completion. Once GA is established, the scheduled date of 50 g GCT testing can be entered.
- Participant MRN Capture Form: This form will document the participant's medical record numbers in Epic and CERNER, which will facilitate future data abstraction.

The following forms will be used on an *as-needed* basis at the screening time point:

- Protocol Deviation Form: This form is to be used for protocol deviations such as the enrollment of an ineligible participant, or in the rare case of breach of confidentiality.
- Withdrawal and Termination Form: The withdrawal and termination form are to be used in circumstances where the participant is no longer interested in participation, is lost to follow-up (LTFU), or is withdrawn for administrative reasons.

Magee-Womens Hospital Clinical and Translational Research Center

All study visits will take place at the Magee-Womens Hospital Clinical and Translational Research Center (MWH CTRC). The CTRC includes examination rooms, a phlebotomy area, consult and interview rooms, a reception area, and workstations for study staff. Registered nurses and laboratory technicians will assist the study team in administering the glucose testing, monitoring patients for adverse events (AE), and will provide phlebotomy and nursing services.

Study staff will schedule participant visits through the CTSI portal. Initial access to the CTSI scheduling system can be obtained by contacting Cindy Schatzman, CTRC director. Study staff will alert the CTRC of cancelations through the CTSI portal, email, or by phone, as soon as possible.

Visit 1: 50 g GCT

Preparation for Visit 1 (50 g GCT)

Once the participant is screened and determined to be eligible, study staff will:

- Schedule the participant for their Visit 1 (50 g GCT) between 24w0d and 28w6d
- Schedule Visit 1 in the CTSI portal and the GDM2 shared team Outlook calendar
- Prepare paperwork for the visit, to include:
    - Informed consent document
    - CTRC Visit cover sheet
    - Research requisition form for the UPMC Clinical Laboratory Building (CLB), to be sent with the study specimen
- Send the participant an appointment reminder and directions to the MWH CTRC via mail or email (see Appendix A)
- Call, text, or email the participant with an appointment confirmation reminder the day before their scheduled visit
    - Participants should be reminded that they do not have to fast, and that their visit will take approximately 1 hour and 30 minutes

Informed Consent

Upon arrival at the MWH CTRC, the participant will be taken by study staff to a private area where they will undergo the informed consent process. All study procedures, risks, and benefits will be explained in detail and the participant will be asked if they have any questions about the study. The participant will be asked if they understand all the terms of participation, and their comprehension of study concepts will be assessed. Both the participant and study member administering the informed consent process will sign the informed consent document (ICD). Study staff will retain the original ICD to file with participant documentation. Two additional copies of the ICD will be prepared: one will be given to the participant and one will be given to the CTRC director for their records.

50 gram Glucose Challenge Test

After the participant has been consented, study staff will give the participation the 50 gram glucola solution, to be ingested within 5-10 minutes. Once the participant has finished drinking the glucola, she will be provided with a timer set to 55 minutes to remind her when it is time for her blood draw (with a five minute cushion). After the 50 g GCT has been administered, study staff and CTRC staff will monitor and assess the participant for any problems with the testing and treat accordingly. If severe symptoms persist, the Maternal-Fetal Medicine (MFM) fellow on-call will be notified. The MFM fellow will consult Dr. Simhan and a further course of treatment decided. The telephone number for the MFM fellow on-call is 412-641-2862. The PI will be notified and an adverse event (AE) report describing the event will be completed in the database.

After the timer goes off, study staff will escort the participant to the CTRC phlebotomy area for their blood draw by the CTRC phlebotomist or trained study staff. The sample will be pneumatically tubed to the UPMC Clinical Laboratory Building (CLB) for processing.

If the participant is unable to complete the 50 g GCT due to inability to drink the glucola solution, keep the solution down, becomes ill, or other issues arise, another attempt to complete the GCT may be scheduled before 28w6d GA. If participant cannot or does not repeat the test, the patient will be withdrawn from the study and her provider notified so that she may complete her testing through them.

If a participant completes the 50 g GCT but refuses further participation in the study, study staff will withdraw the participant from the study. The participant's provider will be alerted through the EMR or fax (see Appendix G), that their patient has been withdrawn from the study and that

they will be unblinded to the participant's 50 g GCT result. The provider will follow up with their patient.

IV Protocol

The CTRC offers the use of MWH's IV Team for participants that are difficult to draw blood from. The use of the IV Team should be arranged in advance with the CTRC, as the CTRC staff will need to prepare IV supplies and schedule the use of a recliner for the duration of the study visit. Once an IV is placed, the participant will remain in the phlebotomy area for the duration of the visit under the supervision of the CTRC nursing staff. Blood draws will then be completed at the usual intervals by the CTRC nursing staff.

Height and Weight Measurements

The participant's height and weight assessment and demographic form can be completed while the participant waits 60 minutes for their blood draw. Study staff will measure the participant's height and weight. Once these measurements are entered into the database, the database will calculate the participant's body mass index (BMI). The CTRC provides a digital scale to measure weight and a stadiometer to measure height.

Participants will be asked to remove their footwear, outerwear, and other objects that could alter height and weight measurements. The participant will be asked to step onto the scale and stand still over the center of the scale with body weight evenly distributed between both feet, arms hanging freely by the sides of the body with their head up and face forward. Weight will be recorded in pounds.

Height will be measured with the participant having her back straight, heels making contact with the wall. The weight of the participant should be evenly distributed on both feet with her legs together. The stadiometer's movable headpiece will then touch the participant's head (hair pressed down) and height recorded in inches.

Visit 1 Forms

The following study forms are to be completed at Visit 1:

- Enrollment/Written Consent Form: The enrollment form documents the informed consent process and records participant agreement to have lab specimens banked.
- Demographic Form: The demographic form will collect information such as the participant's education level, employment status, and household income, race/ethnicity, and housing situation.
- Baseline Clinical Data: The clinical data form captures the participant's height and weight, and calculates BMI.
- 50gm Lab and Repeat Form: This form captures the date and completion of the 50 g test and prompts a repeat 50 g test, randomization, or notification that the participant is positive for GDM (and notification of their provider). The repeat lab form is to be used in cases where the participant did not complete a 50 g GCT. It captures the date and completion of the repeat lab test and prompts randomization, notification that the participant is positive for GDM and their provider is to be notified, or withdrawal from the study if the participant is unwilling or unable to complete the 50 g testing.
- Randomization Form: This form contains the randomization "button". Once the button is clicked, the form will indicate to which arm the participant has been randomized.

The following forms will be used on an *as needed* basis at Visit 1:

- Protocol Deviation Form: This form is used in the event of a protocol deviation, including but not limited to enrollment of an ineligible participant, failure to report AE/SAE in a timely manner, or breach of confidentiality, administration of wrong dose of glucola, or failure to follow lab procedures.
- Adverse Event Form: The AE form will capture and document all adverse and serious adverse events and will prompt immediate review by the study physician in cases of SAEs. Additionally, this form will facilitate any notice to the DSMB and/or IRB.
- (Concomitant) Medication Form: This form is used in the event that a participant is discovered to be using any medication during a visit, hypertension medications after the first trimester, or corticosteroid medications within a specified window (see *Hypertension and Corticosteroid Medications* in Screening Procedures section).
- Withdrawal and Termination Form: The withdrawal and termination form is used when the participant is no longer interested in participation, is lost to follow-up, or was unable or unwilling to complete the 50 g GCT or repeat GCT.

Completing Visit 1

Once the blood draw and all other Visit 1 procedures have been completed, study staff will issue the participant $10.00 in compensation on a University-issued payment card, plus a parking voucher for MWH or $5.00 for transportation reimbursement. If the $5.00 in transportation reimbursement is issued, this is to be issued separately as an expense reimbursement (nontaxable). Study staff will schedule Visit 2 before the participant leaves the CTRC. Staff will relay to the participant that if their 50 g GCT results come back with a value of 200 mg/dL or above, making them ineligible for the study, the participant and their provider will be informed. Study staff will write a progress note documenting Visit 1.

Visit 1 Results

The UPMC CLB should return the patient's results via fax within 1-2 business days of the visit. Once the results are received, study staff will enter the glucose results into the study database. If the glucose value is <200 mg/dL, the participant will be randomized by the database into either the 75 gram or 100 gram Oral Glucose Tolerance Test (OGTT) study arms (see *Randomization* section for procedure). Study staff will write a progress note documenting the participant's GCT result and randomization result.

Critical Glucose Values

If a participant's blood glucose values are critical, indicating hypoglycemia (<55 mg/dL) or hyperglycemia (>250 mg/dL), the UPMC CLB will follow clinical procedure for clinical values by performing a repeat or verification test. If glucose values remain critical after the confirmatory test, study staff will be contacted by the UPMC CLB with the results and follow up with the participant. If participant is non-symptomatic and the database determines the glucose value to be a Severe Adverse Event, Dr. Davis is to be notified. For participants who exhibit symptoms of hypo/hyperglycemia, the Maternal-Fetal Medicine fellow on call is to be contacted at 412-641-2862 for consultation. Dr. Simhan will also be notified. These events will be documented in the participant's progress notes and in the Adverse Event form.

Glucose Challenge Test Results ≥200 mg/dL

If a participant's blood glucose result value is ≥200 mg/dL, they will be excluded from the study because they will be diagnosed with diabetes. Both the participant and her provider will be

unblinded to the value. Study staff will enter an information encounter in Epic or fax a letter with this information to non-Epic providers to relay the abnormal result so that appropriate treatment can be initiated (see Appendix G). The provider may also be contacted by telephone. The study physician will call the participant with their diagnosis and let them know that their provider will be following up with them with a treatment plan.

Randomization Procedures

If the participant's 50 g GCT is less than 200 mg/dL, they are randomized to Arm A (75 g OGTT) or Arm B (100 g OGTT) by the randomization form. Once the glucose value from the 50 g GCT is entered and submitted into the database, study staff will open the randomization form in the database. The randomization form displays a "button", which will then be clicked to randomize the participant to Arm A or Arm B. All baseline measures must be completed and entered into the database and Visit 1 closed out before randomization can be completed. Study participants are to be remain blinded to their randomized study arm until they arrive at the MWH CTRC for their Visit 2. When Visit 2 is scheduled, participants will be told that the randomization visit will take approximately 3.5 hours so as not to unblind them. The rationale for blinding participants to their study arm is preventing dropout based on the knowledge that they have been randomized to the longer test (i.e., 3 hour 100 g OGTT).

Blinding

Providers are blinded to which test their patient completed and the patient's numerical test results. Study staff will notify providers as to whether or not their patient has GDM; they will not be told the specific glucose values. Providers will administer care based on the reported diagnoses. Study investigators, including the PI, will remain blinded to the randomization schema and study outcomes until the completion of the study. The PI or co-investigators will only be unblinded in the following cases:

- 50 g glucose value of ≥200 mg/dL
- 100 g OGTT fasting value >105 mg/dL or 2 hour value >200 mg/dL, if 50 g GCT >130 mg/dL
- Any severe adverse event that warrants further medical intervention
- Symptomatic reactive hypoglycemia (<55 mg/dL)

Visit 2: 75 g or 100 g OGTT

Preparation for Visit 2 (75 g or 100 g OGTT)

Once the participant has been randomized, study staff will:

- Schedule Visit 2 in the CTSI portal and the GDM2 shared team Outlook calendar
- Prepare paperwork for the visit, to include:
    - CTRC Visit cover sheet
    - Research requisition forms for the UPMC Clinical Laboratory Building (CLB), to be sent with the study specimens
    - Visual aids and instructions for 24-hour dietary recall telephone visit (see Appendix D)
- Send the participant an appointment reminder and directions to the MWH CTRC via mail or email (see Appendix A)
- Call, text, or email the participant with an appointment confirmation reminder the day before their scheduled visit
    - Participants should be reminded to fast for 8 hours beforehand, and that their visit will take up to 3.5 hours

75 g or 100 g Oral Glucose Tolerance Test

Participants will arrive at the MWH CTRC for their Visit 2 in a fasting state. Visit 2 will preferably be scheduled in the morning such that participants will not need to wait an extended period of time to eat. This visit should not be scheduled after 11:30 am due to extended fasting time and the hours of the CTRC staff. Study staff will verbally confirm with the participant that they have fasted from food, drink (except water), chewing gum, and tobacco for the previous 8 hours.

Upon arrival to the CTRC, study staff will escort the participant to the phlebotomy area for their blood draw by the CTRC phlebotomist or trained study staff. The sample will be pneumatically tubed to the UPMC Clinical Laboratory Building (CLB) for processing. The fasting blood draw must be obtained before the glucola is given to the participant.

The study staff will confirm the participant's randomization group to verify that the participant receives the correct glucola. Once a participant's randomization assignment has been verified, the participant will receive their glucola from the study staff, which should be ingested within 5-

10 minutes. After the glucola has been ingested, the participant will be given a digital time to set for 55 minutes to remind them of their next blood draw.

Study staff will monitor time in between blood draws and escort the participant to the phlebotomy area for their blood draws at the appropriate time intervals. Participants undergoing the 75 g test will have their blood drawn at the 1 hour mark and 2 hour mark, for a total of 3 blood draws (including fasting blood draw). Participants undergoing the 100 g test will have their blood drawn at the 1 hour, 2 hour, and 3 hour marks, for a total of 4 blood draws (including fasting blood draw). During the course of Visit 2, study staff and the CTRC staff will monitor and assess the participant for any problems with the testing and treat accordingly. If severe symptoms from the test persist, the Maternal-Fetal Medicine fellow on call will consult with Dr. Simhan. The telephone number for the MFM fellow on call is 412-641-2862.

IV Protocol

The CTRC offers the use of MWH's IV Team for participants that are difficult to draw blood from. The use of the IV Team should be arranged in advance with the CTRC, as the CTRC staff will need to prepare IV supplies and schedule the use of a recliner for the duration of the study visit. Once an IV is placed, the participant will remain in the phlebotomy area for the duration of the visit under the supervision of the CTRC nursing staff. Blood draws will then be completed at the usual intervals by the CTRC nursing staff.

Completion of Study Questionnaires

Between blood draws, participants will complete Visit 2 study questionnaires and a 24-hour dietary recall on a study iPad. (Note: The Baseline GDM Beliefs questionnaire is to be administered at the end of the visit, after all questionnaires and blood draws are completed, as this questionnaire assesses how participants felt about the whole of their GDM testing.) After the participant receives their last blood draw, they will be provided with a light snack supplied by the CTRC.

Visit 2 Forms

The following study forms will be completed at Visit 2 (see Appendix B):

- 24-Hour Dietary Recall: This form is a placeholder in the study database, prompting study staff to mark if the assessment was completed or reason for non-completion.

- 24 Hour Dietary Recall Telephone: This form is a placeholder in the study database, prompting study staff to mark if the assessment was completed or reason for non-completion. The second recall should be completed with participants over the phone at a random time, no earlier than 1 week after the visit and up to 4 weeks post-visit.
- Mood Questionnaire: This form captures information regarding general wellbeing, physical health, and thoughts and feelings regarding pregnancy.
- Postpartum Depression Questionnaire: This form assesses signs and symptoms of depression. This is a scored questionnaire, with a score of 13 or higher indicating the likely presence of depression. For a score of 13 or higher, or any answer besides "Never" for question #10 ("The thought of harming myself has occurred to me"), appropriate actions will be taken and clinical staff notified (see *Postpartum Depression Questionnaire* section above).
- Health Habits Questionnaire: This form queries participants about their sleep schedule; exercise habits before and during pregnancy; tobacco, alcohol, and drug use before and during pregnancy; and eating habits.
- Obstetrical History Questionnaire: This form collects general obstetrical history, including menstrual cycle, birth control, pre-pregnancy weight, and the outcomes of previous pregnancies (if applicable).
- Family Health History Questionnaire: This form captures the participant's family history of diabetes and weight/body type.
- 75gm or 100gm Fasting Glucose Lab Form: This form will capture the date and time of blood collection and processing completion, and the date the study staff received the results. It will record 2 hourly values or 3 hourly vales depending on whether the participant was randomized to the 75 g or 100 g test. In cases where the participant was not able to complete the first scheduled test but returned for a second attempt, a repeat lab form will be generated. This will capture the completion date and values of the repeat test. Regardless of a positive or negative diagnosis, the form will prompt study staff to record that they notified the participant and her provider of the results. If the test was not completed, the reason for non-completion will be recorded.
- Clinical and Cytokine Lab Form: The clinical lab form will document the date and time of blood collection, the date and time of specimen processing, and the date the study staff received the results. Values for fasting glucose, insulin, lipid panel, and high-sensitivity c-reactive peptide (hsCRP) are recorded on this form.
- Baseline Patient Beliefs Questionnaire: This form, to be administered after the rest of Visit 2 has been completed, will ask participants about their experience and personal perspectives on screening for GDM.

The following forms will be used on an *as needed* basis at Visit 2:

- Protocol Deviation Form: This form is used in the event of a protocol deviation, including but not limited to enrollment of an ineligible participant, failure to report AE/SAE in a timely manner, breach of confidentiality, administration of wrong dose of glucola, or failure to follow lab procedures.
- Adverse Event Form: The AE form will capture and document all adverse and serious adverse events and will prompt immediate review by the study physician in cases of SAEs. Additionally, this form will facilitate any notice to the DSMB and/or IRB.
- (Concomitant) Medication Form: This form is used in the event that a participant is discovered to be using any medication during a visit, hypertension medications after the first trimester, or corticosteroid medications within a specified window (see *Hypertension and Corticosteroid Medications* in Screening Procedures section).
- Withdrawal and Termination Form: The withdrawal and termination form is used when the participant is no longer interested in participation, is lost to follow-up, or was unable or unwilling to complete Visit 2 or a repeat test.

Postpartum Depression Questionnaire

After the participant has completed their study questionnaires (except the Baseline GDM Beliefs questionnaire), study staff will review the forms for completeness and review the Postpartum Depression questionnaire score. If the participant scores 13 or higher, or answers question 10 ("The thought of harming myself has occurred to me") with any response other than "Never", study staff will contact the participant's OB to notify them and offer mental health resources to the participant.

In extreme cases, where the threat of self-harm is evident, the participant is to be sent to the MWH emergency department (ED) for immediate treatment. Drs. Davis and Simhan are to be immediately notified and Dr. Simhan will follow up with the patient to determine the outcome of the ED evaluation. In these extreme cases, a Severe Adverse Event form will be completed.

Completing Visit 2

Once the blood draws and all other Visit 2 procedures have been completed, study staff will issue the participant $30.00 in compensation on a University-issued payment card, plus a parking voucher for MWH or $5.00 for transportation reimbursement. If the $5.00 in transportation reimbursement is issued, this is to be issued separately as an expense reimbursement

(nontaxable). Study staff will tell the participant to expect a telephone call the following business day with the results of their OGTT. Study staff will also give the participant instructions and visual materials to complete the second 24-hour dietary recall, which will occur randomly within the following 2 weeks. The participant will be told that they will be paid $10.00 to their payment card after the second recall has been completed. Study staff will document Visit 2 in the participant's progress notes.

75 g or 100 g OGTT Laboratory Results

The UPMC Clinical Laboratory will relay glucose and clinical lab results to study staff via fax within one to two business days. Clinical labs (lipid panel, high-sensitivity c-reactive peptide, and insulin) and glucose values will then be entered into the database, which will make the diagnosis of GDM based on criteria for the respective OGTT tests.

Diagnostic criteria of GDM differs between Arm A (75 g OGTT) and Arm B (100 g OGTT) as follows:

Participants randomized to Arm A (75 g OGTT) will be diagnosed under <u>IADPSG</u> criteria. A positive GDM diagnosis under IADPSG criteria is ≥1 abnormal value from the 75 g test:

Fasting glucose value	1 hour glucose value	2 hour glucose value
≥92 mg/dL	≥180 mg/dL	≥153 mg/dL

Participants randomized to Arm B (100 g OGTT) will be diagnosed under <u>Carpenter-Coustan</u> criteria. A positive GDM diagnosis under Carpenter-Coustan criteria is 50 g GCT ≥130 mg/dL (value from Visit 1) <u>and</u> ≥2 abnormal values from the 100 g test:

Fasting glucose value	1 hour glucose value	2 hour glucose value	3 hour glucose value
≥95 mg/dL	≥180 mg/dL	≥155 mg/dL	≥140 mg/dL

"Mild GDM"

For the purposes of study outcomes, the study database will automatically designate participants completing the 100 g OGTT (Arm B) that meet one of the three criteria listed below as "Mild GDM".

1. 50 g GCT ≥130 mg/dL **and** 0 or 1 abnormal values from 100 g OGTT (by Carpenter-Coustan criteria)
2. 50 g GCT <130 mg/dL **and** 1, 2, 3, or 4 abnormal values from 100 g OGTT (by Carpenter-Coustan criteria)
3. 100 g OGTT fasting value ≥92 mg/dL

This is **not** a clinical diagnosis, and participants meeting these criteria will be reported to providers as having a negative GDM diagnosis as they would not have been diagnosed under current clinical criteria. For the purposes of this study, all participants designated as having "Mild GDM" will be selected to return for Visit 3 at 12-months postpartum.

Unblinding Providers to OGTT Results

If a participant's 50 g GCT value is ≥130 mg/dL, and their 100 g OGTT fasting value is ≥105 mg/dL or 2 hour value is ≥200 mg/dL, their provider will be unblinded to their results for ethical and safety reasons, so treatment for GDM can be initiated. These participants would not normally be diagnosed in clinical practice because they had a normal 50 g GCT. These safety thresholds were used in the HAPO Study (Metzger, BE, et al., *N Engl J Med* 2008). Study staff will alert the participant's provider of their results through Epic (or fax for Epic non-users). The study physician will also notify participants via telephone.

Critical Glucose Values

If a participant's blood glucose values are critical, indicating hypoglycemia (<55 mg/dL) or hyperglycemia (>250 mg/dL), the UPMC CLB will follow clinical procedure for clinical values by performing a repeat or verification test. If glucose values remain critical after the confirmatory test, study staff will be contacted by the UPMC CLB with the results and follow up with the participant. If participant is non-symptomatic and the database determines the glucose value to be a Severe Adverse Event, Dr. Davis is to be notified. For participants who exhibit symptoms of hypo/hyperglycemia, the Maternal-Fetal Medicine fellow on call is to be contacted at 412-641-2862 for consultation. Dr. Simhan will also be notified. These events will be documented in the participant's progress notes.

OGTT Result Reporting

Participants will be notified of their 75 g or 100 g OGTT results within 1 or 2 business days of testing. Study staff will notify participants of a negative diagnosis by telephone or letter. In cases of positive GDM diagnosis, study staff will notify the study physician, who will directly call the participant with her diagnosis, answer any questions, and relay that she is to follow up with her provider for treatment. The participant's providers will be notified via Epic letter and encounter or a fax, informing them of the positive or negative GDM diagnosis. Study staff will also document results and notifications in the participant's progress notes. Epic encounters and letters are from Dr. Simhan, Department of Maternal-Fetal Medicine, routed to the participant's OB provider. (See Appendix G.)

Visit 2 Results Back Entry

Once all participants have completed their Visit 2 and delivered, study staff will back-enter all Visit 2 glucose results into participants' Epic EMR for clinical use post-study. At this time, providers will be unblinded to the specific numeric results of their patients' testing, and whether they completed the 75 g or 100 g OGTT. Participants may also request that a paper copy of their results be sent to them after they deliver.

Delivery Time Point

Cord Blood Collection

The study staff will maintain an ongoing list of participants who have completed their randomization visit and are approaching their Estimated Date of Confinement (EDC). The list will facilitate the collection of umbilical cord blood samples and infant assessment at delivery by Obstetric Specimen Procurement Unit (OSPU) staff and study staff. Study staff will provide an updated list on a monthly basis to the OSPU staff so that the procurement team is aware of which patients are in the study and their anticipated delivery dates. OSPU staff and study staff will also use Augr, a clinical application, which sends notifications when study participants have been admitted to MWH. (See *Laboratory Procedures and Protocols* section for additional information regarding cord blood collection procedures.)

If OSPU staff know a participant is in a labor and delivery room (LDR), they will leave blood tubes for the LDR nurses to collect study specimens. LDR nurses have been instructed where to find GDM2 delivery collection packets in the OSPU office if a participant is admitted to LDR and OSPU staff are not available. Some cord blood samples may not be obtained if a participant delivers when OSPU staff is unavailable. OSPU does not collect specimens during obstetric emergencies or precipitous deliveries, etc.

Infant Skinfold Measurement

A flank skinfold measurement will be obtained on infants 24-48 hours after delivery. Study staff will obtain the skinfold measurements during regular business hours of 8:30 am to 5:00 pm, Monday through Friday, and occasional Saturdays. Study staff will visit participants in their postpartum room, where they will also give the participant their delivery gift. The flank skinfold is a diagonal fold taken just above the iliac crest along the midaxillary line. At least two measurements should be obtained with the skinfold calipers. The time of the measurements should also be recorded on a paper infant skinfold assessment form. Staff will then enter this information into the study database.

Some skinfold measurements will not be able to be obtained if a participant delivers or the infant reaches 24-48 hours on a weekend or holiday when staff are unavailable, or if the parents refuse the measurements. Not all infants will be clinically able to undergo skinfold assessment.

Exclusion criteria for the skinfold assessment are as follows:

- Infant admission to the NICU
- Cannot pass "car seat test"
- Infant requires external warming
- <35 weeks of gestational age

Delivery Time Point Forms

The following forms are to be completed at the delivery time point:

- Delivery Cord Blood Collection for C-Peptide Form: This form will collect the date and time of cord blood collection, date and time of processing, type and amount of specimen collected, and record the c-peptide value.
- Delivery Infant Assessment Form: This form will record the date, time, and completion of the infant skinfold measurements, If the assessment was not completed, reason for non-completion will be recorded.
- Infant Medical Record Number Form: This form will document the infant's medical record number for purposes of data abstraction. Study staff will collect the MRN from the infant's EMR.

The following forms will be used on an *as needed* basis at the delivery time point:

- Protocol Deviation Form: This form is used in the event of a protocol deviation, including but not limited to deviation from the cord blood collection or infant skinfold assessment protocols, or a breach of confidentiality.
- Withdrawal and Termination Form: The withdrawal and termination form is used when the participant is no longer interested in participation, is lost to follow-up, or can no longer participate in the study.

Physician Beliefs Questionnaire

The Physician Beliefs Questionnaire will be used to assess providers' views on current GDM testing strategies. An electronic RedCap survey will be sent via email to providers within the clinics the study recruited from, once all study participants have delivered.

Postpartum Telephone Encounters

Those participants with a positive diagnosis of GDM, study diagnosis of "mild GDM", and a random group without GDM, will be followed by study staff through telephone assessments at 3, 6, and 9 months postpartum. These participants will also complete Visit 3 at 12 months postpartum. Those participants identified as "true normal" or participants without GDM are randomly selected for this postpartum follow-up by programming sequences within the study database, created by the data center. After the delivery time point is closed out in the study database, the study database will indicate to study staff whether that specific participant has been selected for postpartum follow-up.

3, 6, and 9 Month Postpartum Phone Calls

The window to complete the 3, 6, and 9 month postpartum phone calls starts two weeks before the "target date" and ends 4 weeks after the "target date". Example: If a participant delivers on 12/1/2017, her 3 month "target date" is 3/1/18, and her window to complete the 3 month phone assessment is 2/15/18 to 3/29/18.

Study staff will administer the phone assessments, which collect basic information regarding the overall health and wellbeing of participants and their infant feeding practices. These phone encounters are also designed to keep study staff in contact with participants in between the delivery and Visit 3 (12 months postpartum) time points. Through continuing contact, participants may be more likely to participate in the 12 month postpartum follow-up and the study staff will be able to document participant health status or changes in contact information.

3, 6, and 9 Month Postpartum Forms

The following forms are to be completed at the 3, 6, and 9 month postpartum time points:

- Health Outcomes Form: This form queries participants about visits to the emergency department, hospitalizations, contraception, pregnancy, or any new information regarding their and their baby's health.
- Infant Feeding Questionnaire: This form captures basic information regarding breastfeeding, formula feeding, and solid food feeding. The form also captures the infant's height, weight, and general health in the previous 3 months.

The following forms will be used on an *as needed* basis at the 3, 6, and 9 month postpartum time points:

- Protocol Deviation Form: This form is used in the event of a protocol deviation, including but not limited to a breach of confidentiality.
- Infant Status Form: This form is used to document any notable changes in the infant's status or custody situation (e.g., death, adoption, loss of custody, hospitalization, etc.)
- Withdrawal and Termination Form: The withdrawal and termination form is used when the participant is no longer interested in participation, is lost to follow-up, or can no longer participate in the study.

Visit 3: 12 Months Postpartum

Those study participants selected to complete the 3, 6, and 9 month postpartum follow-up encounters will be asked to return for a follow-up 75 g OGTT assessment at 12 months postpartum (Visit 3), to be tested for impaired glucose tolerance ("pre-diabetes") or Type 2 diabetes mellitus.

The target window for Visit 3 is between 11 and 14 months postpartum. Participants may choose to schedule the infant assessment portion and the 75 g OGTT at separate times/dates within the Visit 3 target window.

Preparation for Visit 3

Once a participant has been scheduled for her Visit 3, study staff will:

- Schedule Visit 3 in the CTSI portal and the GDM2 shared team Outlook calendar
- Prepare paperwork for the visit, to include:
    - CTRC Visit cover sheet
    - Research requisition forms for the UPMC Clinical Laboratory Building (CLB), to be sent with the study specimens
    - Infant assessment form
    - Visual aids and instructions for 24-hour dietary recall telephone visit (see Appendix D)
- Send the participant an appointment reminder and directions to the MWH CTRC via mail or email (see Appendix A)
- Call, text, or email the participant with an appointment confirmation reminder the day before their scheduled visit
    - Participants should be reminded to fast for 8 hours beforehand, and that their visit will take 2.5 hours

Study staff will review the medical records of participants diagnosed with GDM to determine whether they completed postpartum glucose testing (75 g OGTT, A1c, etc.). If a participant has been diagnosed with prediabetes or diabetes before Visit 3, they will not complete the 75 g OGTT at Visit 3 but will still have their fasting blood draw.

75 g Oral Glucose Tolerance Test

Participants will arrive at the MWH CTRC in a fasting state. The visit will preferably be scheduled in the morning such that participants will not wait an extended period of time to eat. This visit should not be scheduled after 12:30 pm due to extended fasting time and the hours of the CTRC staff. Study staff will verbally confirm with the participant that they have fasted from food, drink (except water), chewing gum, and tobacco for the previous 8 hours. Staff will also verbally re-consent the participant by reviewing Visit 3 procedures and ensuring the participant's agreement to continue participation in the study. This verbal re-consent will be documented in the participant's progress notes.

Study staff will then escort the participant to the phlebotomy area for their blood draw by the CTRC phlebotomist or trained study staff. The sample will be pneumatically tubed to the UPMC Clinical Laboratory Building (CLB) for processing. The fasting blood draw must be obtained before the glucola is given to the participant.

Once the fasting blood draw has been completed, the participant will receive their glucola from the study staff, which should be ingested within 5-10 minutes. After the glucola has been ingested, the participant will be given a digital time to set for 55 minutes to remind them of their next blood draw.

Study staff will monitor time in between blood draws and escort the participant to the phlebotomy area for their blood draws at the appropriate time intervals. Participants will have their blood drawn at the 1 hour mark and 2 hour mark, for a total of 3 blood draws (including fasting blood draw). During the course of Visit 3, study staff and the CTRC staff will monitor and assess the participant for any problems with the testing and treat accordingly. If severe symptoms from the test persist, the Maternal-Fetal Medicine fellow on call will consult with Dr. Simhan. The telephone number for the MFM fellow on call is 412-641-2862.

IV Protocol

The CTRC offers the use of MWH's IV Team for participants that are difficult to draw blood from. The use of the IV Team should be arranged in advance with the CTRC, as the CTRC staff will need to prepare IV supplies and schedule the use of a recliner for the duration of the study visit. Once an IV is placed, the participant will remain in the phlebotomy area for the duration of the visit under the supervision of the CTRC nursing staff. Blood draws will then be completed at the usual intervals by the CTRC nursing staff.

Visit 3 Forms

The following forms are to be completed at Visit 3:

- 24-Hour Dietary Recall: This form is a placeholder in the study database, prompting study staff to mark if the assessment was completed or reason for non-completion.
- 24 Hour Dietary Recall Telephone: This form is a placeholder in the study database, prompting study staff to mark if the assessment was completed or reason for non-completion. The second recall should be completed with participants over the phone at a random time, no earlier than 1 week after the visit and up to 4 weeks post-visit.
- 75gm Fasting Glucose Lab Form: This form captures the date and completion of the 75 g test and determines if a participant is positive for diabetes or prediabetes (and if their physician is to be notified). If the test needs to be repeated, this form captures the repeat testing information.
- Clinical and Cytokine Form: This form documents the date and time of blood collection, the date and time of specimen processing, and the date that the study team received the results. Values for fasting glucose, insulin, lipid panel, A1c, and cytokines including hsCRP, adiponectin, leptin, and free fatty acids are recorded on this form.
- Postpartum Depression Questionnaire: This form assesses signs and symptoms of depression. This is a scored questionnaire, with a score of 13 or higher indicating the likely presence of depression. For a score of 13 or higher, or any answer besides "Never" for question #10 ("The thought of harming myself has occurred to me"), appropriate actions will be taken and clinical staff notified.
- Health Outcomes Form: This form asks participants about visits to the ED, hospitalizations, and any new information regarding their or their baby's health.
- Infant Feeding Questionnaire: This form asks questions regarding breastfeeding, formula feeding, and solid food feeding, height, weight, and general health over the last 3 months.
- Health Since Birth Questionnaire: This form captures the participant's health and weight since they delivered.
- 12-Month Mood Questionnaire: This form captures information regarding general wellbeing, physical health, and thoughts and feelings in the past month.
- 12-Month Health Habits Questionnaire: This form queries participants regarding their general health and wellbeing, including sleep and exercise habits, and information regarding weight gain and loss postpartum.
- Urine Pregnancy Test Form: This form confirms that the urine pregnancy test has been completed and records positive/negative result.
- Clinical Data Form 12-Month Visit: The clinical data form captures the participant's weight and calculates BMI using their height obtained at Visit 1.

- Infant Assessment Form: This form captures the infant's length, weight, head circumference, and skinfold caliper assessments.

The following forms will be used on an *as needed* basis at Visit 3:

- Confirmation of DM Testing: This form will document that study staff reviewed the participant's EMR for postpartum glucose testing, and the results if available.
- Protocol Deviation Form: This form is used in the event of a protocol deviation, including but not limited to failure to report AE/SAE in a timely manner, breach of confidentiality, administration of wrong dose of glucola, or failure to follow lab procedures.
- Infant Status Form: This form is used to document any notable changes in the infant's status or custody situation (e.g., death, adoption, loss of custody, hospitalization, etc.)
- (Concomitant) Medication Form: This form is used in the event that a participant is discovered to be using any medication during a visit, or corticosteroid medications within a specified window (see *Hypertension and Corticosteroid Medications* in Screening Procedures section).
- Adverse Event Form: The AE form will capture and document all adverse and serious adverse events and will prompt immediate review by the study physician in cases of SAEs. Additionally, this form will facilitate any notice to the DSMB and/or IRB.
- Withdrawal and Termination Form: The withdrawal and termination form is used when the participant is no longer interested in participation, is lost to follow-up, or was unable or unwilling to complete Visit 2 or a repeat test.

Visit 3 Questionnaires and Assessments

Between blood draws, participants will complete Visit 3 study questionnaires and a 24-hour dietary recall on a study iPad. After the participant receives their last blood draw, they will be provided with a light snack supplied by the CTRC.

All participants will undergo a urine pregnancy test, as approximately 5% of women are expected to become pregnant by the 12 month postpartum visit. Pregnancy is likely to change the participant's metabolic profile, including glucose values. Pregnant participants may choose to complete the 75 g test at their own discretion. Study staff will offer the option of sending the 75 g OGTT results to their OB providers, which may be used in lieu of a standard clinical 50 g GCT (at their provider's discretion). For pregnant participants who choose this option, results will be evaluated according to IADPSG criteria and routed to their OB provider.

Infants will undergo anthropometric measurements at Visit 3 using the MetroHealth Medical Research Unit protocol found in Appendix E. The study staff will be trained to administer these measurements, which will include length/height, weight, head circumference, and skinfold caliper assessments of the infant's triceps, subscapular area, and flank.

Postpartum Depression Questionnaire

After the participant has completed their study questionnaires, study staff will review the forms for completeness and review the Postpartum Depression questionnaire score. If the participant scores 13 or higher, or answers question 10 ("The thought of harming myself has occurred to me") with any response other than "Never", study staff will check in with the participant to ensure that their providers are aware and offer mental health resources to the participant. If the participant agrees, study staff will notify the participant's provider of their depression screening via Epic.

In extreme cases, where the threat of self-harm is evident, the participant is to be sent to the MWH emergency department (ED) for immediate treatment. Drs. Davis and Simhan are to be immediately notified and Dr. Simhan will follow up with the patient to determine the outcome of the ED evaluation. In these extreme cases, a Severe Adverse Event form will be completed.

Completing Visit 3

Once the blood draws and all other Visit 3 procedures have been completed, study staff will issue the participant $30.00 in compensation on a University-issued payment card, plus a parking voucher for MWH or $5.00 for transportation reimbursement. If the $5.00 in transportation reimbursement is issued, this is to be issued separately as an expense reimbursement (nontaxable).

Study staff will tell the participant to expect a telephone call the following business day with the results of their testing. Study staff will also give the participant instructions and visual materials to complete the second 24-hour dietary recall, which will occur randomly within the following 2 weeks. The participant will be told that they will be paid $10.00 to their payment card after the second recall has been completed. Study staff will document Visit 3 in the participant's progress notes.

After Visit 3, the study staff or investigators may contact the participant by phone, letter, or email, for clarifications of any missing, discrepant, or unclear information reported on the data collection forms or abstracted from their EMR, if necessary.

Visit 3 Laboratory Results

The UPMC Clinical Laboratory will relay glucose and clinical lab results to study staff via fax within one to two business days. Clinical labs (lipid panel, high-sensitivity c-reactive peptide, insulin, and HgbA1c) and glucose values will then be entered into the database, which will make the diagnosis of prediabetes (impaired glucose tolerance) or Type 2 diabetes, based on the **current American Diabetes Association (ADA) criteria**, which are as follows: **A diagnosis of Type 2 diabetes will be made if ≥1 values are abnormal:**

Fasting glucose value	**1 hour glucose value**	**2 hour glucose value**
≥126 mg/dL	*Not used for diagnosis*	≥200 mg/dL

A diagnosis of impaired glucose tolerance (prediabetes) will be made if ≥1 values are within the following ranges:

Fasting glucose value	**1 hour glucose value**	**2 hour glucose value**
100-125 mg/dL	*Not used for diagnosis*	140-199 mg/dL

The database will also indicate elevated lipid values, of which the participant will be notified by the PI:

Triglycerides	**Cholesterol**
≥200 mg/dL	≥160 mg/dL

If their results indicate diabetes or prediabetes, participants will be notified of their results by a study physicians and told to follow up with their primary care provider for treatment. A letter and informational encounter will be entered into the participant's Epic EMR or faxed to Epic non-users to inform providers of the diagnosis. A paper copy of the results will also be mailed to the participant for her personal records. (See Appendix G.)

If the participant's results are negative for diabetes, prediabetes, or elevated lipids, study staff will call the participant to inform her of her non-diagnosis. A paper copy of the result will be mailed to the participant for her personal records. (See Appendix G.)

Visit 3 Results Back Entry

Once all participants have completed their Visit 3, study staff will back-enter Visit 3 glucose and A1c results into participants' Epic EMR for providers' reference. For participants whose results indicate pre-diabetes or Type 2 diabetes mellitus, their glucose and A1c results will be entered into their Epic EMR immediately and routed to their primary care providers. Paper hard copies of the full results will also be sent to participants for their personal records.

Quest Diagnostics Visit

If a participant is unable to return to MWH to complete her Visit 3, the study may offer participants the option to complete their Visit 3 at a Quest Diagnostics location convenient to them. At Quest Diagnostics, they will complete a 75 g OGTT, pregnancy test, and have their weight measured, all identically to the procedures that would have been undertaken at MWH. If a participant completes their Visit 3 at a Quest Diagnostics location, it is preferable that the questionnaires are completed on the same day as testing. The only assessments that study staff would be unable to obtain are the anthropometric infant measurements.

If a participant agrees to complete Visit 3 at a Quest Diagnostics location, study staff will mail them a prefilled laboratory requisition and instructions. The requisition will use the participant's study ID and DOB only (no other identifying information such as name) and instruct Quest Diagnostics staff to bill the GDM2 account. Results will be faxed to the GDM2 office, similarly to the UPMC lab's results, and staff will inform the participant of her results per usual protocol. Once the results are received, study staff will issue payment for Visit 3 to the participant. The payment will be the same as if the participant had returned to MWH for her visit ($30.00, and parking validation or $5.00 for transportation reimbursement).

Data Abstraction

Health Research Record Request (R3)

The Health Research Record Request (R3) team is a single point-of-contact for researchers to request access to components of UPMC-based electronic medical records for research purposes. The GDM2 Study will work with the R3 team to facilitate data abstraction for independent out outcome variables and covariates from the participants' maternal and neonatal EMR. The research team will follow-up with the entire maternal and infant pair cohort with the assistance of the R3 team. Variables will be selected and requested by the PI.

R3 Data Collection

Once written consent is provided and the participant completes the first study visit, at least one prenatal and two postpartum EHR data abstractions of their records will be conducted. R3 staff will abstract information at various time points of the GDM2 Study. The following data will be collected:

- General demographic information will be collected, including maternal age, race, and type of insurance coverage
- Pre-pregnancy weight; all measured prenatal weights; pregnancy-induced hypertension and associated gestational age; delivery or postpartum weight; and last recorded weight prior to pregnancy
- Obstetric history and medical history including type of contraception, medications and medical diagnoses at baseline and delivery, as well as blood pressures at time of delivery
- Last menstrual period before pregnancy; patient-reported pre-pregnancy weight at the first prenatal visit; type of delivery; prenatal and delivery complications
- Number of cigarettes before pregnancy and at each trimester; quantity and frequency of alcohol and drug use
- Information regarding any treatment for gestational diabetes – we will ascertain the existence of GDM treatment including any of the following: medical nutritional therapy; self-monitoring of glucose; insulin therapy with initial dose, dose at delivery, and total maximum dosage; or oral hypoglycemic agents such as glyburide or metformin with initial dose; dose at delivery, and total maximum dosage
- Number of ultrasounds and tests for assessment of fetal wellbeing (biophysical profiles, non-stress tests), date of delivery, and gestational age at delivery
- Information regarding neonatal course, including need for NICU or special care nursery admission; need for intubation or additional respiratory support as well as duration of

such support; hypoglycemia (defined as blood glucose <40 mg/dL in the first 24 hours of life); and hyperbilirubinemia requiring phototherapy, will also be collected
- Labs, diagnostic imaging/tests, and medical history (e.g., height, weight, blood pressure, and diagnoses) from the outpatient, ED, and inpatient record on the maternal and infant pair cohort

NOTE: The EHR also enables the retrieval of clinical and administrative data from certain other area hospitals in the event that women delivery or present to the emergency department at a hospital other than MWH, through the use of "Care Everywhere".

Data Collection Associated with Study Outcomes

To assess the study's main outcomes, data abstraction through the R3 system will collect the following data:

- Small for gestational age (SGA, defined as birth weight ≤10th percentile for gestational age) or large for gestational age (LGA, defined as birth weight ≥90th percentile for gestational age): assessed using the birth weight and gestational age from the delivery record (SGA and LGA will be defined using sex-specific U.S. birth weight curves corrected for implausible ultrasound estimates (Talgi N, et al., *Pediatrics* 2014). Macrosomia will be defined in two ways: birth weight ≥4000 grams and birth weight ≥4500 grams.
- Cesarean delivery: defined as either primary or repeat C-section. We will also include information on the primary indication for the C-section, including prior C-section with no TOLAC (trial of labor after C-section), failure to progress, fetal intolerance to labor, breech presentation, placentia previa or other placental abnormalities, and other.
- Fetal growth and body composition measured using length and weight
- Maternal composite: (1) 3rd or 4th degree vaginal lacerations; (2) postpartum hemorrhage (definied as an estimated blood loss >1000 mL after vaginal delivery or >1500 mL after C-section, with or without need for blood transfusion); (3) pre-eclampsia and hypertensive disorders or pregnancy (defined according to ACOG diagnostic criteria) – will be obtained from the delivery and ICD-9 and -10 diagnostic codes in the EHR
- Neonatal composite: (1) hypoglycemia (defined as blood glucose <40 mg/dL in the first 24 hours of life, measured by heel stick within 1 hour after delivery); (2) hyperbilirubinemia requiring phototherapy (bilirubin measured transcutaneously from 36 hours post-delivery and as needed); (3) stillbirth (absence of fetal heart tones before delivery); (4) birth trauma (defined as shoulder dystocia or brachial plexus injuries) – will be obtained from the lab section of the neonatal EHR

Confidentiality

The collection of sensitive information about participants is limited to the amount necessary to achieve the aims of the research. R3 computer-based files will only be made available to personnel involved in the study with access privileges and passwords. Prior to accessing any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

Laboratory Procedures and Protocols

Specimen Collection

At Visit 1, one 5.0 mL gold top tube will be collected at the 1-hour time point for glucose testing.

At Visit 2, three 5.0 mL gold top tubes and one 3.5 mL lavender top tube will be collected at the fasting time point for fasting glucose, lipid panel, insulin, and high-sensitivity C-reactive peptide (hsCRP) testing. One 5.0 mL gold top tube will then be collected at each hourly time point (1 and 2 hours for the 75 g OGTT; 1, 2, and 3 hours for the 100 g OGTT) for glucose testing.

At delivery, one 3.5 mL gold top tube, one 5.0 mL lavender top tube, and one 5.0 mL gold top tube will be collected, in that specific order.

At Visit 3, three 5.0 mL gold top tubes and one 3.5 mL lavender top tube will be collected at the fasting time point for fasting glucose, lipid panel, insulin, hemoglobin A1c, and high-sensitivity C-reactive peptide (hsCRP) testing. One 5.0 mL gold top tube will then be collected at each hourly time point (1 and 2 hours for the 75 g OGTT).

For Visits 2 and 3 occurring on Saturdays, one extra 3.5 mL lavender top tube will be drawn at fasting.

See Page 63 for Specimen and Laboratory Flow Chart.

Laboratory Processing and Long-Term Specimen Storage

All samples will be processed at the UPMC Clinical Laboratory Building with the exception of specimens collected at delivery, which will be processed by the MWH OSPU team.

All glucose tests, lipid panels, and high-sensitivity C-reactive peptide tests will be run at the UPMC Automated Testing Lab. The UPMC CLB will also run insulin tests at the Immunoserology Lab, and hemoglobin A1c at the Special Chemistry Lab.

Non-esterified free fatty acids, adiponectin, and leptin will be analyzed at the UPMC CLB or Indiana University Metabolic Lab (TBD).

All plasma and serum aliquots will be stored long-term at the Magee-Womens Research Institute.

Visit 1 Laboratory Procedures

The 50 g 1-hour glucose specimen and a completed research requisition (see Appendix C) will be sent from MWH to the UPMC Clinical Laboratory Building (CLB Station #350) via pneumatic tube for processing. The CLB will process the glucose testing. Results will then be faxed to study staff within 1 business day. Specimens from Visit 1 will not be banked in long-term storage.

Visit 2 Laboratory Procedures

The fasting specimens and corresponding completed research requisition will be sent from MWH to the UPMC CLB (Station #350) via pneumatic tube for processing. The CLB will process the fasting glucose, insulin, lipid panel, and hsCRP. The additional two or three hourly glucose specimens will also be sent to the CLB with corresponding completed research requisitions by pneumatic tube. All results will be faxed to study staff within 1 or 2 business days. Fasting adiponectin, leptin, and non-esterified fatty acids will be processed at a separate time, after all participants complete their Visit 2.

Study staff will retrieve an extra gold top tube and lavender top tube directly from the automated testing line at the Automated Testing Lab on the 5th floor of the CLB. CLB staff will centrifuge the tubes and store them until they are retrieved by study staff. These residual specimens will be retrieved by scanning the tube labels printed by CLB staff, sending them to the automated testing line.

Once tubes are processed and received, study staff will aliquot the plasma or serum from each specimen into cryovials and temporarily freeze (-20°C) and store them in the Palmer Lab (Room 3027) freezer. Total aliquots to be frozen in cryovials include: 4 fasting serums, 2 fasting plasmas, and 1 serum aliquot from each hourly glucose specimen, of 1 mL each. If the participant does not consent to banking of specimens for future research tests, study staff will only prepare two 1 mL fasting serum aliquots for cytokine analyses.

Study staff will prepare labels for each cryovial, which specify the participant's study ID, blood draw date and time, date and time of freezing, study arm, specimen type (serum or plasma), study arm, and numerical order within the batch. After each sample is aliquoted, labeled, and frozen, study staff will complete a specimen collection record to log all prepared samples, noting if there will be fewer samples or less volume in a specific aliquot than expected. The Palmer Lab (Room 3027) will temporarily hold frozen specimens in labeled boxes provided by this study.

For long-term storage, study staff will compile specimen collection records, label specimen boxes with study and PI information, and transport the specimen boxes from the Palmer Lab to the Magee-Womens Research Institute (MWRI) within an insulated box of dry ice (to be provided by the CTRC). Study staff have badge access to the MWRI lab where study specimens will be stored. One freezer with specimens is located on the 5th floor of MWRI, where lab benches may be used by study staff to prepare specimen boxes for storage.

Specimen maps will be prepared, with boxes placed and mapped by rows and columns with alphanumerical identification. Specimen collection records will be compiled, specimen maps updated and organized by study staff at each transfer, and all records will be kept in binders in the study office.

Separate boxes are required for each of the following: fasting serum for cytokine analysis, fasting serum, fasting plasma, 1-hour serum, 2-hour serum, and 3-hour serum. Samples will be transferred between lab bench and freezer on dry ice during the entire process. Study staff will organize fasting serums to be used for cytokine analysis into two groups: participants who completed the study at delivery, and participants selected to return for the 12-month postpartum follow-up at Visit 3. All remaining samples will be frozen (-80°C) and stored long-term at MWRI.

Cord Blood Laboratory Procedures

Venous umbilical cord blood will be collected at delivery by OSPU staff for the analysis of C-peptide. Cord blood procurement supplies will be provided on an ongoing basis to the OSPU team, to include 5.0 mL gold top tubes, 3.5 mL gold top tubes, 2 mL cryovial tubes, blank cryovial labels, and labeled specimen boxes for storage. Each month, study staff will provide the OSPU staff with an updated list of expected participant deliveries for the upcoming month and prepared research requisitions for each participant.

When a study participant delivers, the OSPU staff will obtain cord blood samples with the kit provided, and enter specimen and collection information (Cord Blood Collection form) into the study database at the delivery time point. 2 plasma aliquots and 2 serum aliquots of 1 mL each will be collected and banked from the delivery specimens.

Visit 3 Laboratory Procedures

The fasting specimens and corresponding completed research requisition will be sent from MWH to the UPMC CLB (Station #350) via pneumatic tube for processing. The CLB will process the fasting glucose, insulin, lipid panel, hsCRP, and A1c. The additional two hourly glucose specimens will also be sent to the CLB with corresponding completed research requisitions by pneumatic tube. All results will be faxed to study staff within 1 or 2 business days. Fasting adiponectin, leptin, and non-esterified fatty acids will be processed at a separate time, after all participants complete their Visit 3.

Study staff will retrieve the lavender top from the Special Chemistry lab on the 3rd floor of the CLB, after it has been used for A1c testing. This tube will be taken to the 5th floor Automated Testing Lab and centrifuged there. Study staff will also retrieve an extra gold top tube directly from the automated testing line at the Automated Testing Lab on the 5th floor of the CLB. CLB staff will centrifuge the tubes and store them until they are retrieved by study staff. These residual specimens will be retrieved by scanning the tube labels printed by CLB staff, sending them to the automated testing line.

Once tubes are processed and received, study staff will aliquot the plasma or serum from each specimen into cryovials and temporarily freeze (-20°C) and store them in the Palmer Lab (Room 3027) freezer. Total aliquots to be frozen in cryovials include: 4 fasting serums, 2 fasting plasmas, and 1 serum aliquot from each hourly glucose specimen, of 1 mL each.

Study staff will prepare labels for each cryovial, which specify the participant's study ID, blood draw date and time, date and time of freezing, study arm, specimen type (serum or plasma), and numerical order within the batch. After each sample is aliquoted, labeled, and frozen, study staff will complete a specimen collection record to log all prepared samples, noting if there will be fewer samples or less volume in a specific aliquot than expected. The Palmer Lab (Room 3027) will temporarily hold frozen specimens in labeled boxes provided by this study.

For long-term storage, study staff will compile specimen collection records, label specimen boxes with study and PI information, and transport the specimen boxes from the Palmer Lab to the Magee-Womens Research Institute (MWRI) within an insulated box of dry ice (to be provided by the CTRC). Study staff have badge access to the MWRI lab where study specimens will be stored. One freezer with specimens is located on the 5th floor of MWRI, where lab benches may be used by study staff to prepare specimen boxes for storage.

Specimen maps will be prepared, with boxes placed and mapped by rows and columns with alphanumerical identification. Specimen collection records will be compiled, specimen maps

updated and organized by study staff at each transfer, and all records will be kept in binders in the study office.

Separate boxes are required for each of the following: fasting serum for cytokine analysis, fasting serum, fasting plasma, 1-hour serum, and 2-hour serum. Samples will be transferred between lab bench and freezer on dry ice during the entire process. All samples will be frozen (-80°C) and stored long-term at MWRI.

Visits 2 and 3 Occurring on Saturdays

For Visits 2 and 3 occurring on Saturdays, one extra 3.5 mL lavender top tube will be drawn at fasting in addition to the usual specimens. One 5.0 mL gold top tube and the extra 3.5 mL lavender top tube will be held at the CTRC for study staff to aliquot fasting samples there. 2 fasting plasma aliquots and 2 fasting serum aliquots will be spun down, aliquoted, and frozen per usual procedure as noted above in the CTRC lab, and stored temporarily in CTRC freezers until study staff are able to retrieve them for transport to long-term storage at MWRI. A specimen collection record will be completed. The remaining fasting samples (2 5.0 mL gold top tubes and 1 3.5 mL lavender top tube) and hourly glucoses will be tubed to the CLB for processing as usual. Study staff will aliquot and freeze these samples on the following business day per usual procedure.

Specimen and Laboratory Flow Charts

Visit 1: 50 g GCT

Blood Draw Time Point	*# and Type Tube(s) Drawn*	*Test(s) Run*	*# Plasma Aliquot(s)*	*# Serum Aliquot(s)*
1-hour	1 – 5.0 mL gold top	• Glucose	N/A	N/A

Visit 2: 75 g OGTT

Blood Draw Time Point	*# and Type Tube(s) Drawn*	*Test(s) Run*	*# Plasma Aliquot(s)*	*# Serum Aliquot(s)*
Fasting	3 – 5.0 mL gold 1 – 3.5 mL lavender*	• Glucose • Lipid panel o Triglycerides o Cholesterol o VLDL o LDL o HDL • hsCRP • Insulin	4	2
1-hour	1 – 5.0 mL gold top	• Glucose	1	0
2-hour	1 – 5.0 mL gold top	• Glucose	1	0

Visit 2: 100 g OGTT

Blood Draw Time Point	*# and Type Tube(s) Drawn*	*Test(s) Run*	*# Plasma Aliquot(s)*	*# Serum Aliquot(s)*
Fasting	3 – 5.0 mL gold 1 – 3.5 mL lavender*	• Glucose • Lipid panel o Triglycerides o Cholesterol o VLDL o LDL o HDL • hsCRP • Insulin	4	2
1-hour	1 – 5.0 mL gold top	• Glucose	1	0
2-hour	1 – 5.0 mL gold top	• Glucose	1	0
3-hour	1 – 5.0 mL gold top	• Glucose	1	0

*For Visits 2 occurring on Saturdays, one extra 3.5 mL lavender top tube will be drawn, to be processed and aliquoted at the CTRC

Delivery Time Point

Blood Draw Time Point	*# and Type Tube(s) Drawn*	*Test(s) Run*	*# Plasma Aliquot(s)*	*# Serum Aliquot(s)*
Delivery (Cord Blood)	1 – 3.5 mL gold 1 – 5.0 mL lavender 1 – 5.0 mL gold (to be drawn in this specific order)	• C-peptide	2	2

Visit 3: 75 g OGTT

Blood Draw Time Point	*# and Type Tube(s) Drawn*	*Test(s) Run*	*# Plasma Aliquot(s)*	*# Serum Aliquot(s)*

Fasting	3 – 5.0 mL gold
	1 – 3.5 mL lavender*
		• Glucose
		• Lipid panel
		  ○ Triglycerides
		  ○ Cholesterol
		  ○ VLDL
		  ○ LDL
		  ○ HDL
		• hsCRP
		• Insulin
		• A1c
			4	2

1-hour	1 – 5.0 mL gold top	• Glucose	1	0
2-hour	1 – 5.0 mL gold top	• Glucose	1	0

Clinical Laboratory Protocols

Testing for glucose, insulin, lipids, high-sensitivity C-reactive peptide (hsCRP), glycosylated hemoglobin A1c, and c-peptide will occur at the UPMC Clinical Laboratory Building under the supervision of Dr. Octavia Palmer. Protocols for these tests are available in their entirety and may be obtained by contacting study staff or Jeffrey Tischler, Lead Medical Technologist at the CLB (tiscjt@upmc.edu).

Glucose

Glucose is measured using Beckman Coulter AU680 and AU5800 analyzers. In the Beckman Coulter AU System Glucose procedure, glucose is phosphorylated by hexokinase (HK) in the presence of adenosine triphosphate (ATP) and magnesium ions to produce glucose-6-phosphate (G-6-P) and adenosine diphosphate (ADP). Glucose-6-phosphate dehydrogenase (G6P-DH) specifically oxidizes G-6-P to 6-phosphogluconate with the concurrent reduction of nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide, reduced (NADH). The change in absorbance at 340/380 nm is proportional to the amount of glucose present in the sample.

Insulin

Insulin is measured using IMMULITE® 2000. Insulin is a solid-phase, enzyme-labeled chemiluminescent immunometric assay. The solid phase (bead) is coated with monoclonal murine anti-insulin antibody. The patient sample and the reagent is incubated together with the coated bead for 60 minutes. During this time, insulin in the sample forms the antibody sandwich complex with the monoclonal murine anti-insulin antibody on the bead, enzyme conjugated polyclonal sheep anti-insulin antibody and enzyme conjugated monoclonal murine anti-insulin antibody in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

Cholesterol

Cholesterol is processed and analyzed with cholesterol esters in serum are hydrolyzed by cholesterol esterase (CHE). The free cholesterol produced is oxidized by cholesterol oxidase (CHO) to cholest-4-en-3-one with the simultaneous production of hydrogen peroxide (H_20_2),

which oxidatively couples with 4-aminoantipyrine and phenol in the presence of peroxidase to yield a chromophore.

High Density Lipoprotein

HDL is measured using the Beckman Coulter AU System HDL-Cholesterol test (HDL-C) is a two reagent homogenous system for the selective measurement of serum or plasma HDL-Cholesterol in the presence of other lipoprotein particles. The assay is comprised of two distinct phases. In phase one, free cholesterol in non-HDL-lipoproteins is solubilized and consumed by cholesterol oxidase, peroxidase, and DSBmT to generate a colorless end product. In phase two, a unique detergent selectively solubilizes HDL-lipoproteins. The HDL cholesterol is released for reaction with cholesterol esterase, cholesterol oxidase, and a chromogen system to yield a blue color complex, which can be measured bichromatically at 600/700nm. The resulting increase in absorbance is directly proportional to the HDL-C concentration in the sample.

Triglycerides

The triglycerides in the sample are hydrolyzed by a combination of microbial lipases to give glycerol and fatty acids. The glycerol is phosphorylated by adenosine triphosphate (ATP) in the presence of glycerol kinase (GK) to produce glycerol-3-phosphate. The glycerol-3-phosphate is oxidized by molecular oxygen in the presence of GPO (glycerol phosphate oxidase) to produce hydrogen peroxide (H_2O_2) and dihydroxyacetone phosphate. The formed H_2O_2 reacts with 4- aminophenazone and N,N-bis(4-sulfobutyl)-3,5-dimethylaniline, disodium salt(MADB) in the presence of peroxidase (POD) to produce a chromophore, which is read at 660/800 nm. The increase in absorbance at 660/800 nm is proportional to the triglyceride content of the sample.

High-Sensitivity C-Reactive-Peptide

Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incidence light due to reflection, absorption, or scatter. In the Beckman Coulter AU System procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is the result of complexes formed during the antigen-antibody reaction between the CRP of the patient serum and the rabbit anti-CRP antibodies coated on latex particles.

C-Peptide

C-peptide is a solid-phase, two-site chemiluminescent immunometric assay. The solid phase (bead) is coated with monoclonal murine anti-C-peptide antibody. The patient sample and the reagent are incubated together with the coated bead for 30 minutes. During this time, C-peptide in the sample forms the antibody sandwich complex with monoclonal murine anti-C-peptide antibody on the bead and enzyme-conjugated monoclonal murine anti-C-peptide antibody in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

Glycosylated Hemoglobin A1c

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 uses nonporous ion-exchange high performance liquid chromatography (HPLC) for rapid, accurate, and precise separation of HbAlc from other hemoglobin fractions. Analysis is carried out without off-line specimen pretreatment or interference from Schiff base. The analyzer dilutes the whole blood specimen with Hemolysis & Wash Solution, and then injects a small volume of the treated specimen onto the TSKgel Glyco HSi Variant Column. Separation is achieved by utilizing differences in ionic interactions between the cation exchange group on the column resin surface and the hemoglobin components. The hemoglobin fractions (designated as Ala, Alb, F, LAlc+, SAIC, AO, and H- Var) are subsequently removed from the column material by performing a stepwise elution using Elution Buffers HSi Variant 1, 2, and 3 with different salt concentrations. The separated hemoglobin components pass through the LED photometer flow cell where the analyzer measures changes in absorbance. The analyzer integrates and reduces the raw data, and then calculates the relative percentages of each hemoglobin fraction. The analyzer prints the numerical results and plots a chromatogram showing changes in absorbance versus retention time for each peak fraction. An analysis requires 1.6 minutes.

Adiponectin

TBD

Leptin

TBD

Non-Esterified Fatty Acids

TBD

Adherence and Retention

The GDM2 primary investigator and study team have extensive knowledge of cohort studies and clinical trials with similar participants; this will be valuable in the retention of participants. Based on experience, several strategies will be applied to maximize adherence and minimize drop-out:

- We will limit the number of in-person study visits to three (two during pregnancy, one at 12 months postpartum), and schedule study appointments on the same day as prenatal visits when possible.
- Participants will remain blinded to which test they are randomized until they return for Visit 2. This will minimize drop-out based on participants' knowledge that they have been randomized to the longer test
- Study staff will maintain regular contact with participants prior to reach study appointment, reminding participants of their appointments and reviewing preparation instructions.
- Study staff will also visit participants at MWH after they deliver, to complete the infant assessment and deliver a small baby gift. Participants will be told at this time whether or not they have been selected for postpartum follow-up, and what to expect if they have been selected.
- Scheduled telephone assessments at 3, 6, and 9 months postpartum for those selected participants will also serve to keep study staff in contact with participants.
- We will request the name and telephone number of an emergency contact or someone who will "always know where the participant is."
- We will update participants' contact information as needed. Contact information may be gleaned from the participant's Epic EMR.
- We will offer monetary compensation for study visits on a University-issued debit card, a small gift at delivery, and transportation reimbursement or parking validation for study visits.
- We will conduct initial orientation sessions with the clinics we plan to recruit from, and will frequently correspond with them regarding the study protocol.

Study Withdrawal and Termination

A drop-out or attrition rate of approximately 15% is expected and has been accounted for in the statistical sample size. Potential participants will be made aware at telephone screening and during informed consent that their participation is voluntary and that they may withdraw from

the study at any time for any reason. It will be emphasized that withdrawal will have no bearing on a participant's current or future medical care.

To formally withdraw consent for participation, participants are advised to provide a written and dated notice of their decision, to be sent to the principal investigator at the address listed on the informed consent document. Additionally, participants may withdraw in-person or through any method they choose to contact study staff (email, telephone, text, etc.).

Participants will also be told that it is possible to be removed from the study by the investigators in the following cases: participant meeting exclusion criteria; participant's medical care has been transferred outside of MWH; participant is unable to complete study visits within expected timeframe; or participant experiences several prenatal complications or pre-term delivery.

All of the above information will be provided to participants in the informed consent document. Study staff will complete and submit the Withdrawal and Termination Form (see Appendix B) in the study database in cases of dropout, exclusion, or other circumstances where study participation is inappropriate.

Data Management and Quality Control

Center for Research on Health Care Data Center

The Center for Research on Health Care Data Center (CRHC-DC) will work with the principal investigator and study team to standardize all procedures and training in areas such as participant recruitment, measurement, assessment, data entry, data management, and data security.

The CRHC-DC provides state-of-the-art data management and analysis services to the University of Pittsburgh's researchers. Their mission is to provide investigators with consistent, high-quality information technology including database development, data management, and statistical services. The CRHC-DC team provides expertise in all phases of research, and is committed to quality assurance and research integrity. The CRHC-DC offers secure equipment to provide data management, storage, and analysis services while ensuring high security and confidentiality of research data and samples.

Data Collection

Study questionnaires and forms are paperless, and an electronic System for Data Management (eSYSDM) for this project has been developed based on the study protocol. eSYSDM facilitates the generation of clean datasets by guiding interviewers through the data collection process in such a way as to display only questions and screens that are appropriate for the particular participant, eliminating the possibility of most incorrect entries. eSYSDM also performs important tracking functions by monitoring screening information, eligibility status, follow-up interviews due, and study group assignment to ensure that the required data collection instruments are administered within the time constraints dictated by the study protocol. The eSYSDM will be stored on a local network accessible only to select research team members with password privileges. All files will be backed-up daily, archived weekly, and stored.

Manual Data Entry

Data will be entered on PCs, laptops, and tablets; this allows for mobile computing and better functionality. Study personnel are assigned unique login credentials to access only the data they are permitted to manage. Only designated study staff will have access to the database (including participant's personal information); the PI will have limited access to the database to prevent unblinding.

Before beginning study procedures where data collection and tracking are involved, study staff will log onto the device they are using through a secure web server. An additional log-in and password is then required to access the database. Once the screening process has been started in the database, participant ID numbers are generated and data capture and tracking begins.

Data Quality and Integrity

Data quality and integrity will be ensured by the following:

- Standard methods of data collection and recording specified in this manual of procedures
- Staff will attend a formal workshop on research integrity at the beginning of the study or upon hire, and will attend refresher courses as dictated by the University of Pittsburgh's research regulations
- Random audits on a sample of participants to verify accuracy and completion of study data collection

Other data quality assurance measures will include detailed documentation of computer operations and data editing procedures, and meetings with study staff to review any changes in procedure. The CRHC0DC also has specific data quality measurements that will be implemented. These include verifying the data, out-of-range data checks, and repeated evaluation of the data process.

Data Corrections

Corrections to data are to be held to a minimum. Making sure that data is secure from unauthorized changes or access is important to ensure the data's accuracy and integrity. Only database programmers and statisticians assigned to the GDM2 project will have rights to the database, files, and directories that contain project data. The CRHC-DC programmer will use version control software to manage changes made to databases and websites. All revisions are kept and can only be accessed by the programmer.

In cases where study staff determine data submitted in a study questionnaire requires modification, the CRHC-DC will be notified of the incorrect data entry and make the appropriate changes. Both the CRHC-DC team and study staff will track these changes.

Data Security

The CRHC-DC maintains numerous secure servers and computers, which provide access to both the internet and the CRHC-DC intranet. Servers are located in a secured server room which contains an alarm system, temperature control, and a double lock on the door with a tracking keycard entry system. All servers use hardware fault tolerance methods, and are housed in a secure rack with dedicated UPS power sources, to assure the 24/7 uptime and continued availability of data.

The CRHC-DC's servers utilize 128-bit SSL security for online real-time data entry. The center's SQL server, which is used for database and data storage, also offers 128-bit SSL security and has limited access via network firewall. The CRHC-DC website and database development server is located behind a firewall with access only available to the developers on the intranet. The University of Pittsburgh's Computing Services and Systems Development (CSSD) department ensures that all software and hardware are running at optimal performance and systems are secure to the latest industry standards. CSSD will scan production servers on a monthly schedule to review performance.

Data and Safety Monitoring

Institutional Data and Safety Monitoring Board

An Institutional Data and Safety Monitoring Board (IDSMB) has been created and organized by the Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh, to review the GDM2 Study and ensure the wellbeing of the study's participants. This independent panel of experts has been established to monitor the study's progress, efficacy, and safety.

Membership

The members of the IDSMB have been selected by the IDSMB Coordinators with suggestions put forth by the PI. The IDSMB is composed of experts in maternal-fetal medicine, obstetrics and gynecology, pediatrics, and biostatistics. Members of the IDSMB are independent and are not affiliated with the study in any way, and have no financial, scientific, or other conflict of interest. Study collaborators and personnel are not eligible to serve on the study's IDSMB.

Katherine Himes, MD, MS has been elected to serve as the IDSMB Chairperson. Dr. Himes is responsible for overseeing IDSMB meetings in consultation with the IDSMB coordinators. Dr. Himes will also oversee safety with the IDSMB coordinators; they are to be contacted in cases of severe adverse events or unanticipated problems.

IDSMB Responsibilities

The initial responsibility of the IDSMB was to approve the GDM2 Study. The IDSMB met for the first time on February 25, 2015, to review the Institutional Review Board (IRB) approval letter and IRB-approved protocol and informed consent document. The IDSMB voted and approved the study to begin.

The IDSMB agreed to meet every 6 months during the course of the study to:

1. Review the research protocol, informed consent document, and plans for data and safety monitoring;
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk vs. benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors affecting study outcomes;

3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of participants or the ethics of the study;
4. Review clinical center performance, make recommendations, and assist in the resolution of problems reported by the PI;
5. Protect the safety of the study participants;
6. Report on the safety and progress of the study;
7. Make recommendations to the PI, and if required, to the NIH, concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;
8. Monitor the confidentiality of the study data and the results of monitoring;
9. Assist the PI by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

IDSMB Board Process

IDSMB meetings are confidential, and therefore closed to the public. The PI, study staff, study statistician, and other members of the study team as necessary, will attend the meetings. The Chairperson can call an emergency meeting of the IDSMB at any time after reviewing any serious adverse event report, unanticipated problem report, or should questions of participant safety arise.

IDSMB Meeting Formats

The IDSMB meetings consist of an open session and two closed sessions; these formats may be modified as needed.

Open Session

Open IDSMB meetings will be attended by the IDSMB members, IDSMB coordinators, principal investigator, study staff, and will always include the study biostatistician. Issues discussed will include conduct and progress of the study, including patient accrual, compliance with protocol, data quality, adherence, and safety. Patient-specific data and treatment group data may not be presented in the open session.

Closed Session (without the PI and study staff)

These closed sessions will be attended by the IDSMB members, IDSMB coordinators, and the study biostatistician. Discussions in closed meetings are confidential, as unblended outcome data may be reviewed. The IDSMB may request unmasking of data for either safety or efficacy reasons or if there are developments in risks or benefits to participants.

Closed Session

Only the IDSMB members and IDSMB coordinators will attend these closed sessions. Information will be discussed that was presented in the open and other closed sessions, and decisions made regarding continuation or termination of the study, protocol modification, or other changes relevant to the conduct of the study. The IDSMB will also vote on the frequency of the next meeting.

Should the IDSMB decide to issue a termination of the study, a full vote is necessary. In the event of a split vote, majority vote will rule and a minority report appended. Reasons for termination include and are not limited to:

- Serious adverse events in the intervention or dominating subgroup
- Greater than expected beneficial effects
- Statistically significant difference by the end of the study is improbably
- Logistical or data quality problems that cannot be corrected
- Recruitment issues

IDSMB Reports

Reports are to follow the IDSMB report template. Meeting documents/reports will be prepared by the PI's study data analyst or study staff and distributed to the IDSMB coordinators at least one week prior to a scheduled meeting. Further information or modifications to these documents/reports may be requested by the IDSMB. Following the meeting, the minutes are shared with the IDSMB members only and are confidential. A copy of the minutes is kept in the IDSMB file.

Letters from the IDSMB

A formal letters containing the recommendations for continuation and action items/modifications will be prepared by the IDSMB chair and coordinators and will be sent to the IDSMB members and principal investigator. It is the responsibility of the PI to distribute the meeting summary to all co-investigators, the study sponsor, and to the IRB during the study's annual review.

Communication with the IDSMB/Access to Interim Data

Access to the accumulating endpoint data will be limited to as small a group as possible. Limiting the access to interim data to the IDSMB members will relieve the PI of the burden of deciding whether it is ethical to continue to randomize participants and will help protect the study from bias in participant entry and/or evaluation.

Confidentiality

The study visits will be conducted at the CTRC at Magee-Womens Hospital, which is equipped to ensure the protection of patient privacy. The collection of sensitive information about participants will be limited to the amount necessary to achieve the aims of the research so that no unnecessary sensitive information is collected.

Paper-based records will be kept in a secure location and only be available to study personnel. Computer-based files will be made accessible to study personnel by access privileges and passwords. Prior to accessing any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. Whenever feasible, identifiers will be removed from study-related information and data.

If a participant withdraws from the study, any personal medical information that was recorded or samples obtained for the research study before the withdrawal may continue to be used by the study.

During data collection, the personal identifiers on study questionnaires and samples are replaced by a unique study ID. After the required data retention period, the link between the assigned tudy ID and the participant's identity will be destroyed so that nothing can be tracked back to the individual. The data will then be rendered completely anonymous.

Adverse Event Reporting Guidelines

During the course of the study, all adverse events (AEs) and serious adverse events (SAEs) will be monitored, documented, and if causal, reported to the IDSMB and IRB. AEs and SAEs will be captured in the study database using the Adverse Events form. The form will prompt study staff to notify the PI of SAEs for review. Every effort will be made to follow a participant who has had a negative reaction to any study intervention or procedure.

Adverse Events (AEs)

An adverse event (AE) is any unfavorable medical occurrence, which may include abnormal signs (e.g., abnormal physical exam or laboratory finding), symptoms, or disease, temporally associated with, but not necessarily considered related to, the participant's participation in the study. These events are usually of a non-serious nature and are not reportable in accordance with the University of Pittsburgh Institutional Review Board's (IRB) guidelines for "Reportable Events" as they do not pose a risk to study participants.

Adverse events that take place during the course of the study will be classified under the Common Terminology Criteria for Adverse Events (CTCAE), a descriptive terminology used for Adverse Event (AE) reporting. AEs will be categorized as expected or unexpected, in terms of the nature, severity, or frequency, as outlined in the consent form. AEs will be graded using the CTCAE system and relatedness assessed by the PI, and presented to the IDSMB members at IDSMB meetings.

Serious Adverse Events (SAEs)

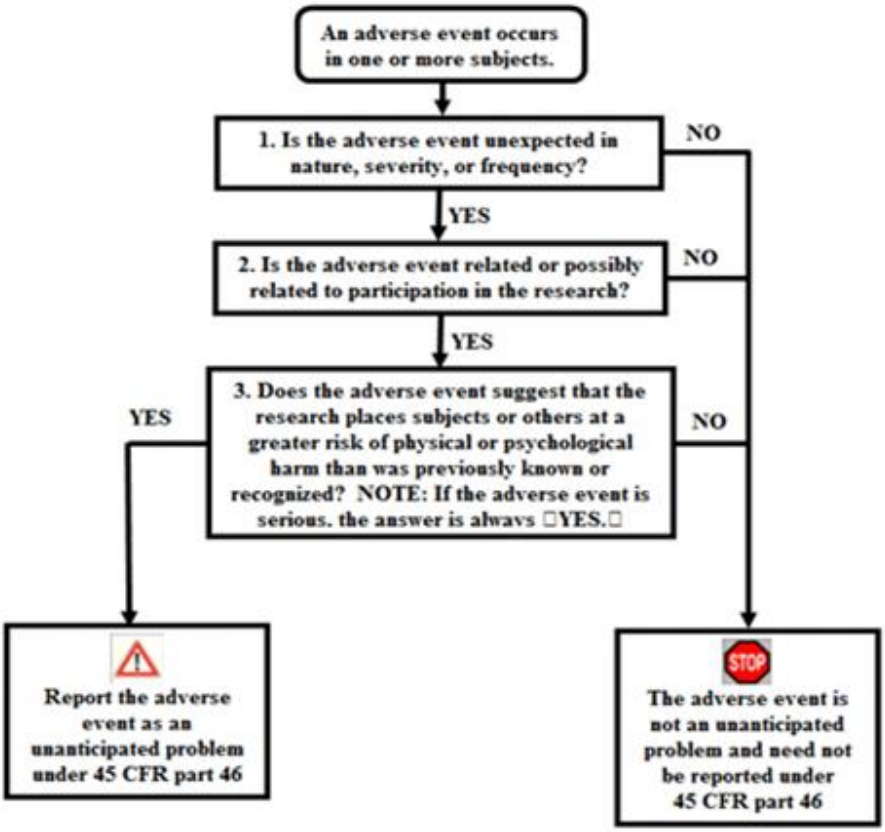
Serious adverse events (SAEs) or "unanticipated problems involving risk to participants or others" are characterized as symptoms which are harmful to the participant and result in significant outcomes, which are reportable to the IRB and IDSMB.

Examples of serious adverse events include:

- Death
- Life-threatening medical events that place a participant at immediate risk of death from the event as it occurred
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity as a result of the study intervention

- Events that, based upon appropriate medical judgment, may jeopardize the participant's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

The flow chart below provides an algorithm for determining whether an adverse event meets the definition of an "unanticipated problems involving risk to participants or others":



Adverse Events which follow the above figure, that meet the criteria of unexpected, fatal or life- threatening, and related or possibly related to the research intervention must be reported to the IRB and the IDSMB Chair and Safety Officer (Dr. Katherine Himes) within 24 hours of learning of the event. If necessary, a subsequent follow-up report with the details of the event will be submitted as well.

All other reportable adverse events will be submitted to the IRB within 10 business days of the investigator learning of the event. Reportable events will be submitted through the University of Pittsburgh IRB's PittPRO system; the "Reportable Event" online submission process must be used in order to submit a report. The smart form questions will prompt a response to questions related to the adverse event.

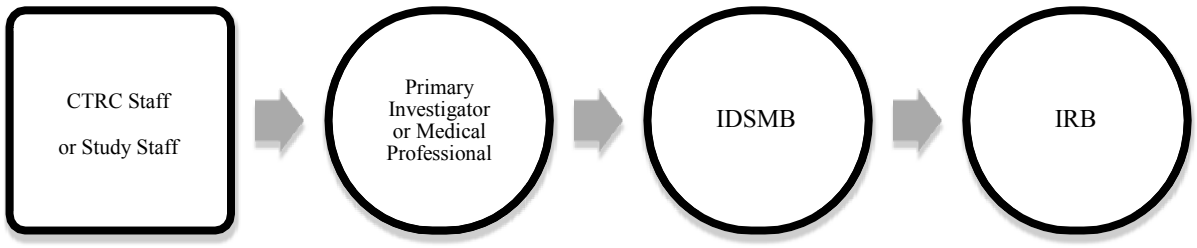
SAE and AE reporting guidelines and further instructions on submitting a report in the PittPRO system can be found in the University of Pittsburgh website, http://www.irb.pitt.edu/.

AE and SAE Assessment Guidelines Specific to the GDM² Trial

Key Criteria: to determine if the event is unexpected, related to participation in the research study and involves risk to human participants or others.

If an adverse event meets the criterion of unexpected, related or possibly related, and poses risk of harm to other participants, study staff will notify the principal investigator within 24 hours, who will then inform and the IDSMB Chair and Safety Officer (Dr. Katherine Himes). Dr. Himes will review and submit the event to the IDSMB, who will discuss the IDSMB recommendations and submit the SAE to the University of Pittsburgh IRB.

In cases of an SAE, the following schematic is to be used:



To evaluate GDM2 Study AEs and SAEs, a licensed medical professional will apply the following assessment criteria:

Unexpected Medical Events

These are medical events that are not described in the current IRB-approved protocol or informed consent, taking into account the characteristics of the participant population being studied (i.e. pregnant women).

Expected Medical Events

- Symptoms and risk related to normal pregnancy progression such as nausea, vomiting, fatigue, urinary frequency, increased or decreased appetite, transient dizziness, mild back or breast pain or discomfort, mild mood changes, miscarriage, preterm delivery, stillbirth, low birth weight, problems with placenta, and birth defects
- Symptoms related to fasting for at least 8 hours and related hypoglycemia: headache, nausea, and lightheadedness
- Symptoms related to hypoglycemia such as fainting, fast heart rate, sweating, shakiness, difficulty paying attention, sudden moodiness or irritability, loss of consciousness
- Symptoms related to venous blood draw such as bruising, bleeding, swelling, and pain, fainting, lightheadedness, and infection at the injection site
- Symptoms related to consuming the glucose solution for the diabetes testing such as brief nausea, vomiting, tiredness, lightheadedness, and upset stomach

While the above medical events may be expected, they will be collected for outcome purposes.

Event Severity using Common Terminology Criteria for Adverse Events (CTCAE)

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on these general guidelines:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated limiting age- appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Event Relatedness

Very Likely Related: The incident, experience, or outcome is more likely than not caused study procedures.

- A reasonable time course would be within the 1-4 hours the participant is receiving oral glucose tolerance testing.
- Symptoms abate once the study product is discontinued and patient has received a snack or drink.
- Symptoms are not explained by other factors such as concomitant medications or current illness

Probable: There is reasonable possibility that the incident, experience or outcome may have been caused by study procedures.

- A reasonable time course would be within 24 hours the participant either fasting for the study or receiving the oral glucose tolerance testing.
- Symptoms may be explained by other factors such as concomitant medications or current illness

Possible: There is a possibility that the incident, experience or outcome may have been caused by study procedures.

- A reasonable time course would be within 25-48 hours the participant fasting for the study, receiving the OGTT, or final blood draw.
- Symptoms may be explained by other factors such as concomitant medications, current illness, or other healthcare procedures.

Doubtful: There is a reasonable doubt that the incident, experience or outcome was not caused by study procedures.

- Symptoms may be explained by other factors such as concomitant medications, current illness, or other healthcare procedures.

Not Related: There is complete assurance that the incident, experience or outcome could not have been caused by any study procedures.

Study Completion and Closeout

Study Completion and Closeout Procedures

This study will be complete when the target enrollment number has been reached and all research procedures have been completed, or allotted time to complete the study has passed. If the investigator is no longer using identifiable data for analysis, the study completion process may be initiated as no further IRB oversight is required. The study will not close until the sponsor conducts the final closeout visit, as an intervention or interaction with participants may be needed to complete the research data.

The investigator must submit a final report for the Early Termination or Study Completed activities for IRB review via the PittPRO website.

The following are to be addressed to the IRB for the final report:

- Since the study began, how many participants have been entered into this research study at all sites under the authority of the University of Pittsburgh IRB? Do not include those participants who failed to meet the inclusion criteria during screening.
- Total number of participants approved to undergo research related procedures at all sites under the authority of the University of Pittsburgh IRB.
- Did participant accrual reflect the ethnic and racial demographics of Pittsburgh and the surrounding area and/or the relevant patient population of the UPMC; or the demographics of the alternate site(s) where this research is being conducted?
- Have there been any unanticipated problems that were not previously reported that meet the University of Pittsburgh reporting guidelines? If yes, you must immediately submit an unanticipated problem report, which must be available for the IRB's consideration during review of this final report.
- Have you already provided, or do you plan to provide, your study participants with a summary of study results?
- Summarize the outcomes and conclusions of this study. Describe the extent to which the specific aims of this study were addressed and discuss the study's impact on the relevant scientific/medical issues.

A final Data and Safety Monitoring Plan (DSMP) report is to be uploaded into PittPRO as described in the approved study.

Early Termination of Study

The study may be canceled or stopped prematurely before targeted enrollment numbers have been reached and/or all required research procedures have been completed. The study sponsor, PI, federal agency, or local IRB may terminate the study early for reasons including but not limited to: change in risk/benefit assessment, loss of funding, new information, etc.

Retention of Study Documentation

The investigators may continue to use and disclose, for research purposes, identifiable information related to participation in this research study for a minimum of five years after final reporting or publication of a project. Following the required data retention period, secured long- term retention of any documents will occur and they will be rendered anonymous. The majority of documents (both electronic and paper) will be de-identified from the start of the study. After the study has been closed, study-related files may be given to the PI for long-term storage.

Table of Changes from Version IV to Version V

Pg	Header	Description of Change
-	-	**Updated:** All references to WePay changed to "University issued payment card" (WePay system phased out end of 2018 and replaced with Vincent system)
-	-	**Removed:** All references to study ID card (did not use)
-	-	**Updated:** All references to OSIRIS changed to PittPRO – new IRB system
-	-	**Updated:** All references to Heinz Lab (closed in 2018) changed to UPMC Clinical Laboratory Building (CLB)
vii-viii	List of Abbreviations	**Updated:** List of Abbreviations
10-11	GDM2 Co-Investigators	**Updated:** Contact information for Dr. Scifres and Dr. Catalano
14	GDM2 Principal Study Staff	**Removed:** Project Coordinator (Alexandra Illes)
14-15	GDM2 Principal Study Staff	**Updated:** Study staff responsibilities after departure of coordinator
16	GDM2 Clinical Team	**Removed:** GSPH Heinz Laboratory Director (Dr. Joseph Zmuda) and Manager (Beth Hauth)
17	GDM2 Clinical Team	**Updated:** Replaced David Lykins with Sharon Price (MWRI Lab Liaison)
18	GDM2 Data Center Staff	**Added:** Diane Comer (CRHC-DC Data Analyst)
19	GDM2 Regulatory Staff	**Updated**: Replaced Ann Lee with Lisa DeSantes (IRB)
24	Recruitment Plan	**Added:** Added WomanCare, Wiesenfeld/Updike, UOA NIA, OGAP, and OPC clinics in list of clinics
24	Recruitment Plan	**Removed:** OPC Purple and Western PA Women's Health
24	Recruitment Plan	**Updated:** Identified clinics as public or private providers
25	In-Clinic Recruitment	**Removed:** Introductory letter recruitment (did not use)
25-26	Additional Recruitment Methods	**Added:** WIC Office, list of UPMC hospitals, digital message boards
27	Screening Procedures	**Updated:** Clarified that dumping syndrome caused by gastric bypass surgery precludes participation, not gastric bypass surgery per se

27	Screening Procedures	**Updated:** Clarified severe liver disease indicated by elevated AST/ALT values
28	Hypertension and Corticosteroid Medications	**Updated:** Clarified that low-dose or baby aspirin (LDASA or BASA) is acceptable
28	Hypertension and Corticosteroid Medications	**Updated:** Added list of common hypertension and corticosteroid medications
31	Magee-Womens Hospital Clinical and Translational Research Center	**Updated:** Corrected location of MWH CTRC
32	50 gram Glucose Challenge Test	**Added:** Study samples are tubed from MWH to UPMC CLB for testing
33	IV Protocol	**Added:** Section regarding use of MWH IV team for study visits
34	Visit 1 Forms	**Removed:** Positive GDM Results – Notification Form (does not exist in database, notification of providers documented in Form 11 – 50gm Lab and Repeat Lab)
34	Visit 1 Forms	**Added:** Description of Concomitant Medication Form
35	Critical Glucose Values	**Updated:** All critical glucose values are documented as Adverse Events (AE); only contacted Dr. Davis when database AE form indicated critical value is a Serious Adverse Event (SAE)
36	Blinding	**Updated:** Clarified cases in which the PI or co-I's are unblinded
37	75 g or 100 g Oral Glucose Tolerance Test	**Updated:** Latest time Visit 2 scheduled is 11:30 am instead of 11:00 am
37	75 g or 100 g Oral Glucose Tolerance Test	**Added:** Study samples are tubed from MWH to UPMC CLB for testing
38	Visit 2: IV Protocol	**Added:** Use of MWH IV team for study visits
39	Visit 2 Forms	**Added:** Postpartum Depression Questionnaire – Score of 13 OR answer of anything other than "Never" to Question 10 regarding thoughts of self-harm
39	Visit 2 Forms	**Updated:** 24-Hour Dietary Recall Telephone - Follow-up dietary recall to be completed at either 32w0d or up to 2 weeks after Visit 2

39	Visit 2 Forms	**Removed:** 75gm or 100gm Repeat Fasting Glucose Lab Form – integrated into Form 14 ; 75gm or 100gm Fasting Glucose Lab
39	Visit 2 Forms	**Removed:** Positive GDM Results – Notification Form (does not exist in database, notification of providers documented in Form 14 – 75gm or 100gm Fasting Glucose Lab)
40	Visit 2 Forms	**Added:** Description of Concomitant Medication Form
40	Postpartum Depression Questionnaire	**Updated:** Study staff offer to contact providers to notify of high EPDS score, and offer resources; in severe cases, will be reported as SAE
41	75 g or 100 g OGTT Laboratory Results	**Updated: "**C-reactive peptide" to *high sensitivity* C-reactive peptide
41	75 g or 100 g OGTT Laboratory Results	**Removed:** Cytokines run at Visit 2 (not run in real time at Visit 2)
41	75 g or 100 g OGTT Laboratory Results	**Updated:** Clarified 75 g OFTT diagnosis is ≥ 1 (one *or more*) abnormal value(s); 100 g OGTT diagnosis is ≥ 2 (two *or more*) abnormal values (previously noted as only 1 or only 2)
41-42	"Mild GDM"	**Added:** Section regarding "Mild GDM" results
42	Unblinding Providers to OGTT Results	**Added:** Citation for HAPO Study
42	Critical Glucose Values	**Added:** Any results indicating hypo- or hyperglycemia are reported as Adverse Events
43	Visit 2 Results Back Entry	**Added:** Section regarding back entry of Visit 2 results to participants' EMR, for clinical use post-study
44	Delivery Time Point	**Added:** OSPU also does not collect specimens in cases of medical emergency or precipitous delivery
44	Infant PEA POD Assessment	**Removed:** Entire section – PEA POD never used in study due to unavailability (substituted skinfold measurements instead)
44	Infant Skinfold Measurement	**Updated:** Infant skinfold measurements will be obtained between 24-48 hours after delivery
44	Infant Skinfold Measurement	**Added:** Parents may also refuse skinfold measurements
47	3, 6, and 9 Month Postpartum Forms	**Added:** Description of Infant Status Form
49	Visit 3 IV Protocol	**Added:** Use of MWH IV team for study visits

50	Visit 3 Forms	**Removed:** Positive GDM Results – Notification Form (does not exist in database, notification of providers documented in Form 14 – 75gm Fasting Glucose Lab)
51	Visit 3 Forms	**Added:** Description of Infant Status Form and Concomitant Medication Form
51	Visit 3 Questionnaires and Assessments	**Added:** Participants who are pregnant at Visit 3 may choose to have their 75 g OGTT results sent to their OB provider in lieu of their regular GDM testing
52	Postpartum Depression Questionnaire	**Updated:** Study staff offer to contact providers to notify of high EPDS score, and offer resources; in severe cases, will be reported as SAE
52	Completing Visit 3	**Updated:** Follow-up dietary recall is not scheduled, to avoid biasing patient
53	Visit 3 Laboratory Results	**Updated:** Clarified diagnostic criteria for impaired glucose tolerance and Type 2 diabetes (*one or more* abnormal values)
53-54	Visit 3 Laboratory Results	**Added:** Database will also prompt staff to notify PI of high triglycerides or cholesterol values, to notify participant
54	Visit 3 Results Back Entry	**Added:** Section regarding back entry of Visit 3 results to participants' EMR, for clinical use post-study
54	Quest Diagnostics Visit	**Updated:** Clarified that participants will complete a 75 g OGTT at Quest Diagnostics, and option is only available for Visit 3
55-57	Data Abstraction	**Updated:** CARe service has been replaced by Health Record Research Request (R3) service
56	Data Collection Associated with Study Outcomes	**Added:** ICD-10 procedure and diagnostic codes also used in R3 data abstraction
58-62	Laboratory Procedures and Protocols	**Updated:** Study staff handle all lab procedures, did not use research technician
58	Specimen Collection	**Added:** Section listing specimens collected at each visit
59-60	Visit 2 Laboratory Procedures	**Updated:** Cytokine labs not run in real time; analyzing lab TBD by PI
61	Visit 3 Laboratory Procedures	**Updated:** Cytokine labs not run in real time; analyzing lab TBD by PI
62	Visits 2 and 3 Occurring on Saturdays	**Added:** Section regarding special specimen collection and laboratory procedures for Visits 2 and 3 occurring on Saturdays

63-64	Specimen and Laboratory Flow Charts	**Updated:** Specimen and Laboratory Flow Charts; cytokine labs not run in real time, analyzing lab TBD
67-68	Clinical Laboratory Protocols	**Updated:** Cytokine processing procedures and lab TBD
69	Adherence and Retention	**Removed:** Study website and Facebook page never implemented