STUDY PROTOCOL

Medical Optimization & Management of Pregnancies with Overt Type 2 Diabetes (MOMPOD)

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MEDICAL OPTIMIZATION & MANAGEMENT OF PREGNANCIES WITH OVERT TYPE 2 DIABETES (MOMPOD)

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MOMPOD001v19

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List of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
BG	Blood glucose
BID	Twice a day
BMI	Body mass index
BP	Blood pressure
BPP	Biophysical profile
BW	Birthweight
CBC	Complete blood count
CBG	Capillary blood glucose
CGM	Capillary glucose monitoring
CRF	Case report form
DCC	Data coordinating center
DSMB	Data and Safety Monitoring Board
EDC	Expected Date of Confinement
EKG	Electrocardiogram
EFW	Estimated fetal weight
FBG	Fasting blood glucose
FDA	Food and Drug Administration
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IBS	Irritable bowel syndrome
ICU	Intensive care unit
IDS	Investigational drug services
IND	Investigational new drug
IVF	Intravenous fluids
IVH	Intraventricular hemorrhage
LGA	Large for gestational age
LMP	Last menstrual period
NICU	Neonatal intensive care unit
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NPO	Nothing per oral
NST	Non-stress test
OHA	Oral hypoglycemic agent
PHI	Protected health information
PK/PD	Pharmacokinetics/pharmacodynamics
PI	Principal investigator
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SD	Standard deviation
SGA	Small for gestational age
SMFM	Society for Maternal-Fetal Medicine
SVT	Supraventricular tachycardia
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal
UNC	University of North Carolina
UP	Unanticipated Problem

Study Summary

Title	MEDICAL OPTIMIZATION & MANAGEMENT OF PREGNANCIES WITH OVERT TYPE 2 DIABETES (MOMPOD)
Short Title	MOMPOD
Protocol Number	001v19
Phase	Phase III Clinical trial
Methodology	Randomized, double-blinded
Study Duration	Women will be randomized between 10 weeks 0 days and 22 weeks 6 days gestation and followed until 30 days after infant delivery. Infant outcomes will be followed until 30 days of age.
Study Sites	A complete list of study site(s) is available in the Manual of Operations Appendix
Data Coordinating Center	University of North Carolina Chapel Hill NC
Objective	To compare the safety and efficacy of insulin versus insulin plus metformin for treatment of T2DM complicating pregnancy
Number of Subjects	950

Diagnosis and Main Inclusion/Exclusion Criteria	Diagnosis and Inclusion Criteria
	• Maternal age 18-45 years at enrollment
	• Singleton pregnancy with no known fetal anomalies
	• Overt T2DM
	  ○ Preexisting T2DM requiring medical treatment (oral agent or insulin) or
	  ○ Overt diabetes diagnosed at < 22 weeks 6 days gestation, using either one-step method (75 gm GCT with at least one abnormal value: FBG≥ 92, 1 hr > 180 or 2 hr > 153 g/dl) or two-step method, requiring medical treatment (50 gm GCT > 135 mg/dl followed by 100 GCT with at least two values above thresholds: FBG > 90, 1 hr >180, 2 hr > 155, 3 hr > 140 mg/dl); or other method (e.g. A1C ≥ 6.5%, OR fasting CBG > 126 mg/dL, OR random CBG ≥ 200 mg/dL
	• Willingness to use insulin and study agent only; no other diabetes medical therapy permitted while on study
	• Gestational age at randomization between 10 weeks 0 days and 22 weeks 6 days by menstrual dating confirmed by ultrasound or ultrasound alone
	• Informed written consent
	Exclusion Criteria
	• Multiple gestation (A woman with a twin gestation that spontaneously loses one fetus and retains the second fetus or is electively reduced to a singleton prior to 14 weeks is eligible for participation)
	• Suspected or known fetal major structural or chromosomal abnormality
	• Known pre-existing chronic renal disease (creatinine ≥ 1.5 mg/dL)
	• Known medical contraindications to metformin (history of lactic acidosis)
	• Active liver disease or known liver abnormalities (acute viral hepatitis; ALT or AST > 2x ULN)
	• Medical conditions that predispose the woman to GI distress (Crohn's disease, ulcerative colitis, irritable bowel syndrome, celiac disease)
	• Current or past history of alcohol abuse
	• Known abnormalities in B12 metabolism (pernicious anemia; intrinsic factor deficiency, prior partial or complete gastrectomy, any type of bariatric surgery)
	• Participation in another study that could affect the primary outcome
	• Participation in MOMPOD during a previous pregnancy
	• Unwilling or unable to take insulin
	• Unwilling or unable to swallow the study agent capsule or consume an inert ingredient in the study agent capsule.

	• Other significant chronic medical or psychiatric illness that, in the Investigators opinion, would prevent participation in the study.
Study Product, Dose, Route, Regimen	Metformin 500 mg BID, orally x 1 week (up to 3 wks until tolerance achieved) followed by 1000 mg BID Matching placebo Randomized 1:1, stratified by study site and timing of diabetes diagnosis/baseline gestational age (4 categories: preexisting diagnosis and GA < 18 weeks, preexisting diagnosis and GA ≥18 weeks, diagnosis during pregnancy and GA < 18 weeks, diagnosis during pregnancy and GA ≥18 weeks)
Duration of administration	From enrollment to infant delivery

Outcomes	Primary Outcome: Composite neonatal adverse outcome defined as the proportion of infants that have one or more of the following at birth: • Neonatal hypoglycemia, defined as CBG < 40 mg/dL or any hypoglycemia that requires IVF treatment, or • Birth trauma (umbilical artery cord pH < 7.0) or • Birth trauma (shoulder dystocia with brachial plexus injury, or clavicular or humeral fracture, or ≥ 3 more maneuvers to relieve) or • Hyperbilirubinemia that requires phototherapy within the first 72 hours after delivery, or • Delivery < 37 weeks' gestation, or • Miscarriage (fetal loss < 20 weeks), stillbirth (fetal loss ≥ 20 weeks), neonatal death (death prior to 28 completed days) • LGA infant (birth weight > 90th percentile for gestational age), or • SGA infant (birth weight < 10th percentile for gestational age) or • Low birth weight (< 2500 gm) infant Key Secondary Outcomes: • Neonatal fat mass (%), calculated by infant measurements and skin-fold thickness (anthropometrics) • Maternal clinically relevant hypoglycemia (CBG < 60 mg/dL regardless of symptoms~~)~~ Secondary Exploratory Outcomes: • Maternal weight gain defined as change in weight from randomization until time of delivery, adjusted for gestational age at time of randomization • Maternal side effects such as nausea, vomiting, diarrhea • Maternal compliance determined by pill counts • Maternal intention to breast or formula feed • Adverse maternal outcomes, e.g. death, diabetic ketoacidosis, ICU admission/intubation, renal failure • Maternal obstetrical complications, e.g. placental abruption, preeclampsia • Neonatal metabolic complications other than hypoglycemia or hyperbilirubinemia, e.g. polycythemia; NICU admission > 48 hours/length of stay; intubation, grade 3 or 4 IVH • Postpartum infant feeding experience at 30 days

Statistical Methodology	Incidence of the primary outcome (composite adverse neonatal outcome) will be compared between treatment groups using logistic regression adjusting for study site, timing of diabetes diagnosis (preexisting versus during pregnancy), gestational age at randomization and baseline maternal BMI. The odds ratio and 95% CI will be calculated. Mothers who discontinue from the study prior will be imputed using the distribution of values in the placebo group. Statistical significance is determined relative to p=0.044, to adjust for a planned formal interim analysis. Categorical secondary outcomes will be similarly analyzed with logistic regression, and continuous secondary outcomes will be similarly assessed by analysis of covariance (ANCOVA). Variables that are not normally distributed will be assessed via nonparametric ANCOVA. The key secondary outcomes will be evaluated for statistical significance relative to 0.05 using a step-down strategy. An independent DSMB will review safety outcomes on a regular basis, including formal statistical tests for worsening of the primary outcome in the metformin group. A formal interim analysis to evaluate for early overwhelming efficacy will be performed after 50% and 75% of subjects have delivered and completed follow-up. A formal interim analysis to evaluate for futility will be performed after 75% of subjects have delivered and completed follow-up.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and International Standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. The Eunice Kennedy Shriver National Institute of Child Health and Human Development funds the study. Dr. Kim Boggess holds the FDA IND (125594).

1.1 Background

Diabetes is a serious and growing public health problem

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, and is characterized by varying degrees of insulin deficiency and resistance. In the U.S., T2DM affects greater than 15 million people, over half of which are women. Almost 2 million women of reproductive age (age 18-44 years) have T2DM. T2DM accounts for majority of the diabetes diagnosed in reproductive age women, and complicates ~100,000 pregnancies annually. As shown in Figure 1, the prevalence of T2DM complicating pregnancy is increasing, due in part to the increasing prevalence of obesity.[1, 2] The increase in prevalence is expected to worsen; the International Diabetes Federation projects that the number of women who enter pregnancy with overt T2DM will double by 2030. *T2DM is the most common type of overt diabetes complicating pregnancy and represents a critical public health issue.*

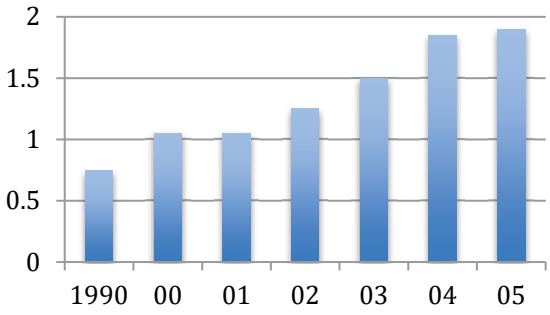

Figure 1. Percent of pregnancies complicated by T2DM is increasing in the U.S.

Pregnancy exacerbates insulin resistance

The physiologic changes of pregnancy are designed to supply glucose to the fetus and placenta. The fetus grows several-fold in size over the second half of gestation, as does its absolute rate of glucose utilization. Placental glucose transfer to the fetus, therefore, must increase to meet the increasing metabolic requirements for glucose of the larger, growing fetus. Placental hormones increase the transplacental glucose concentration gradient, increasing the maternal glucose concentration relative to the fetus. There is transient maternal hyperglycemia after meals due to increasing insulin resistance and transient hypoglycemia between meals and at night due to the continuous fetal draw. These changes can significantly stress maternal physiology, such that the insulin resistance characteristic of T2DM can worsen.[3] *The insulin resistance in T2DM complicating pregnancy creates challenges for adequate treatment to optimize maternal glucose control.*

T2DM is associated with significant maternal and infant morbidity

Poorly controlled pre-gestational T2DM is associated with adverse pregnancy outcomes [4] including miscarriage, congenital birth defects, fetal growth disturbance (both over- and under-growth) [5], preterm birth, preeclampsia, and stillbirth.[6] Up to one-third of pregnancies complicated by T2DM are complicated by early delivery, both medically-indicated and spontaneous preterm birth.[7] ~20% of pregnant women with T2DM develop preeclampsia and ~30% deliver infants that are either small or large-for-gestational age compared to women without T2DM. While maintaining euglycemia within strict parameters is the mainstay of treatment for pre-gestational diabetes and has been shown to reduce fetal overgrowth, *knowledge gaps regarding optimal therapy in pregnant women with overt T2DM exist and must be addressed if we are to successfully reduce the morbidity of T2DM in pregnancy.*

T2DM is also associated with fetal programming of obesity and T2 DM in adulthood

Infants born to women with overt T2DM are at increased risk for childhood obesity and overt T2DM in adulthood compared to siblings born after non-diabetic pregnancies.[8-10] There are epidemiological and experimental studies demonstrating that intrauterine hyperglycemia predisposes the offspring to obesity.[11-13] Studies have shown that offspring exposed to maternal over nutrition, obesity, T1DM and T2DM and GDM have high risk for T2DM and obesity in adult life.[14-17] Offspring of women with T2DM are 8 times more likely to develop T2DM as adults when compared to offspring of non-diabetic women.[18] *The implications of T2DM*

complicating pregnancy reach far beyond infant birth. This proposal lays the groundwork for long-term follow up of infants exposed to metformin in-utero.

Metformin is the preferred treatment of T2DM when nonpregnant
The American Diabetes Association and the European Association for the Study of Diabetes recommend that metformin therapy (in absence of contraindications) be initiated, concurrent with lifestyle intervention, at the time of T2DM diagnosis.[19] Metformin is considered optimal for initial therapy for T2DM[19-21] because of glycemic efficacy [22, 23] absence of weight gain [23, 24] fewer hypoglycemic episodes [25], general tolerability [26, 27] and favorable cost. [28]

Metformin is a logical treatment choice for treatment of overt T2DM in pregnancy
Current recommendations for the medical management of overt T2DM complicating pregnancy include frequent monitoring of blood glucose combined with dietary management and insulin therapy to achieve euglycemia.[29] Use of oral hypoglycemic agents has recently gained acceptance for treatment of gestational diabetes (GDM). The efficacy of oral hypoglycemic agents for treatment of GDM is comparable to insulin, with fewer side effects and more patient preference.[30, 31] In a large randomized clinical trial, Rowan and colleagues[32] found that in women with GDM, metformin (alone or in combination with insulin) was not associated with an increase in perinatal complications when compared with insulin alone. There were fewer maternal hypoglycemic events (3 vs. 8%, P=.008), and less weight gain (0.4 vs 2 kg, P<.001) among women treated with metformin compared to insulin alone. Two year follow-up of infants of mothers enrolled in the study demonstrated no adverse effects, and suggested a reduction in visceral body fat.[33]

In a retrospective case-control study of women with overt T2DM, the same authors found comparable maternal outcomes between women treated with metformin versus insulin.[34, 35] These data taken together suggest that metformin may be a useful modality for treatment of T2DM complicating pregnancy. A trial to determine the optimal treatment of overt T2DM in pregnancy is needed. This proposal will compare the effectiveness of insulin mono-therapy versus insulin plus metformin for treatment of overt T2DM complicating pregnancy; establish a bank of maternal specimens for future study of the effect of metformin use during pregnancy; and create a cohort to follow for long-term health effects of in utero exposure to metformin.

1.2 Investigational Agent

Metformin is a biguanide oral hypoglycemic agent that reduces blood glucose levels, predominantly by improving hepatic and peripheral tissue sensitivity to insulin without affecting insulin secretion. All biguanides, including metformin, exist as positively charged protonated forms as physiologic pH. There is very little binding to plasma proteins. Metformin, because of it's short-chain, hydrophilic chemical concentration, undergoes very little hepatic metabolism and is eliminated by renal excretion.[36] **This important distinction reduces the risk for lactic acidosis compared to other biguanides.**

The pharmacokinetic properties of metformin have been investigated in healthy and diabetic volunteers; while data is limited, metformin PK/PD appears to be unaffected by presence of diabetes. When administered orally, metformin gastrointestinal absorption is incomplete with 20-30% of the dose recovered in feces. Doses of 500 – 1500 mg have an absolute oral bioavailability of 40-60%.

Once absorbed, metformin displays a log-linear PK/PD with oral doses up to 1500 mg. Higher maximum plasma concentrations are observed following 850 mg BID compared to 500 mg BID (~ 30% difference). Metformin concentrations do not appear to be correlated with fasting blood glucose levels.

1.3 Preclinical Data

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity or teratogenicity. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.[37] However, there are no experimental animal studies cited in the product labeling.

Pregnant mice given metformin 300 mg/kg throughout most of gestation did not have alterations of body weight or food intake of dams; metformin-exposed fetuses weighed less.[37-39] Following birth, compared to non-exposed pups, metformin-exposed pups may have differential gene expression in response to environmental factors such as high fat diet.

Metformin crosses the placenta via specific transporters, and fetal concentrations are only slightly lower than maternal concentrations. Plasma metformin concentrations appear to be less in pregnant compared to non-pregnant women due to the higher glomerular filtration rate during pregnancy. There is minimal transport of metformin into breast milk.[40]

1.4 Clinical Data

In the U.S., since 1994, metformin has been approved for use for the treatment of type 2 diabetes. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities.[41]

According to Reprotox®, human experience with metformin use in pregnancy is reassuring, although the number of exposed pregnancies is limited. The use of metformin may be associated with an increased maternal risk for preeclampsia [42], although recent data contradicts this finding.[43] The FDA has labeled metformin as category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. (www.fda.gov/ohrms/dockets/dailys/02/May02/053102/800471e6.pdf) Of important note, a recent randomized clinic trial found that among obese women without diabetes, the antenatal administration of metformin from 12-18 weeks until delivery reduced maternal weight gain but not neonatal birth weight; reduced risk for preeclampsia by almost half, and was not associated with any adverse fetal effects.[43]

1.5 Rationale

- T2DM is a significant public health problem that affects up to 100,000 pregnancies annually in the US.
- Current recommendations for treatment of overt T2DM complicating pregnancy are founded on data regarding the treatment of Type 1 diabetes.
- Metformin is preferred for the treatment of T2DM in non-pregnant individuals and appears to confer non-glycemic benefits.
- A trial to determine the optimal treatment of overt T2DM in pregnancy is needed. This proposal will compare the efficacy and safety of insulin mono-therapy versus insulin plus metformin for treatment of overt T2DM complicating pregnancy; establish a bank of maternal specimens for future study of the effect of metformin use during pregnancy; and create a cohort to follow for long-term health effects of in utero exposure to metformin.

2 Study Objective

The **objective** of this study is to compare the safety and efficacy of insulin mono-therapy versus insulin plus metformin for treatment of T2DM complicating pregnancy.

3 Study Design

3.1 General Design

This is a randomized double-blind clinical trial of insulin plus placebo versus insulin plus metformin for the treatment of overt T2DM complicating pregnancy. Women will be randomized between 10 weeks 0 days and 20 weeks 6 days gestation and followed until 30 days after delivery. Neonate outcomes will be followed until 30 days of age.

All study subjects will receive standard surveillance and treatment for overt T2DM in pregnancy, which may include but is not limited to:

- Daily prenatal vitamin
- Supplemental folic acid
- Nutrition counseling and dietary recommendations
- Insulin therapy as prescribed by primary clinician (obstetrician or endocrinologist). The decision of the primary clinician (obstetrician or endocrinologist) on insulin dosing will be guided by standard guidelines, based on the protocols that are used at the participating clinical trial centers (see below)

- Instruction on capillary glucose monitoring; recommendation to test capillary blood glucose at least 4 times/day; goal capillary blood glucose parameters will be communicated to the subject by her primary clinician (obstetrician or endocrinologist).
- Subject's primary clinician (obstetrician or endocrinologist) will make as-needed adjustments in insulin dosing based on patient-recorded CBG measurements.
- Blood and urine sampling for hematologic, liver, and kidney function at primary obstetric clinician discretion.
- Ultrasound assessments of fetal size and well-being at primary obstetric clinician discretion.
- Fetal surveillance by NST (30 minutes of continuous fetal heart rate monitoring) or BPP (30 minutes of ultrasound to monitor for fetal breathing, movement, fluid) at primary obstetric clinician discretion.
- Routine care in labor and delivery, including but not limited to insulin therapy.

Guidelines for insulin management have been created based on current strategies used at the study sites. These guidelines are detailed below and in Section 8.2. Briefly, insulin dosing will be weight-based and administered as 2-3 daily injections; insulin dose adjustments will be made at the discretion of the study site primary clinician (obstetrician or endocrinologist) using glycemic goals that are based on ADA guidelines, also detailed in Section 8.2. Women will test capillary blood glucose levels daily as fasting, and either one or two hours postprandial (PP), per protocol at each clinical site, with goals as listed below. The primary obstetrician or endocrinologist will manage insulin dosing to achieve these goals as closely as possible.

In addition to above standard care, enrolled and randomized subjects will receive surveillance and treatment solely for study purposes, including:

- Instruction to stop any other diabetes or OHA medication and begin/continue insulin. All subjects will begin taking the study agent 24-72 hours after randomization (e.g. with the evening meal the day AFTER randomization). This allows those who have been on an oral agent previously to have at least a 24 hour washout period. For instances where the bottle cannot be given to the patient at the randomization visit, deliver the bottle to the patient within 72 hours of randomization visit.
- Daily administration of study agent: one capsule (metformin 500 mg or placebo) twice daily for 7 - 21 days based on study agent tolerance, followed by two capsules (metformin 1000 mg or placebo) twice daily. Drug tolerance is defined on a per-week basis as: 1) subject's reported tolerance of the symptoms of nausea/diarrhea/vomiting and 2) less than 2 episodes of self-reported hypoglycemia as manifested by a CBG < 60mg/dL.
- Subjects will be instructed on how to manage symptoms at home including taking the study agent with meals and use of over the counter medications to relieve symptoms (nausea, diarrhea, and vomiting). If she has **two or more** self-reported hypoglycemia episode (CBG < 60mg/dL), she will be instructed to call their provider.
- Subjects will be instructed to increase study agent if she is tolerating the lower dose. If not, she will remain on the lower dose for up to 3 7-day periods. Once increased to two capsules BID, she will be contacted weekly to determine tolerance at the higher dose.
- If the subject is unable to tolerate the study agent after a maximum of 21 days at either dose, she will be discontinued from the study agent. All subjects who discontinue study agent will be followed through delivery.
- If the subject reports intractable GI symptoms or hypoglycemia during the phone calls to assess study agent tolerance, study staff will educate the subject on timing for taking agent with food and will remind her of the medications she can use to relieve symptoms. If she experiences hypoglycemia, study staff will instruct her to contact her primary clinician (obstetrician or endocrinologist) to evaluate if insulin dosing my need to be adjusted.
- Intractable symptoms are defined as any nausea, vomiting, or diarrhea despite the use of medications to decrease these symptoms.
- Study visits should occur approximately monthly to coincide with prenatal visits. At these visits we will assess compliance and side effects and dispense study agent.
- Blood draw at 24-30 weeks' gestation to store serum for future studies.
- Subjects will be instructed to discontinue oral study agent (metformin or placebo) at the onset of labor, induction of labor, or the morning of a scheduled cesarean delivery. No metformin will be administered

during labor or in anticipation of scheduled cesarean delivery, when patients are asked to remain NPO (nothing per oral) for 12 hours prior to procedure.
- Chart abstraction for maternal and delivery data (up until maternal discharge) and neonatal data (up until infant discharge or until 30 days of age, whichever comes first)
- Phone call or in-person contact with the mother 30-45 days following delivery to check for serious adverse events and neonatal outcomes.
- Within 72 hours of delivery, measurement of neonatal fat mass (anthropometrics) measured by skin fold caliper measurements unless the infant is < 28 weeks gestation or the infant's condition is unstable.

3.1.1 Randomization and Blinding

Randomization for enrolled subjects will occur at 10 weeks 0 days to 22 weeks 6 days of gestation. Enrolled subjects will be assigned to placebo or metformin in a 1:1 ratio in a permuted block design, stratified by study site and timing of diabetes diagnosis/baseline gestational age (4 categories: preexisting diagnosis and GA < 18 weeks, preexisting diagnosis and GA ≥18 weeks, diagnosis during pregnancy and GA < 18 weeks, diagnosis during pregnancy and GA ≥ 18 weeks). The randomization sequence will be prepared and maintained centrally by the UNC Data Coordinating Center (DCC). A statistician not otherwise involved with the study will create the randomization scheme, which will be implemented electronically within the web-based data management system. All study staff will be blinded to the allocation scheme until the end of the study. Emergency unblinding is available 24/7 for designated staff through the web-based data management system.

3.1.2 Informed Consent Criteria

Each MOMPOD Study Site will develop a Site-specific written consent form using the template consent form provided by the MOMPOD Coordinating Center. Each Site is responsible for obtaining IRB approval and written informed consent for each enrolled subject. Each Site will develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form will be provided to the enrolled subject. A person fluent in their language will enroll women who are not fluent in English. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded from participation.

3.2 Study Outcomes

3.2.1 Primary Study Outcome

The primary study outcome is a composite adverse neonatal outcome, defined as a combination of the proportion of infants that have:

- Neonatal hypoglycemia, defined as CBG < 40; or any hypoglycemia that requires treatment with I.V. fluids or glucose gel (Note: all cases of unmeasured CBG are considered as not meeting criteria, since it is not standard of care to routinely measure CBG for all neonates)
- Birth trauma, defined as umbilical artery cord pH < 7.0, or Shoulder dystocia with brachial plexus injury, or clavicular or humeral fracture, or $\underline{\geq}$ 3 more maneuvers to relieve (Note: all cases of unmeasured pH are considered as not meeting criteria, since it is not standard of care to measure umbilical cord pH on all infants. In a study of over 11,000 term infants none of the 11 cases of pH < 7.05 were associated with an Apgar score < 3 at 5 minutes [44]
- Hyperbilirubinemia that required infant phototherapy within the first 72 hours after delivery
- Delivery < 37 weeks' gestation
- Miscarriage (fetal loss < 20 weeks), stillbirth (fetal loss $\underline{\geq}$ 20 weeks), neonatal death (death prior to 28 completed days), as defined by the Centers for Disease Control National Center for Health Statistics [www.cdc.gov/nchs; accessed 10/21/2016]
- Large-for-gestational age (LGA) infant (birthweight > 90^{th} percentile for gestational age)[45]
- Small-for-gestational age SGA infant (< 10^{th} percentile for GA) or low birth weight (< 2500 gm) [45]

In cases for which classification of the primary outcome is not straight-forward, event status will be reviewed by blinded MOMPOD Study investigators.

3.2.2 Secondary Study Outcomes

Key Secondary Outcomes:

- Infant fat mass (%) as measured by anthropometrics, calculated using the following:
  - Birth weight [chart abstracted]
  - Recumbent length [chart abstracted]
  - Head circumference [chart abstracted]
  - Right upper mid-arm circumference, measured by study staff
  - Right triceps skin fold, measured by study staff
  - Right subscapular skin fold, measured by study staff
  - Right flank skin fold, measured by study staff
- Maternal clinically relevant hypoglycemia (CBG < 60 mg/dl regardless of symptoms)

Exploratory Secondary Outcomes:

- Maternal weight gain defined as change in weight from randomization until time of delivery, adjusted for gestational age at time of randomization
- Maternal side effects such as nausea, vomiting, diarrhea
- Maternal compliance determined by pill counts
- Maternal intention to breast or formula feed
- Adverse maternal outcomes, e.g. death, diabetic ketoacidosis, ICU admission/intubation, renal failure
- Maternal obstetrical complications, e.g. placental abruption, preeclampsia
- Neonatal metabolic complications other than hypoglycemia or hyperbilirubinemia, e.g polycythemia; NICU admission > 48 hours/length of stay, hyperbilirubinemia requiring phototherapy, intubation, grade 3 or 4 IVH
- Postpartum infant feeding experience at 30 days

3.2.3 Additional Study Outcomes

- Biospecimen collection**:**

  One 5 mL tube of blood will be drawn at 24-30 weeks' gestation. Maternal serum will be frozen at -80°C for future studies. These studies (to be funded by future applications to NIH, local or other funding sources) will include a comprehensive assessment of the role and interactions of clinical, biological and biophysical factors (e.g., maternal obesity, smoking, hyperlipidemia, and ultrasound findings) on the occurrence and severity of maternal and neonatal outcomes. Examples of biomarkers to be measured include but are not limited to A1c, sFlt-1, PlGF, leptin, and C-peptide.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Maternal age 18-45 years at enrollment
2. Informed written consent
3. Singleton fetus with no known or suspected anomalies
4. Overt type 2 diabetes, defined as either:
   - Pregestational type 2 (overt) diabetes requiring medical treatment (oral agent or insulin), or
   - Overt diabetes diagnosed at < 22 weeks 6 days gestation, using either one-step method (75 gm GCT with at least one abnormal value: FBG$\geq$ 92, 1 hr > 180 or 2 hr > 153 g/dl) or two-step method requiring medical treatment (50 gm GCT > 135 mg/dl followed by 100 GCT with at least two values above thresholds: FBG > 90, 1 hr >180, 2 hr > 155, 3 hr > 140 mg/dl); or other method (e.g. A1C $\geq$ 6.5%, OR fasting CBG > 126 mg/dL, OR random CBG $\geq$ 200 mg/dL
5. Willingness to use insulin and study agent only; no other diabetes medical therapy permitted while on study

6. Gestational age at randomization between 10 weeks 0 days and 22 weeks 6 days by menstrual dating confirmed by ultrasound or ultrasound alone

4.2 Study Gestational Age Determination

Gestational age is determined in the following manner, and is denoted “study gestational age”. The “study EDC” is based on the study gestational age. If the pregnancy is conceived by in-vitro fertilization, study gestational age is calculated from the date of embryo transfer and the embryo age at transfer. If the pregnancy is conceived spontaneously (including ovulation induction and artificial insemination) information from the LMP and earliest dating ultrasound are used to assign study gestational age. The following algorithm is used:

- The first day of the LMP is determined, and a judgment made as to whether or not the patient has a “sure” LMP date.
- If the LMP date is sure, Study Gestational Age is determined by a comparison between the gestational age by LMP and by the earliest dating ultrasound. The first dating ultrasound must have been conducted before 22 weeks 6 days by LMP. If the ultrasound confirms the gestational age calculated by LMP as in the Table1 below, the LMP gestational age will be used as the Study Gestational Age. Otherwise, Study Gestational Age will be determined based upon the ultrasound measurement.

  Table 1.

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
Up to 13 weeks 6 days	+5 days
14 weeks 0 days to 22 weeks 6 days	+7 days

- If the LMP date is unsure, measurement(s) obtained at the patient’s first dating ultrasound examination is used to determine the Study Gestational Age. The first dating ultrasound must be conducted before 20 weeks 6 days.
- The data management system creates a locked record of the study EDC at randomization. This serves as a record of the EDC at the time of randomization to keep track of the patient’s stratum and eligibility. For other purposes like clinical care and data analysis, the study EDC can be updated before 30 weeks gestation based on an ultrasound taken before 21 weeks gestation.

4.3 Exclusion Criteria

1. Multiple gestation (A woman with a twin gestation that spontaneously loses one fetus and retains the second fetus or is electively reduced to a singleton prior to 14 weeks is eligible for participation)
2. Suspected or known fetal structural or chromosomal abnormality
3. Known pre-existing renal disease (creatinine $\geq$ 1.5 mg/dL)
4. Known medical contraindications to metformin (history of lactic acidosis)
5. Acute liver disease or known liver abnormalities (acute viral hepatitis, AST/ALT > 2x ULN)
6. Known medical conditions that predispose a woman to GI distress (Crohn’s disease, ulcerative colitis, irritable bowel syndrome (IBS) , celiac disease)
7. Current or past history of alcohol abuse
8. Abnormalities in B12 metabolism (pernicious anemia, intrinsic factor deficiency, prior partial or complete gastrectomy, any type of bariatric surgery)
9. Participation in another study that could affect primary outcome,
10. Randomization in MOMPOD during a previous pregnancy
11. Unwilling or unable to take insulin
12. Unwilling or unable to swallow the study agent capsule or consume an inert ingredient in the study agent capsule.

13. Other significant chronic medical or psychiatric illness that, in the Investigators opinion, would prevent participation in the study.

4.4 Subject Recruitment and Screening

Study personnel will review outpatient records or prenatal records under a limited waiver of HIPAA granted by the Institutional Review Board to determine if a patient meets eligibility requirements. If eligible, study personnel will approach medical provider to determine appropriateness of patient to serve as a study subject. If appropriate, study personnel will invite the patient to serve as a study subject.

Study personnel will describe the study in detail and review the study protocol with the patient. Women agreeing to participate will sign a consent form; one copy will be placed in their medical record, and a copy will be given to the patient for her records.

4.5 Early Study Agent Discontinuation or Study Withdrawal of Subjects

Subjects may choose to stop double-blind study agent or withdraw from the study at any time and for any reason. If the subject stops study drug after titration to therapeutic dose then the subject may be restarted on study medication at discretion of the PI or treating physician unless the patient meets one of the specific stopping rules below. If a subject permanently discontinues study agent, the site will still collect the blood specimen, fetal measurements and outcome data. In rare instances, a subject may be withdrawn from the study if in the opinion of the investigator it is not in the subject's best interest to continue study participation.

Specific rules to stop study agent for an individual subject:

- Maternal side effects that cannot be managed with oral medication. Subjects may experience nausea, vomiting or diarrhea as a result of study agent. It will be challenging to distinguish symptoms of pregnancy from side effects of metformin. Women will be instructed to take the study agent with meals, to reduce potential for side effects. Those who experience GI symptoms will be offered routine medication management (anti-emetics). If the subject is unable to tolerate the study agent after 21 days on one capsule BID or after 21 days on two capsules BID, she will discontinue the study agent. However, study participation and data collection will continue until study completion.
- Maternal or fetal complication believed to be related to study agent
- Study agent may also be discontinued in cases of unmanageable, irreversible, or serious AE
- Study agent will be continued from randomization until delivery, even if the subject requires home bed rest or hospitalization for medical or obstetrical reasons, unless medical contraindications develop (e.g. acute renal insufficiency defined as creatinine $\geq$ 1.5 mg/dL or liver disease defined as AST/ALT > 3x ULN)

Data Collection and Follow-up for Subjects who Discontinue Study Agent:

Subjects who discontinue double-blind study agent will continue to have maternal and neonate data collected through study completion. Every effort will be made to collect the blood specimen, neonatal measurements, and maternal and neonatal outcome data on all randomized subjects, even if they discontinue study agent or deliver at a non-study hospital.

4.5.1 Staff Training and Monitoring of Proficiency

The Co-PIs, Co-I, and Project Coordinator will train study staff on all aspects of the study protocol (e.g., screening, recruitment, enrollment, randomization; study visit data collection; specimen and data collection). Training sessions to orient staff to protocol and data collection forms will be held by webinar teleconference. Following training, all study staff must demonstrate proficiency in the protocol implementation as defined in the MOMPOD Manual of Procedures/Operations. Once proficiency is demonstrated, individual study staff will gain password protected access to the electronic data entry website and can begin screening and recruitment of subjects. The DCC will generate data quality queries on an ongoing basis to inform sites of continued data collection proficiency.

Dr. Berry (Co-PI) or her designee will train the local study site project managers and staff on the proper technique for infant measurements via webinar teleconference using a standardized system used in previous studies.[46, 47] Despite offering many benefits (low costs, easy to perform, little equipment required),

anthropometric assessments are challenging due to their vulnerability to measurement errors and lack of reliability. Unreliability can occur due to imprecision, referring to the measurement error variance due to intra- and inter-observer variability [48, 49]. Imprecision can arise from inadequate or improper training of personnel, difficulties in measurement of certain anthropometric characteristics such as skinfolds, and instrumental or technical errors.

We created the step by step approach in the Manual of Operations for all anthropometric measurements and a training video to teach bicep circumference and tricep, subscapular and flank skinfolds. To measure inter-rater reliability, sites will be chosen at random by the DCC and for that entire month all infant bicep circumference and tricep, subscapular and flank skinfolds will be measured twice by different staff members. Inter-rater reliability will be analyzed quarterly by calculating a inter-rater reliability coefficient. This allows timely feedback to be given to the site project managers and study staff, and corrective measures taken quickly of reliability is not adequate.

5 Analysis Plan

Analyses will follow the Intention-to-Treat (ITT) principle in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention or discontinued study agent prior to delivery. Primary analyses will be based on the Intent-to-Treat population, which includes all randomized subjects who took at least one dose of study agent. In addition, a secondary analysis of the primary outcomes will be completed for the Per-Protocol (PP) population, defined as a subset of the ITT population who took assigned double-blind study agent until the time of delivery without any major protocol deviations. Major protocol deviations include violations in inclusion and exclusion criteria at enrollment and poor compliance with study drug, defined as subjects taking less than 50% of study drug. All major protocol deviations will be identified without regard to treatment or outcome.

Descriptive statistics, chi-squared tests and analysis of variance (ANOVA) will be used to characterize subjects enrolled and randomized to determine comparability of the two intervention groups at baseline for characteristics considered to be prognostic for the primary outcome such as maternal body mass index (BMI), parity, and medical co-morbidities.

5.1 Primary Outcome

Incidence of the primary outcome (composite adverse neonatal outcome) will be compared between treatment groups using logistic regression adjusting for study site, timing of diabetes diagnosis (preexisting versus during pregnancy), gestational age at randomization (as a continuous measure), and baseline maternal BMI. Any sites with low enrollment may be pooled for statistical analyses. Odds ratio and 95% CI will be calculated, as well as number needed to treat to prevent the composite adverse neonatal outcome. Subjects who discontinue from the study and therefore have unknown primary outcome will be considered as events. Statistical significance is determined relative to p=0.044, to adjust for the formal interim analysis (see section 5.5)

Sensitivity analysis of the primary outcome will include:

(a) Complete case analysis excluding subjects who discontinue from the study and therefore have unknown primary outcome

(b) Multiple imputation of missing values for the primary outcome, which assumes study drop-outs are missing at random, and

(c) Subjects who discontinue from the study will be considered as events

(d) Analysis of the Per-Protocol population.

5.2 Additional Analyses of the Primary Outcome

Pre-specified subgroup analyses will be conducted for factors that may be related to the outcome measures: maternal BMI (obese versus non-obese), gestational age at time of randomization (10-<14 weeks, 14-<18 weeks, 18-<21 weeks), and timing of diabetes diagnosis (preexisting vs during pregnancy), and by compliance

level. Interaction tests will be used to determine whether the addition of metformin significantly differs across subgroups such as obesity (BMI $\geq$ 30 kg/m^2), and reported compliance/adherence. P-values of 0.10 will be considered indicative of significant subgroup differences.

We will perform other analyses to assess treatment effectiveness, adjusting for additional baseline patient characteristics (covariates). The objectives of these analyses are to estimate the influence of covariates on the outcome and to use covariates to improve the estimated difference between treatment groups. A logistic regression model will be created to identify and estimate the effect of multiple prognostic factors on the occurrence of the composite adverse neonatal outcome. These analyses will be considered exploratory in nature and will not be viewed as providing confirmatory tests of hypotheses. Descriptive analyses will also evaluate treatment groups differences for each of the components of the composite outcome.

5.3 Secondary Outcomes

There are two key secondary outcomes: infant fat mass (%) as measured by anthropometrics, and proportion of subjects with maternal clinically relevant hypoglycemia. Statistical significance of treatment group comparisons for the key secondary outcomes will be evaluated in a step-down fashion in order to preserve the study-wise type 1 error rate. If the primary outcome is found statistically significant (at $p < 0.044$), then infant fat mass will be evaluated relative to p=0.05. If found statistically significant, then the incidence of maternal hypoglycemia will be evaluated relative to p=0.05. If any statistical test in this order fails to reach statistical significance, then subsequent parameters will not be evaluated for statistical significance.

Analyses of all other secondary outcomes are considered exploratory in nature and will not be viewed as providing confirmatory tests of hypotheses. There will be no adjustment for multiple comparisons of the exploratory secondary outcomes, and p-values will be provided for descriptive purposes only.

Treatment groups will be compared for categorical secondary outcomes with logistic regression, and for continuous secondary outcomes with analysis of covariance (ANCOVA). Variables that are not normally distributed will be assessed via nonparametric ANCOVA. All analyses will adjust for study site, timing of diabetes diagnosis (preexisting versus during pregnancy), gestational age at randomization, and maternal BMI.

Further logistic regression and ANCOVA models will be used to identify and estimate the effect of multiple prognostic factors on secondary outcomes. Interaction tests will be used to determine whether the addition of metformin significantly differs across subgroups such as obesity (BMI $\geq$ 30 kg/m^2), reported compliance/adherence, etc.

5.4 Sample Size Calculation

The MOMPOD Study originally proposed to enroll 1200 participants to achieve 1080 completed mother-infant dyads. Our original sample size assumed a primary outcome event rate of 25% and had 94% power to detect a 0.60 effect size of metformin compared to placebo. The study is currently at the end of year 2 (which was extended to 12/31/2019 through a no cost extension due to delays in startup).

As of October 15, 2018, we have enrolled 255 participants, and with 24/month will achieve our new sample size in 23 months. The MOMPOD Study is scheduled to end in 26 months, in 12/31/2021. A smaller sample size ensures that the study will finish on time. We believe that this can be accomplished without sacrificing scientific integrity of the study.

Our initial sample size of 1200 assumed a 25% primary outcome event rate, an estimate based on limited published data on outcomes in pregnancies complicated by type 2 diabetes and from extrapolating from outcome data in gestational diabetes. Preliminary data on the first 102 MOMPOD women to deliver show that the primary outcome event rate is substantially higher than originally estimated. 73 (72%) of 102 of live births experienced the primary composite outcome, and 5 (2%) of 221 of women with current gestational age >20 weeks had a miscarriage or stillbirth. This difference is significant: it demonstrates the morbidity experienced by pregnant women with type 2 diabetes and further exemplifies the need for alternative strategies to care for these women.

In May 2019, we revised the target sample size 950 women based on the overall event rate and discontinuation rate. A 10% loss to follow-up leaves 855 subjects with complete data and follow-up (427 per

arm). We expect an additional 10-20% of subjects will discontinue the study agent for any reason including side effects or intolerance, but will contribute follow-up data. This sample size gives adequate power over a range of expected primary outcome event rates, with type I error set at 0.044 (reduced from 0.05 for interim analysis), and maintains reasonable power assuming that 20% of subjects immediately stop taking study agent. Published data suggest that up to 30% of pregnant women with T2DM have an adverse neonatal outcome.[4-7]

Table 2. Sample Size and Power Calculation

Sample size (completers)	Power (%)	Power (%) if 10% of metformin group stops study agent	Power (%) if 20% of metformin group stops study agent	Overall Event Rate (%)	Placebo Event Rate (%)	Metformin Event Rate (%)	Odds Ratio	Linear Reduction (%)[a]
1200 (1080)[b]	94	88		25	30	20.5	.60	32
950 (855)	89	82	72	75	80	70	.60	12
950 (855)	92	85	77	70	76	65	.60	16
950 (855)	95	90	80	60	66	54	.60	18
950 (855)	96	93	85	50	57	44	.60	23

a Linear reduction is difference in event rates divided by placebo event rate
b This row represents the original power and sample size target

As noted in Table 2, our approach gives us at least 72% power to detect an odds ratio of 0.60 for metformin versus placebo, assuming a 20% discontinuation rate and an 80% event rate in the placebo group. Other scenarios assuming a lower primary outcome rate in the placebo group will yield 77%-85% power to detect a treatment difference.

5.5 Interim Analysis

We will perform a formal interim analysis to evaluate for early overwhelming efficacy after 50% and 75% of subjects have delivered and completed follow-up. We will also perform a formal interim analysis to evaluate for futility after 75% of subjects have delivered and completed follow-up.

For assessing early efficacy, the significance level for the interim and final analysis will be based on Lan-DeMets α-spending functions with O'Brien-Fleming boundaries in order to maintain the study-wise α level at 0.05. The α level will be 0.0031 at 50%, 0.0183 at 75% and 0.044 at the final analysis. The exact α level at the interims will be determined based on the actual percent of data available at the interim. Assuming 90% power at the end of the study, there is a 26% chance of meeting the stopping boundary at the first interim and 69% chance of meeting the stopping boundary at the second interim.

Futility will be assessed at 75% based on conditional power. The DSMB may recommend study stop due to futility if the upper limit of the 80% confidence interval for conditional power does not exceed 50%.

A formal interim analysis for safety will be conducted beginning one-year after enrollment and then every six months, to test whether the primary composite adverse neonatal outcome is significantly worse in the insulin/metformin group compared to the insulin/placebo group using Lan-DeMets α-spending functions with Pocock boundaries. Based on a one-sided alpha level of 0.025, the DSMB may consider stopping the trial at each of six interim looks if the p-value < 0.007 corresponding to worse composite neonatal outcome in the insulin/metformin group. The DSMB will not evaluate for early efficacy except as described above at 75%.

Analyses will be performed by the independent unblinded study statistician and presented to the DSMB, which will make recommendations regarding further conduct of the trial. The DSMB charter will include thresholds and rules for trial stoppage based on formal safety, efficacy, and futility limits. Safety monitoring is described in detail in Section 9.

6 Intervention

All subjects will receive insulin and metformin, 500 mg twice daily, or placebo, from enrollment for one week and then metformin 1000 mg or placebo twice daily until delivery.

6.1 Preparation and Administration of Study Agent

Village Compounding Pharmacy will provide the blinded study agent (metformin and placebo) to the research sites. Study agent will be dispensed to subjects in a single bottle of 120 opaque capsules containing either 500 mg metformin or placebo matched to appearance and taste. Randomization will be performed via the web-based data management system and a reporting feature within the system will indicate which bottle to dispense to the study subject at each study visit. Study visits should occur approximately monthly to coincide with prenatal visits. Study agent will be bottled in 30-day quantities. Bottles will be labeled with the subject identification number. Subjects will be instructed to take study agent with food, as one capsule (500 mg metformin or placebo) twice a day for 7 or up to 21 days depending on study agent tolerance (see section 3.1) then two capsules (1000 mg metformin or placebo) twice a day, until delivery. Subjects will be instructed that if they miss a dose to continue with dosing and not double up to account for missed dose.

6.2 Subject Compliance Monitoring

Subjects will be queried at study visits by study staff regarding compliance with study regimen. Capsule counts will be done on all returned bottles. The sites will remind the subject to bring her bottles with her to study visits and make every attempt to retrieve all used and unused bottles of study agent.

6.3 Prior and Concomitant Therapy

Subjects will have clinical treatment decisions made by the primary physician (obstetrician and/or endocrinologist), independent of study participation. All subjects will receive standard care as noted previously.

7 Receiving, Storage, Dispensing and Return

7.1 Receipt of Supplies

Village Compounding Pharmacy will store metformin and placebo and ship to participating clinical sites as needed. Study sites will keep an investigational agent supply log.

7.2 Storage of Study Agent

The study agent will be stored at the clinical site in a cool, well-ventilated locked area and kept away from heat, sources of ignition, and from incompatibles such as oxidizing agents, moisture.

7.3 Dispensing of Study Agent

The local study site is responsible for arranging blinded study agent (metformin or placebo) to be dispensed to subjects. Regular reconciliation will be performed to document study agent assigned to and returned from the subject.

7.4 Destruction of Study Agent

At the completion of the study, there will be a final reconciliation of study agent received by the site, dispensed to subjects, returned from subjects, and remaining Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused investigational agent according to each hospital's investigational agent policy. Metformin or placebo destroyed on site will be documented in the study files.

8 Study Procedures

8.1 Eligibility

Study staff will review records on a daily basis. Eligibility for participation is outlined above. Eligible women will be approached after study staff obtains verbal consent to do so from the primary provider.

Women screened will be assigned a unique study ID that will be used to identify all study data collection forms and research specimens. The master list linking the unique study ID with subject PHI will be kept in a secure location either in a locked cabinet or on a password protected computer/server with folder access control.

8.2 Study intervention and procedures

The assigned study agent will be given to the subject by the study staff. Study visits should occur approximately monthly to coincide with prenatal visits. Study staff will dispense study agent, discuss compliance and side effects and perform pill counts on returned bottles. The sites will remind the subject to bring her bottles to her appointment, and make every effort to retrieve all bottles of study agent.

Clinical care will continue per recommendations of the primary obstetrician and/or endocrinologist caring for the patient. The primary obstetrician and/or the primary endocrinologist will make decisions regarding insulin dosing based on the following standardized guidelines for maternal and fetal surveillance, and timing of delivery:

All sites will use weight-based insulin dosing, split as two to three injections using a combination of short and intermediate-acting insulin. These guidelines are based on currently accepted care[50] as well as routine practice at the study sites. Choice of insulin is at primary obstetric or endocrinologist discretion based on insurance coverage and provider preference. Rapid acting insulins include Novolog, Apidra and Humalog. Short acting insulins include Humulin R and Novolin R. Intermediate insulins include Humulin N, Novolin N, and NPH. Long acting insulins include Detemir and Lantus. Total daily insulin dose and type of insulin will be recorded and considered in data analysis as described in statistical analysis section.

Table 3

MOMPOD Study Insulin Dosing Guidelines By Trimester		
	First	Second/Third
Weight based dosing (U/kg/day)	0.4-0.7	0.7-1.2

Subjects will be instructed to do blood glucose monitoring daily as fasting, and either one or two hour postprandial with glycemic goals listed**.** These goals are based on ADA guidelines and are generally accepted as standard of care. Women are typically considered in adequate glycemic control if >50% of measured CBG are within these ranges, however individual practice patterns may vary. Insulin dose changes made based on reported CBG will be at the discretion of the primary clinical provider, and insulin dosing adjustments will be recorded at each study visit.

Table 4.		
MOMPOD Study Capillary Blood Glucose Goals *		
Fasting	**1 hr postprandial**	**2 hr postprandial**
< 95 mg/dL	< 140 mg/dL	< 120 mg/dL
*Based on ADA guidelines		

Clinical management of the infant after delivery will be per standard treatment dictated by the pediatrician or neonatologist caring for the baby.

Study procedures include:

- Twice daily study agent (placebo or metformin) in addition to insulin therapy
- Monthly study visits to query side effects, dispense study agent, and assess compliance.
- Blood collection at 24-30 weeks for serum storage for future study. Specimens will be frozen at -80 degrees C for future studies. These studies (to be funded by future applications to NIH, local or other funding sources) will include a comprehensive assessment of the role and interactions of clinical, biological and biophysical factors (e.g., BP levels, maternal obesity, smoking, hyperlipidemia, and ultrasound findings) on the occurrence and severity of maternal and neonatal outcomes.
- Chart abstraction for maternal and delivery data (up until discharge) and neonatal data (until 30 days of age or until discharge, whichever occurs first)
- Study phone call at 30-45 days of age to check for neonatal and maternal adverse events
- Contact information for future follow-up studies

8.3 Laboratory Specimen Handling Procedures

Whenever possible, the blood sample will be taken at the time of a regularly scheduled clinical blood draw. However, if no clinical blood draw is scheduled during the time period, the patient will be asked to provide a sample from a separate blood collection scheduled at her convenience. Specimens will be labeled with the subject's unique study ID, centrifuged at 2000 x g for 10 minutes. Resultant serum will be aliquoted into 1 mL fractions and stored at -70C.

8.4 Data Collection

Every effort should be made to obtain complete data on all randomized mothers and neonates, even if the mother has discontinued study agent or does not deliver at the study hospital.

8.4.1 Schedule of Assessments

Study visits should occur approximately monthly to coincide with prenatal visits. At each visit the medical record will be reviewed for intervening problem visits, hospitalizations, insulin dosing adjustments, etc. and data recorded. Staff will ask subjects about symptoms and events since the previous visit; blood glucose logs will be reviewed and data abstracted (or logs copied for later abstraction); maternal weight and blood pressure will be recorded.

The following forms will be completed at each study visit:

Table 5. Schedule of Assessments

Study Encounter Name	**Screening/ Enrollment Visit(s)**	**7-day Contact ****	**14-day Contact ****	**21-day Contact ****	**28, 35, 42-day Contact ****	**Prenatal Study Visits *****	**Delivery Visit**	**30-day Postnatal Contact**
Screening, informed consent, inclusion/exclusion, medical history, randomize	X							
Dispense study agent	X					XXX		
Dose escalation from 500 mg BID to 1000 mg BID		X**	X**					
Collect study bottle, pill count of returned bottles						XXX	X or plan to obtain	
Record total daily insulin dosing (from enrollment through delivery)	X	X	X	X	X	XXX	X	
Maternal side effects, symptoms, episodes of hypoglycemia, adverse events		X	X	X	X	XXX	X	
Maternal serious adverse events		X	X	X	X	XXX	X	X
Copy of glucose log						XXX	X or plan to obtain	
Blood draw						24-30 weeks' gestation		
Maternal breastfeeding intention questionnaire						24-30 weeks' gestation		
Measure infant anthropometrics							Within 72 hours of delivery	
Collection of delivery and neonatal outcomes							X	X
Neonatal adverse events and serious adverse events							X	X
Maternal breastfeeding questionnaire_postpartum								X

** Dose is to be escalated at Day 7 and no later than Day 21 per subject's study agent tolerance. Day 28, Day 35 and Day 42 contacts to occur only If indicated per subject's study agent tolerance. All study agent tolerance contacts can be via telephone or in-person (such as during regularly scheduled pre-natal visits).
*** Study visits should occur approximately monthly to coincide with prenatal visits

8.4.2 Data entry system

Data entry will be via a web-based data management system managed by the DCC. Clinical center staff will enter the data. Data edit and validity checks and reports for missing fields are built into the system. An online tutorial for the data management system is provided by the DCC. All data entry staff will be certified by the DCC prior to data entry for the study.

9 Safety and Adverse Events

The MOMPOD Steering Committee and the DSMB are jointly responsible for safety monitoring. Site PIs, Steering Committee members and/or their designated site study staff will conduct medical monitoring for UPs, AEs, and SAEs and record and report them to their institutional IRB as outlined below (sections 9.3, 9.5). The Study PI responsible for correspondence (Dr. Boggess) will notify the DSMB, FDA, and IRBs regarding UPs, AEs, and SAEs as appropriate.

Detailed information concerning AEs and SAEs will be collected and evaluated throughout the trial. The DCC reports all AEs and SAEs to the DSMB. The DSMB reviews all AEs, SAEs and other interim safety data and provides a report to the PIs and the IRBs. All SAEs are to be entered into the data monitoring system within 48 hours of learning of the SAE. SAE reporting is described below in Section 9.3.

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, agent package insert etc.)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

Maternal Adverse Events
An AE, in general, is a clinically significant untoward medical occurrence, whether or not considered study-related, which occurs during the conduct of a clinical trial. **Clinically significant** AEs are determined by assessment of the study investigator.
For this study, an AE **does not** include:

- Hospitalization for fewer than 168 hours for preterm premature rupture of membranes, preterm labor, or preterm delivery of newborn after 23 weeks gestation.
- Maternal procedures (e.g., surgery, endoscopy, tooth extraction); the condition that leads to the procedure is considered an AE;
- Pre-existing diseases or conditions present or detected prior to the start of study agent administration that do not worsen (e.g., hypertension; asthma; migraines, others);
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition, social and/or convenience reasons or for infant delivery;
- Overdose of either study agent or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation;
- Events prior to randomization or first dose of study agent.
- Hospitalization or in-patient observation <24 hours for evaluation of potential labor or fetal well-being, when no other medical indications were present and the participant is sent home with minimal treatment.

Maternal Serious Adverse Events
A ***serious AE*** is any AE not excluded above that, as determined by the investigator or the sponsor, results in any of the following outcomes:

- Hospitalization >168 hours for rupture of membranes, labor, or delivery

- Hospitalization >24 hours for other reasons or prolongation of existing hospitalization
- Death
- Life-threatening AE ("life-threatening" means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant disability or incapacity
- *Major* congenital anomaly or birth defect (e.g., defect of major organ system such as a heart or brain defect; minor congenital anomalies such as choroid plexus cysts or renal pelvis dilation are not considered major birth defects)
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Expected Maternal Serious Adverse Events

Conditions common in pregnant high risk mothers who have T2DM will be considered expected for IND reporting purposes: hypertension, pre-eclampsia, nausea or vomiting that requires hospitalization before 20 weeks gestation (hyperemesis), fetal congenital anomalies, short cervix, preterm premature rupture of membranes, preterm labor, preterm delivery of newborn, spontaneous abortion before 20 weeks' gestation, IUFD after 20 weeks' gestation, asthma exacerbation, pulmonary embolism (PE), venous thromboembolism (VTE), diabetic ketoacidosis (DKA), glycemic complications: low blood sugar (hypoglycemia) or high blood sugar (hyperglycemia), diabetic coma, colitis, kidney stones, pyelonephritis, urinary tract infection (UTI), hepatitis C, HELLP syndrome, galactorrhea. The most serious risk of metformin is lactic acidosis, which occurs in 1 in 30,000 patients.[52-55] Less serious potential risks of metformin include gastrointestinal distress (10%), headache (< 10%), or muscle aches (<10%). These events are considered expected.

Infant Adverse Events

Guidelines for infant AEs and SAEs for the MOMPOD Study are detailed in the **Table 6** below, as outlined by the NICHD Pediatric Trials Network.[51] and listed under the Infant Serious Adverse Events section.

Table 6.

Infant Outcomes Based on Pediatric Trials Network Experience	
Adverse Event	**Serious Adverse Event**
Gastrointestinal NEC Intestinal perforation	*Gastrointestinal* NEC Bell stage II or III Perforation with intra-abdominal free air proceeding pneumatosis
Musculoskeletal Fracture with immobilization only	*Musculoskeletal* Fracture requiring surgical intervention
Pulmonary Respiratory failure requiring oxygen Pneumothorax present but no treatment required Apnea, any Pulmonary hypertension, any	*Pulmonary* Respiratory failure requiring mechanical ventilation Pneumothorax requiring intervention (e.g. chest tube, nitric oxide, milrinone, sildenafil)
Neurological Seizure, no medical treatment IVH grade I or II	*Neurological* Seizure requiring medical treatment IVH grade III or IV PVL on imaging
Cardiology Hypotension, no pharmacologic treatment EKG QT_c prolongation 460-485 ms SVT resolving spontaneous or with noninvasive maneuvers (vagal maneuvers)	*Cardiology* Hypotension requiring treatment with pressors EKG QT_c prolongation >485 ms SVT requiring medical treatment or cardioversion
Infectious Disease	*Infectious Disease*

Wound infection requiring topical treatment only	Other infection proven by culture (urine, blood, sputum, cerebrospinal fluid) requiring antimicrobials
Ophthalmologic Conjunctivitis requiring local treatment ROP, any stage not requiring treatment	*Ophthalmologic* Conjunctivitis requiring systemic intervention or treatment ROP, Any stage requiring surgical or medical treatment
Otolaryngology Hearing impairment	*Otolaryngology* Confirmed hearing loss, unilateral or bilateral

Infant Serious Adverse Events

For infants a ***serious AE*** is any AE that is listed as serious in Table 6 OR, as determined by the investigator or the sponsor, results in any of the following outcomes:

- Hospitalization >96 hours or longer than the maternal hospitalization following delivery
- Re-hospitalization >24 hours after discharge
- Death
- Life-threatening AE ("life-threatening" means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant disability or incapacity
- *Major* congenital anomaly or birth defect (e.g., defect of major organ system such as a heart or brain defect; minor congenital anomalies such as choroid plexus cysts or renal pelvis dilation are not considered major birth defects)
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the infant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Expected Infant Serious Adverse Events

Conditions common in infants of T2DM will be considered will be considered expected for IND reporting purposes: all infant AE and SAEs listed in Table 6, congenital birth defects identified during pregnancy or within 30 day postnatal follow up period, preterm delivery (either spontaneous or medically-indicated), birthweight < 10th% or > 90th percentile for gestation age, infant respiratory distress syndrome, transient tachypnea of the newborn, hyperbilirubinemia requiring phototherapy, polycythemia, hypocalcemia, hypoglycemia, or neonatal demise. Also, all the events listed in Table 6. Infant Outcomes Based on Pediatric Trials Network Experience will also be considered expected.

Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up for the mother is defined as 30 days following drug discontinuation (at any time prior to delivery or following delivery) and for the infant as until 30 days of life. Serious adverse events related to labor and delivery should be recorded for subjects who discontinue study drug early but continue in the study even if it is post 30 days after their last dose of study drug.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Post-study Adverse Event

Local site PIs will follow all unresolved AEs until the events are resolved, the subject is lost to follow-up, the subject withdraws from the study or the AE is otherwise explained. Subjects will be instructed to notify the study staff at their local institution if they experience an event that might be related to the study agent, even if it

occurs following completion of participation. Primary clinicians (obstetrician and endocrinologist) will also be instructed to notify study staff if their patient experiences an event that might be related to the study agent.

Abnormal Laboratory Values
There are no clinical laboratory tests performed as part of this study, but clinical labs may be measured as standard care for the patient. A clinical laboratory abnormality will be documented as an AE if both of the following conditions are met:

- The laboratory abnormality is not refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity that requires active management (e.g., discontinuation of the study agent, more frequent follow-up assessments, or further diagnostic evaluation and management)

9.2 Recording of Adverse Events

At each contact with the subject, study staff will seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs will be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, and grouped under one diagnosis.

AEs will be categorized as mild, moderate or severe. Mild AEs are those characterized as asymptomatic or mildly symptomatic, with no intervention needed; moderate is defined as those with symptoms requiring local or noninvasive interventions. A severe AE is characterized as incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

MPIs and local site PIs will conform to the reporting timelines, formats and requirements of the various entities to which they are responsible. For any Serious Adverse Events that are potentially related to the study agent, the data coordinating center must be notified immediately (within 24 hours of site learning of the event) and enter as much of the SAE form as can be completed into CDART. For any maternal, fetal, or neonatal deaths or other life-threatening events a copy of the patient's medical record pertaining to the event should be made and a death certificate requested when available. If an autopsy is performed, a copy of the report should be collected as well. All sites need to report deviations per their site IRB protocol.

9.3.1 Sponsor reporting: Notifying the FDA

The study sponsor (in this case, the corresponding PI, Dr. Boggess) is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as 'IND safety reports'. The following describes the safety reporting requirements by timeline for reporting and associated type of event based off of the date that the data was entered into CDART if it is uncommon and strongly associated with study agent exposure otherwise once determined to qualify for reporting by the study coordinator.

- **Within 7 calendar days**
  Any study event that meets SAE requirements and is:
  - Determined to be related to the study agent, and
  - Unexpected as defined under IND reporting requirements, and
  - Fatal or life-threatening as defined under IND reporting requirements
    OR
  - A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting
- **Within 15 calendar days**
  Any study event that meets SAE requirements and is:
  - Uncommon and known to be strongly associated with exposure to the study agent
    OR
  - Determined to be related to the study agent, and
  - Unexpected as defined by IND reporting requirements, and

- Serious as defined under IND reporting requirements, but not fatal or life threatening
  OR
- A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting

Additional reporting requirements: Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process: Serious adverse events requiring FDA notification may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 9.3.

9.4 Stopping Rules

9.4.1 Study stopping rules

The study will be stopped based on DSMB review as described below in Section 9.7

9.4.2 Individual subject stopping rules

Specific rules to stop study agent for an individual subject

- Delivery
- Maternal side effects that cannot be managed with oral medication. Subjects may experience nausea and vomiting or diarrhea as a result of metformin. It will be challenging to distinguish symptoms of pregnancy from side effects of metformin. Women who experience GI symptoms will be offered routine medication management (anti-emetics, etc.). As described in Section 4.5, if symptoms are intolerable and are not relieved by routine medical treatment after 14 days subjects will discontinue study agent. However, we will collect the blood specimen, neonatal measurements, and maternal and infant outcomes.

9.5 Medical Monitoring

Each site-PI will oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 11 Study Monitoring, Auditing and Inspecting). Medical monitoring includes a regular assessment of the number and type of serious AEs. In the event of an SAE, reporting occurs as described in Section 9.3. In addition, if a subject develops a SAE, the subject's obstetric care provider in collaboration with the site PI and the trial unblinded medical monitor will ascertain the safety of continuing the intervention.

9.6 Unblinded Medical Monitor

The trial has a designated unblinded medical monitor, who is otherwise uninvolved with the study, and not a member of the DSMB. The medical monitor will review each reported SAE, to evaluate the PI's assessment of relationship to study agent and expectedness, and to ensure that the site PI follows the patient appropriately. In cases of emergency, unblinding materials will be made available to the unblinded medical monitor or a study PI (Drs. Boggess or Berry) if the unblinded medical monitor is not available. The medical monitor can share unblinded information about the study agent to other health care professionals, including the site PI if unblinding of the site PI is determined by the study PI and the medical monitor.

9.7 Independent Data Safety Monitoring Board

An independent DSMB will provide oversight to assure that the trial accrues at a sufficient rate, and that the safety and privacy of all study subjects is assured. DSMB members are not involved in any aspect of the trial operation. The DSMB will function under a charter that specifies guidelines or operation. Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the trial. The DSMB will review all treatment-emergent adverse events, all serious adverse events (SAEs) and other interim safety data

and will provide a report of recommendations to the Steering Committee and to the local IRBs.

In addition to SAE review by the unblinded medical monitor, the DSMB will receive a monthly update of SAEs and a full report of safety data periodically per DSMB decision to review study progress, to monitor the conduct of the study for safety concerns, and to conduct the formal interim analyses for efficacy, futility and safety described in section 5.5, Interim Analysis). The DSMB will make recommendations about the conduct of the study for safety concerns. The DSMB could recommend to either continue the study; suggest a protocol modification; temporarily halt enrollment to allow further safety investigation; or to end the study early. To maintain the blind for the entire study team, an independent statistical analysis team at the UNC CSCC will produce the closed session report with unmasked treatment groups. Closed reports will be maintained behind a firewall with access only by the unblinded team.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigators, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.2.1 Case Report Electronic Forms

The study electronic case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded and all missing data will be explained. For ease of data collection, paper forms can be used by the site, in which case the paper form becomes part of the source documents.

10.2.2 Records Retention

MPIs and local site PIs will retain study essential documents and specimens for up to 10 years following study completion.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The MPIs and local site PIs will monitor the study to ensure quality and integrity of data collected. He/She/They will review study files, participant medical records, and regulatory documents, consent forms and allocate adequate time for other study monitoring activities. The MPIs and local site PIs will also ensure that the

monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

MPIs and local site PIs will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). PIs will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11.3 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The subject will sign the consent form, and the investigator-designated research professional obtaining the consents.

12 Study Organization and Administration

12.1 Organization and Funding

The study is funded by the NICHD and conducted by the MOMPOD Trial Consortium comprising 10 clinical centers with the Clinical and Data Coordinating Centers at UNC Schools of Medicine (OBGYN) and Nursing, and Public Health (Biostatistics) respectively.

12.2 Steering Committee

The MOMPOD Steering Committee (SC) will oversee implementation including: finalizing the clinical protocol, training and certification, monitoring recruitment, data coordination and quality control, DSMB recommendations, and IRB-compliance. The SC will also make final decisions about data analysis and interpretation, secondary analyses, presentation at scientific meetings and publications (including authorship). Key investigators/members of the SC are shown below. The SC will meet monthly by teleconference and will hold an annual face-to-face meeting ideally to coincide with the SMFM Annual Meeting in February. Decisions will be made by consensus (preferably) or simple majority. The SC will be made up of the PI from each clinical site, a representative from the DCC and the NICHD program officer.

12.3 Study Timelines

We anticipate completing the study in 4.5 years or 54 months including start-up (months1-6), enrollment (months 7-48), finalize data management/primary analysis (months 48-54). Research staff training and clinical provider training will be initiated and enrollment will start soon after. There will be overlap in these activities as sites and centers start at different times.

13 Conflict of Interest

All investigators will follow the University conflict of interest policy. None of the investigators have a conflict of interest.

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