USE OF HOME-DELIVERED MEALS TO REDUCE EXCESSIVE GESTATIONAL WEIGHT GAIN FOR HIGH-RISK WOMEN

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Use of home-delivered meals to reduce excessive gestational weight gain for high-risk women
Study Description:	This single-arm trial tests the feasibility, acceptability, and preliminary efficacy of a meal delivery intervention for managing gestational weight gain among pregnant women with overweight/obesity who are receiving prenatal care at University of Alabama at Birmingham (UAB) clinics. All study participants receive the meal delivery intervention.
Objectives:	The study objective is to test the feasibility, acceptability, and preliminary efficacy of a meal delivery intervention for managing gestational weight gain among predominantly African American and low-income pregnant women with overweight/obesity.
Endpoints:	The primary outcome is participant adherence to the 25-week study intervention.
Study Population:	Participants will be 35 women aged 18-40 years with singleton pregnancies of ≤15 weeks gestational age with overweight/obesity and receiving prenatal care at UAB clinics.
Phase:	N/A
Description of Study Intervention:	Participants receive a meal delivery intervention beginning at ~15 weeks gestation and continuing until 40 weeks gestation (~25 weeks). The meal delivery intervention consists of 10 home-delivered meals per week provided by a local meal delivery company supplemented by written meal plans and grocery lists to help low-income pregnant women with overweight/obesity manage gestational weight gain. Participants are given Wi-Fi/Bluetooth-enabled body weight scales to monitor their weekly weight gain during the trial. Participants also receive weekly check-in telephone calls with study interventionists to promote adherence.

Study Duration:	Up to 27 weeks
Subject Duration:	Up to 27 weeks

1.2 SCHEDULE OF ACTIVITIES (SOA)

Measure	Baseline[a]	Follow-up[b]
Process Data (Aim 1)		
Recruitment[c]	Ongoing	
Attrition[c]	Ongoing	
Adherence[d]	Ongoing	
Adverse Events[d,e]	Ongoing	
Treatment Satisfaction[d]	Ongoing	
Gestational Weight Gain (Aim 2)		
Weight at first PNC visit[e]	X	
Weight at last PNC visit[e]		X
Patient-Reported Outcomes (Aim 3)		
Food Insecurity[d]	X	X
Perceived Stress[d]	X	X
Diet Satisfaction[d]	X	X
Self-efficacy[d]	X	X
Other Relevant Variables		
Demographic Data[d,e]	X[d]	X[e]
Medical History[e]		X
Birth Outcomes[e]		X
[a]13-15 weeks gestation; [b]35-36 weeks gestation; [c]indicates data collected from/generated by research team; [d]indicates data collected from/generated by participants; [e]indicates data collected from medical records. PNC=prenatal care		

2 INTRODUCTION

2.1 STUDY RATIONALE

Over 50% of women in the U.S. enter pregnancy with overweight/obesity, and about half of women gain in excess of Institute of Medicine gestational weight gain (GWG) guidelines. [1,2] Low-income and racial/ethnic minority women are disproportionately affected. [3-6] Pre-pregnancy overweight and excessive GWG independently increase the risk for adverse perinatal complications,[1,7] gestational diabetes,[7] and postpartum weight retention. [8,9] Further, the metabolic perturbations associated with overweight/obesity and excessive GWG may program offspring metabolism as to increase the child's long-term risk for obesity, type 2 diabetes, and cardiovascular disease (CVD).[10-14] Thus, interventions

preventing excessive GWG have important health implications for both mother and child. Unfortunately, even the most intensive behavioral interventions have largely failed to produce substantial improvements in GWG adherence and, in turn, perinatal outcomes, particularly among women with overweight/obesity.[15-17] Thus, innovative approaches to GWG management are needed. Despite demonstrated success for managing other medical conditions, the use of meal delivery for managing weight in pregnancy has not been studied. One study utilized meal replacement shakes and bars as part of a behavioral intervention for reducing GWG in women with overweight.[18] Meal replacements were key to intervention success.[18] Increased meal replacement intake, but not behavioral counseling session attendance, was related to lower rates of GWG.[18] However, compliance to the meal replacement prescription was low.[18] Instead, the use of culturally appropriate, home-delivered meals may be more palatable and offer a unique approach to managing GWG. The purpose of the proposed pilot study is to test the feasibility, acceptability, and preliminary efficacy of a meal delivery intervention targeting excessive GWG among predominantly African American and low-income pregnant women with overweight/obesity using a rigorous and efficient quasi-experimental design.

2.2 BACKGROUND

In the U.S., the prevalence of pre-pregnancy overweight/obesity continues to rise. Over 50% of women have pre-pregnancy overweight/obesity.[2,3] Women of lower socioeconomic status and from certain racial/ethnic minority groups are disproportionately affected[3] and, therefore represent "priority populations" (i.e., those deserving priority in public health and clinical efforts).[19] The prevalence of obesity is an estimated 31-45% higher in high poverty compared with low poverty neighborhoods.[20] Additionally, it's estimated over 53% of Black women have pre-pregnancy overweight/obesity compared to 39% of white women.[20] Further, about half of all women and 55-73% of women with overweight/obesity exceed the 2009 Institute of Medicine (IOM) gestational weight gain (GWG) guidelines.[20,21] This is extremely concerning, as both pre-pregnancy overweight/obesity and excessive GWG are independently associated with increased risk for adverse perinatal complications including gestational diabetes, hypertensive disorders of pregnancy, and birthing a large-for-gestational age (LGA) neonate.[7] In the longer term, maternal pre-pregnancy overweight/obesity and excessive GWG increase the risk for maternal postpartum weight retention (i.e., weight gain related to pregnancy) and subsequent obesity, as well as the child's subsequent risk for obesity, Type 2 diabetes, and cardiovascular disease (CVD). [8,9,10-14] Interventions aimed at achieving a healthy weight pre-conception are difficult given about half of pregnancies in the United States are unplanned.[22] Thus, there is great interest in interventions for preventing excessive GWG due to the important health implications for both mother and child, particularly among priority populations.

Unfortunately, even the most intensive behavioral interventions have largely failed to produce substantial improvements in GWG adherence and, in turn, perinatal outcomes, particularly among women with overweight/obesity. Based on meta-analyses, 50% of women receiving lifestyle intervention still exceed IOM GWG guidelines.[17] The small effect on GWG with lifestyle intervention does not show a clear benefit on maternal-child health outcomes, such as the prevalence of preeclampsia, gestational diabetes, neonatal hypoglycemia, LGA, or NICU admission relative to standard care.[17,23]

Most conventional GWG interventions are intensive, comprehensive, and involve high participant burden as they require significant effort as well as substantial psychological and physical resources (e.g., self-regulation, problem-solving, time, financial means, access to healthy foods).[17,24-26] Such

interventions may not adequately address the social determinants of health (SDH) that contribute to disparities and disease burden in priority populations. SDH are “the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness”, which include factors such as income, education, race/ethnicity, access to care, and residential environment.[27] Most GWG interventions also fail to address the psychological (e.g., stress, low self-efficacy) and material (e.g., food insecurity, transportation) barriers and needs of low-income and minority women in particular.[17,24-26] Further, achieving meaningful and sustained behavior change may be especially challenging during pregnancy, as women face additional stressors and barriers.[28-30] Commonly cited barriers to appropriate GWG include lack of time for cooking and shopping, limited access to healthy food, lack of basic cooking skills, and confusion on how to operationalize vague directives to “eat healthy.”[31] Women with a higher body mass index (BMI) may have more perceived barriers and lower self-efficacy to healthy behavior change during pregnancy.[32] A simplified approach targeting a few key behaviors may be particularly well-suited for under-resourced settings and populations.[33] Additionally, GWG strategies are needed that more effectively address insufficient and/or diminished effort and resources, which may be particularly helpful for priority populations.

Meal delivery overcomes many barriers common to GWG interventions that disproportionately burden priority populations. The provision of prepared meals to women’s homes provides access to healthy food, thereby providing a physical and financial resource to support healthy eating regardless of income, geographic location, or access to transportation. Meal delivery reduces the time and effort involved for meal planning, shopping, and preparation and requires less cognitive and behavioral self-regulation. In addition, pre-portioned meals offer a direct approach to modifying the home food environment, which can support healthy habit formation and improve weight outcomes.[34,35]

Previous studies in non-pregnant populations demonstrate that meal delivery is a clinical- and cost-effective tool for the management of weight, type 2 diabetes, and CVD.[36-40] However, use of meal delivery for managing health and weight in pregnancy has not been studied. One study utilized meal replacement shakes and bars as part of a multi-component behavioral intervention for reducing GWG in women with overweight.[18] Meal replacements were key to intervention success.[18] Increased meal replacement intake, but not behavioral counseling session attendance, was related to lower rates of GWG, and adjustment for the use of meal replacements removed the significant treatment effect.[18] The meal replacement intervention was also effective at reducing weekly GWG prior to 26 weeks gestation.[18] Thus, meal replacements may be an effective strategy for managing GWG early in pregnancy, which is suggested to be particularly important for improving maternal-child health outcomes.[41-45] However, compliance to the meal replacement prescription was low.[18] While women in the intervention group were instructed to consume 14 meal replacement shakes or bars per week (i.e., 2 per day), on average they reported consuming only about 5 meal replacements per week (about 0.75 per day).[18] Meal replacements score low on the hedonic scale, are generally not well-liked, and are limited in variety, all of which may negatively impact adherence, particularly during pregnancy when women are likely to experience food aversions.[46,47] Instead, the use of culturally appropriate, home-delivered meals may be more palatable and offer a unique approach to managing GWG.

Meal delivery has additional health benefits that may be particularly impactful during pregnancy. In non-pregnant priority populations, the provision of healthy, home-delivered meals has been shown to improve food insecurity[40,48,49] and self-efficacy,[50] reduce stress,[51] and participants report high levels of treatment satisfaction.[52] These factors may have important impacts on maternal-child health. For instance, food insecurity and lower self-efficacy have each been associated with increased GWG and exceeding GWG recommendations.[53] Additionally, greater household food insecurity during pregnancy is

associated with greater stress, GWG, and postpartum weight retention, as well as increased risk of gestational diabetes and preterm delivery.[54-57] Greater perceived stress during pregnancy is suggested to have a negative impact on child cognitive development and has been associated with significantly greater risk of preterm birth.[56,58,59] Thus, by potentially improving these constructs, meal delivery may confer additional benefits for maternal-infant health independent of GWG.

If meal delivery is an effective GWG management strategy, such programs may be sustainable given the cost-savings demonstrated in other populations (e.g., individuals with diabetes, CVD).[36-40] In 2020, Medicare Advantage was expanded to allow coverage of home-delivered meals.[60] As such, a rising number of insurers have begun piloting meal delivery programs to address SDH as part of chronic disease management.[61-66] There are now hundreds of contracts between medically-tailored meal providers and health insurance plans nationwide.[67] There are also a growing number of meal delivery programs participating in healthcare innovation projects and receiving reimbursement for Medicaid, Medicare, and dually-eligible populations in at least 17 states.[63,68] Thus, there is the long-term possibility for meal delivery for GWG to be offered as a covered health care service, thereby providing an accessible community resource and shift in health care policies.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study involves providing a healthy meal delivery intervention to promote appropriate GWG among low-income pregnant women. Those with conditions that may put them at increased risk or unique nutritional needs that would make the meal delivery intervention inadvisable will be excluded. Although unlikely, participants may experience normal and temporary physiologic reactions or weight fluctuations associated with healthy dietary changes, such as flatulence (frequency: rare; severity: mild). There is a risk of experiencing an allergic reaction to meals, which is judged to be low as participants self-select meals from provided menus with ingredients. Additionally, participants will be asked to report any food allergies or intolerances at baseline and the PI (who is a registered dietitian) will work with the study's meal delivery partner to accommodate participant food allergies and intolerances, as needed. Participants will also be provided with meal plans designed by the PI in accordance with current micronutrient and macronutrient recommendations for pregnant women.

Concerning weight fluctuations will be investigated and adjustments will be made to meal plans or study procedures, if necessary. Participants will also be closely monitored for any negative effects relating to the meal delivery intervention. Should it be determined that continued participation is contraindicated for a participant, they will be withdrawn from the study. Given that this is a non-invasive meal delivery intervention, we do not anticipate that withdrawals will be common. There is a risk of foodborne illness with meal delivery which is judged to be low as we are partnering with an experienced meal delivery company that operates in compliance with local, state, and federal food safety regulations. All meals will be delivered in insulated packaging with frozen gel packs to keep food cold in transit and meal delivery times will be scheduled with participants. In compliance with the Alabama Department of Public Health, home-delivered meals can be safely stored in the refrigerator for 7 days. Thus, fully prepared, refrigerated meals will be delivered once per week to participants' homes. All meals will also come with re-heating instructions. In the unlikely event a participant experiences distress from completing any of the self-report surveys, she will be allowed to skip items or discontinue the assessment. There is a low

risk of emotional or psychological discomfort from participants answering personal questions about their health, eating, and activity behaviors.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants will receive 10 healthy meals per week during the 25 week intervention at no cost to them. Participants in the study may feel less stress by saving time on planning, shopping, and preparing meals, improving food insecurity, and may feel good about themselves by eating a healthier diet during pregnancy. Having a healthier diet and less stress could have additional mental and physical health benefits.

Meal delivery may reduce inappropriate GWG and improve cardiometabolic health management, diet quality, food security, stress, and reduce barriers to healthy eating in pregnancy. This is important given that over 50% of women in the U.S. enter pregnancy with overweight/obesity, and about half of women gain in excess of Institute of Medicine GWG guidelines. This is extremely concerning, as both pre-pregnancy overweight/obesity and excessive GWG are independently associated with increased risk for adverse perinatal complications and CVD. Black and lower income women are also disproportionately burdened by obesity, which further increases the risk for adverse health outcomes. To-date, traditional diet and weight management programs for pregnant women have been largely unsuccessful. Participation in this study may enhance our understanding of meal delivery as a strategy for improving maternal health among underserved populations. Given the health risks associated with excessive GWG and the challenges of successful weight management in pregnancy, such information is clinically relevant and has potential for public health impact. Ultimately, results could inform public policy to leverage programs and/or modify insurance coverage to promote sustainability, which would have a meaningful public health impact on both short and long-term maternal health.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a meal delivery intervention trial in which pregnant women who are ≤ 15 weeks pregnant and enroll in the study will receive 10 meals per week beginning at 14-16 weeks gestation until 40 weeks gestation (~25 weeks total).

Recruitment will primarily occur through UAB prenatal clinics, which is consistent with successful recruitment strategies employed in our previous studies with pregnant women. The study coordinator will work with Dr. Subramaniam (Co-I) and staff at these sites to recruit women planning to deliver at UAB for the study. Women will be told about the study at the first prenatal visit. Interested women will contact study personnel in clinic or by phone to receive more information about the study and undergo an initial phone screening to assess initial eligibility. Supplemental recruitment efforts will include posting study flyers in UAB obstetrics offices, childcare centers, announcements on the local news station, and through local Facebook groups (e.g., pregnancy support and local obstetrics groups) and other local social media platforms. If we determine that more intensive recruitment strategies are needed, then subsequent efforts will include more frequent visits to each practice by our study coordinator to meet with staff to identify potential participants and direct recruitment of patients from waiting rooms.

Participants recruited from UAB prenatal care clinics will be screened by telephone by the study coordinator to determine basic eligibility criteria and assess patient's interest and availability. Those meeting initial eligibility criteria will be oriented to the program, including the receipt of materials describing the study along with a consent form, which can be provided in-person, through the mail, and/or secure video link. After orientation, gestational age based on the dating ultrasound and BMI at the first prenatal care visit will be obtained from medical records to confirm eligibility. The study coordinator will notify participants of their eligibility and schedule a time to complete the informed consent (verbal consent will be recorded) and baseline assessment with participants by phone or secure videoconferencing (Zoom).

Interested and eligible women will be scheduled to attend an Enrollment/Baseline Assessment visit during which informed consent will be completed. Those who consent to enroll in the study will then complete baseline study measurements including surveys and anthropometrics.

Within 1-2 weeks of completing the baseline assessment, participants will receive their first study meal delivery order. All participants will receive the study meal delivery intervention until 40 weeks gestation (or ~25 weeks total). During the study intervention, participants will be emailed a weekly Qualtrics survey to complete to report intervention adherence.

To maximize complete data, participants will complete a follow-up visit when they are 35-36 weeks gestation consisting of survey measures. However, participants will continue to receive the meal delivery intervention until they reach 40 weeks gestation.

3.2 END OF STUDY DEFINITION

While Primary Completion will be defined as the date the last participant receives the meal delivery intervention and weight at the first and last prenatal visit were obtained from all participant medical records (for the calculation of the gestational weight gain outcome), the End of Study will be the date of completion of all participant medical record data abstraction, as these data will provide necessary data to characterize secondary outcomes and necessary covariates for the conduct of our statistical analyses.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

We will recruit 35 women with confirmed singleton pregnancies who are receiving care and planning to deliver at UAB Hospital. Eligibility criteria include: 1) gestational age ≤ 15 weeks as assessed by ultrasound, 2) overweight/obesity (BMI ≥ 25 kg/m^2) determined at study entry based on weight measured at the first prenatal care visit, 3) age 18+ years, 4) ability to communicate in verbal/written English, 5) have Wi-Fi or Bluetooth internet connection in their home (for digital Wi-Fi enabled study scale) and 6) residing within the delivery radius of the meal delivery company. The sample will reflect the demographics of women receiving prenatal care at UAB clinics (47% minority, 42% Medicaid, 61% high school graduate/GED or less).

4.2 EXCLUSION CRITERIA

Exclusion criteria include: 1) self-reported major health conditions (e.g., heart disease, cancer, renal disease, and Type 1 or Type 2 diabetes), 2) current substance abuse, 3) current treatment for serious psychiatric disorder (schizophrenia, bipolar disorder), 4) known fetal anomaly, 5) planned termination of pregnancy, 6) past history or current diagnosis of anorexia or bulimia, 7) current use of one or more of the following medications: Metformin, systemic steroids, antipsychotic agents, anti-seizure medications or mood stabilizers that would be expected to have a significant impact on body weight, medications for ADHD including amphetamines and methylphenidate, or any teratogenic agent Class D, 8) participation in another dietary and/or weight management intervention during pregnancy, 9) unwilling or unable to do any of the following: give informed consent; understand and communicate in verbal and written English; consume prepared meals delivered weekly.

4.3 SCREEN FAILURES

Interested women who do not meet study inclusion criteria will be informed of this decision by study staff and reassured that this will not change the quality of the services and care that they receive through the University of Alabama at Birmingham.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

We have a strong track record of retaining participants in pilot studies as well as long-term observational and randomized controlled trials of nutritional and weight management interventions. We will employ a variety of retention strategies used successfully in the past. First, all participants will receive a meal delivery intervention at no-cost to them, including the delivery of 10 culturally-relevant meals of their choosing per week to their home for ~25 weeks (beginning 14-16 weeks until 40 weeks gestation) and copies of written meal plans with grocery lists to promote appropriate integration of prepared meals into their diet. We will also provide participants with monetary incentives when completing assessments, including $20 at the baseline assessment (13-15 weeks gestation) and $20 at follow-up (35-36 weeks gestation). Telephone-based assessments will be used to reduce participant burden and maximize data collection. Birthday cards, holiday cards, and participant newsletters will be mailed to individuals during the study to maintain study engagement. Finally, participants' relationships with well-trained and attentive staff are a key factor to retention, and we have assembled an experienced team to ensure this.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Beginning at 14-16 weeks gestation, participants will receive 10 fully-prepared, refrigerated lunch/dinner-style meals per week, ending at 40 weeks gestation. Prior studies in both non-pregnant and pregnant cohorts indicate that providing 10 meals or meal replacements/week is effective for weight management.[36,40] Also, lunch/dinner meals will be provided because inhibitory control ("willpower") declines over the course of the day.[69] We will partner with a local meal delivery company to prepare and deliver meals. We chose to partner with a local company for their culturally-relevant

meal options that can be further modified to accommodate participant allergies, aversions, and other specific dietary needs. Provided meals are designed to provide 25-35% of daily energy needs per meal with about 45-65% of calories from carbohydrates, 10-35% of calories from protein, and 20-35% of calories from fat, which is in accordance with the 2020-2025 Dietary Guidelines for Americans nutritional goals for pregnancy.[70] Participants will select from a menu of 10-14 meals, which changes weekly to provide variety over time. Participants will place meal orders with their study interventionist who will submit weekly orders to the meal delivery partner. During these weekly contacts, interventionists will also provide brief behavioral support, including evidence-based strategies of problem-solving, action-planning, and principles of motivational interviewing, to help women identify and navigate dietary adherence barriers (e.g., consuming prepared meals when household members are eating other foods). The coordinator will document the duration and topics discussed. In the event a participant does not place their weekly order, the coordinator will select their meals for the week based on participant preferences, allergies, and aversions collected at baseline. This will ensure meal orders are placed on-time and participants receive the appropriate amount of meals each week. In compliance with the Alabama Department of Public Health, home-delivered meals can be safely stored in the refrigerator for 7 days. Thus, fully prepared, refrigerated meals will be delivered once per week to participants' homes. All meals come with re-heating instructions and are ready in <2 minutes in the microwave.

To supplement provided meals, participants will receive a variety of written meal plans with grocery lists corresponding to their estimated energy needs during each trimester of pregnancy. Trimester-specific energy needs will be calculated using the USDA Dietary Reference Intake Calculator for Medical Professionals with gender, age, height, weight, activity level, and trimester of pregnancy as inputs.[71] Meal plans will be used to help promote adherence and integration of prepared meals into their diet for appropriate GWG. Appropriate GWG will be determined based on the IOM 2009 GWG guidelines[72] and participants BMI at the first prenatal care visit. Meal plans will be designed by Registered Dietitians to comply with current micronutrient and macronutrient recommendations for pregnant women.[70] Participants will be instructed to self-weigh at least weekly and will be given a Wi-Fi-enabled digital scale that will transmit recorded weights to their study interventionist who will monitor for potentially concerning weight fluctuations.

5.1.2 DOSING AND ADMINISTRATION

Participants in the study receive 10 lunch/dinner-style meals per week delivered to their homes free of charge for a total of ~25 weeks. Participants will select the 10 meals that they want each week from a weekly rotating menu that includes nutrition and ingredient information to accommodate participants with food aversions or allergies. Participants place meal orders weekly with study staff who will submit orders to the meal delivery partner. If a participant does not place their weekly order, study staff will select meals based on participant preferences and allergies collected at baseline to ensure they receive meals each week. Each week of the intervention, participants will be automatically sent an electronic survey to report the number of study-provided meals consumed by participants (versus others in the household versus thrown out).

5.2 STUDY INTERVENTION COMPLIANCE

As mentioned above, participants place meal orders weekly with study staff who will submit orders to the meal delivery partner. If a participant does not place their weekly order, study staff will select meals based on participant preferences and allergies collected at baseline to ensure they receive meals each week. Each week of the intervention, participants will be automatically sent an electronic survey to report the number of study-provided meals consumed by participants (versus others in the household versus thrown out). Study staff completing weekly check-in calls with participants will document the duration and topics discussed.

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Participants will continue to receive the study intervention until 40 weeks gestation. The study intervention may be discontinued for a participant if a clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study intervention would not be in the best interest of the subject.

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to complete 3 scheduled check-in visits in a row or fails to complete the follow-up visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

Assessments will occur at baseline (13-15 weeks gestation) and follow-up (35-36 weeks gestation) to collect data for Aims 1 and 3 and are estimated to take < 60 minutes. Assessments may be completed in-person or remotely by telephone/Zoom, based on participant preference. Remote assessments are designed to reduce participant burden and maximize data collection.

Process Data (Aim 1) will be collected to allow for the assessment of recruitment, attrition, adherence, adverse events, and treatment satisfaction.

Recruitment. Total number of participants screened and enrolled and reasons for ineligibility or disinterest will be tracked and used to calculate recruitment rates and frequencies/reasons for refusal.

Attrition. The proportion of enrolled participants who complete the follow-up visit will be tracked and assessed.

Adherence. Participants will be emailed or sent a text message with a link to a brief online survey each week of the intervention. In the online survey, participants will confirm they received 10 meals for the week and report the number of delivered meals they consumed.

Adverse Events. Each week participants will be asked to report any adverse events via the online survey.

Treatment Satisfaction. Satisfaction with the meal delivery intervention will be assessed using both quantitative and qualitative methods. The weekly online survey will allow participants to rate how satisfied they were with each meal they received (e.g., smell, appearance, texture, taste) using a 5-point Likert scale. At the follow-up assessment, treatment satisfaction will be assessed using a modified version of the questionnaire developed as part of a previous meal delivery intervention study, which includes questions about satisfaction with meal quality, meal plans, and the delivery process.[52] Qualitative data on treatment satisfaction will be collected at follow-up by trained interviewers who will complete one-on-one, 30-minute interviews with each participant. Interviews will be conducted remotely (via telephone or Zoom). Interviews will be conducted using guides developed by the research team. Topics explored will include satisfaction with the meal delivery process, the meals themselves, and suggestions for how to improve the intervention. Interviews will be digitally-recorded and transcribed verbatim for analysis.

Gestational Weight Gain (Aim 2) will be calculated based on weight at the first and last prenatal care visits retrieved from medical records. Dates of the weight measurements will also be collected to determine the number of days between measurements. For this aim, we will utilize a non-randomized weighted control group derived from de-identified hospital records using the Informatics for Integrating Biology and the Bedside (i2b2) system. The same weight and date measurements will be extracted from the medical records of weighted controls for comparison of GWG.

Patient-Reported Outcomes (Aim 3) will be collected via questionnaire at both the baseline and follow-up assessment visits. (a) Food Insecurity will be assessed using the 18-item U.S. Household Food Security

Survey, which measures food security status among adults, children, and the entire household over the past 30 days.[73] (b) Stress will be assessed using the 10-item Perceived Stress Scale (PSS-10), which is a measure of how unpredictable, uncontrollable, and overloaded respondents find their lives over the past month. [74,75] (c) Diet Satisfaction will be measured using a modified version of the validated Diet Satisfaction Questionnaire, a 28-item measure consisting of 5 subscales assessing satisfaction with following a weight-management diet.[76] (d) Self-efficacy related to weight and healthy eating will be evaluated using an abbreviated 4-item version of a questionnaire used with pregnant women.[53]

Other Relevant Variables. In addition to the outcomes listed above, information on participants' demographics, medical history, and birth outcomes will be collected via medical record review.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely related** – the AE is known to occur with the study intervention and clear evidence of a causal relationship between the study intervention and the AE. There is a temporal relationship between the study intervention and AE and possible alternate etiology(ies) have been ruled out.
- **Probably related** – in the judgment of a reasonable investigator, it is probable though cannot be definitively determined that the study intervention caused the AE. There is a temporal relationship between the study intervention and the event and evidence to suggest a causal relationship between the study intervention and the AE, though alternative etiologies cannot be ruled out.
- **Possibly Related** – possibly related means there is some likelihood in the judgment of a reasonable investigator that the incident, experience, or outcome may have been caused by the procedures involved in the research
- **Unlikely Related** – It is unlikely, but not impossible, in the judgment of a reasonable investigator that the administration of the study intervention caused the event. No alternate etiology has been established.
- **Definitely Unrelated** – There is no reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

7.2.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Study Coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- All Unanticipated Problems (UPs) will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): The primary aim of this study is to assess the feasibility and acceptability of the meal delivery intervention. Hypothesis 1: We will be able to recruit 35 participants (over 9 months), achieve 80% adherence to the intervention protocol, observe no serious adverse events directly attributable to the intervention, and attain high levels of treatment satisfaction.

- Secondary Efficacy Endpoint(s): The secondary aims are to investigate the preliminary efficacy of the meal delivery intervention on GWG, and to investigate changes in patient-reported outcomes including food security, stress, diet satisfaction, and self-efficacy. Hypothesis 2: Meal delivery will result in lower total GWG and a lower proportion of women with excessive GWG compared to a non-randomized but weighted control group derived from de-identified hospital records. Hypothesis 3: Patient-reported outcomes will show significant improvements pre- to post-intervention.

8.2 SAMPLE SIZE DETERMINATION

To accomplish the aims, this effort will enroll 35 pregnant women in the meal delivery intervention arm who meet study inclusion/exclusion criteria and consent to participate in this study. Non-randomized matched controls will be obtained from de-identified hospital records. Based on a review of the electronic health record, a total of n=8,303 pregnant women in the same age and BMI category as the treatment group received prenatal care at the UAB hospital in 2020. Hence, our total sample size is anticipated to be greater than 8000. The primary objective of a pilot feasibility study is not to be a definitive well-powered trial but to conduct a pilot study that is sufficiently large to estimate design parameters such as the bias and precision of the pooled standard deviation of the changes in the outcomes as well as assess feasibility parameters.[77,78] In cases with low prevalence of treatment like the current effort, Propensity score (PS) matching and inverse probability treatment weighting (IPTW) can yield correct estimates of treatment effect unless the true confounders and the variables related only to the outcome are not included in the PS model.[79] Next, for normally distributed outcomes, the relative gain in precision of the pooled standard deviation (SDp) is less than 10% (for every five subjects added per group) once the total sample size is 70. For true proportions between 0.1 and 0.5, we find the gain in precision for every five subjects added to the pilot sample is less than 5% once the sample size is 60. Adjusting the required sample sizes for the imprecision in the pilot study estimates can result in excessively large definitive RCTs and also requires a pilot sample size of 60 to 90 for the true effect sizes considered here. It is therefore recommended that an external pilot study has at least 70 measured

subjects (35 per group) when estimating the SDp for a continuous outcome.[80] Our sample size is substantially greater than the recommended sample size of 12 per arm for feasibility studies.[81] This will help us plan a well-powered confirmatory study. Accounting for the bias and precision of the estimated pooled standard deviation can help us conduct rigorous power and sample size calculations for a subsequent confirmatory study. While this study is not intended to be a confirmatory study and in fact intended to help us plan a confirmatory study, we provide power calculations to indicate the detectable effect size. Our calculations indicate that we will have 80% power to detect a minimally detectable effect size of 0.6 (Cohen's d) at a type one error rate of 0.05. This is assuming a two-sample t-test assuming unequal variance with unbalanced allocation, sample size of 29 completers in the meal delivery arm after accounting for 15% attrition and at least 6,612 controls.

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

To explore the feasibility and acceptability of the intervention, we will recruit 35 participants and assess feasibility metrics (recruitment, attrition, adherence, and adverse events), and conduct in-depth qualitative interviews which will be coded using a deductive and inductive approach, after pilot testing. The comparative efficacy of the intervention with respect to standard care will be assessed by deriving control participants from de-identified hospital records using i2b2. Person-level inverse probability weights (stabilized and truncated as needed) will be used to balance covariates between the intervention and control group. Weighted linear mixed models will then be used to regress our primary outcome of interest (i.e. total GWG) on the intervention, and socio-demographic and pregnancy-related confounding variables. Finally, to investigate hypothesized changes in patient-reported outcomes (food insecurity, stress, diet satisfaction, and self-efficacy), we will model their levels at post-intervention and use pre-intervention levels and other demographic and pregnancy-related variables as covariates.

8.3.2 ANALYSIS OF THE PRELIMINARY EFFICACY ENDPOINT(S)

In Aim 1 we will collect feasibility metrics about recruitment, attrition, adherence, adverse events, and treatment satisfaction. Quantitative feasibility and acceptability outcomes will be summarized using descriptive statistics (means, standard deviations, counts, proportions, and 95% confidence intervals). Specifically:

1. Recruitment: Calculated as the proportion of eligible screened women who enroll, along with frequencies and reasons for refusal.
2. Retention/Attrition: Evaluated as the proportion of enrolled participants completing the 25-week follow-up assessment.
3. Intervention Adherence: Calculated as the mean proportion of delivered study meals consumed weekly, evaluated against our feasibility benchmark of ≥80% adherence.
4. Treatment Satisfaction: Mean scores and item frequencies will be calculated for weekly 5-point Likert meal ratings and post-intervention satisfaction questionnaires.

Qualitative data for our study will be collected via semi-structured telephone/Zoom exit interviews using an interview guide developed by the research team based on our content expertise and previous work.[52,82] Interview questions will be designed to query participant satisfaction with the structure and dose of the meal delivery intervention and satisfaction with the content and quality of the provided meals and meal plans with follow-up probes to elicit participants' recommendations for improving the

intervention for further use. The initial interview protocol will be piloted with our first 2-3 participants. The purpose of the pilot interviews will be to assess question clarity, identify gaps in the protocol, and improve the flow of the interview (e.g., reorder questions to avoid redundancies). Two trained members of the study team will participate in each of the 2-3 pilot interviews to take notes on how to refine the interview protocol and ensure interviews are conducted in a consistent manner. Subsequent interviews will be conducted by these same two trained study team members. All interviews will be recorded and subsequently transcribed verbatim.

Qualitative data analysis, consisting of coding, synthesis, and memo writing, will utilize at least three study team members to mitigate issues of bias and thus, provide greater confidence in the coding and analysis process. To analyze qualitative data, we will independently review transcripts to assess themes and will then use an iterative process to develop and refine the codebook. Our coding process will include two stages and utilize a deductive and inductive approach. An initial set of five transcripts will be coded by at least two study team members followed by a comparison of coded transcripts to assess interrater reliability and identify specific places where codes were applied inconsistently. Discrepancies in code application will be resolved through team meetings to discuss why particular codes were applied and ways to resolve these inconsistencies (e.g., refining codebook, assigning multiple codes). Based on the final codebook, all transcripts will be coded independently by at least two study team members and then compared again to reach 100% consensus. Inductive analysis will then be used to derive common themes to identify potential intervention refinements. These methods are similar to those used previously by our team to inform intervention development.[82-84] NVivo, a computer-assisted qualitative analysis software package, will be used for the analysis.

8.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

All statistical analyses will be conducted in an intent-to-treat manner.[85] Statistical significance will be evaluated at a 2-tailed hypothesis-wise error rate of 0.05. Aim 2 seeks to compare those receiving the meal delivery intervention with a non-randomized but weighted control group derived from de-identified hospital records. Based on a review of data obtained from the electronic health record, a total of n=8,303 pregnant women in the same age and BMI category as the treatment group received prenatal care at the UAB hospital in 2020. Quasi-experimental designs like the one proposed in this effort can overcome some limitations of observational studies with regards to establishing causality.[86] For each quantitative outcome, the primary analysis for the average treatment effect will employ an intent-to-treat analysis of covariance with the baseline measure of the outcome as the covariate, the corresponding post-intervention outcome measurement as the dependent variable, and the meal intervention as the main factor. For the primary outcome i.e. total GWG, our analyses will focus on using linear mixed models with a random effect for participant ID. Accordingly, we will regress our outcome of interest on the exposures using time point indicators (in this case pre and post time points), assuming appropriate variance-covariance structure as used for repeated measures. Note that, if linearity assumptions are violated, to account for non-normal distributions and/or lack of homogeneity of variance, we will use the generalized linear modeling framework. We recommend that in pilot trials the focus should be on descriptive statistics and estimation, using confidence intervals, rather than formal hypothesis testing and that confidence intervals other than 95% confidence intervals, such as 85% or 75%, be used for the estimation. The confidence interval should then be interpreted with regards to the minimum clinically important difference.

Of note, several previous research efforts with pre-post designs have used ANCOVA (controlling for baseline levels of the outcome measures; addresses the regression to mean related issues[87]) or ANOVA

with a change score as the outcome as the analyses of interest, with the former being more powerful in cases of complete follow-up. However, since loss to follow-up is common in pre-post studies, a mixed model based analyses applied to all available data that works under missing at random assumption is generally found to be more powerful than an ANCOVA accounting for missing data using multiple imputation (MI) techniques. Further, the power of ANCOVA after MI decreases as the rate of missingness increases.[85] This effort will, however, also conduct the traditional ANOVA and ANCOVA based regression models as secondary analyses and compare the estimates and their confidence intervals, along with the goodness of fit measures such as Cp statistic and the Akaike Information Criteria (AIC) with those from the mixed models. Both of these measures are useful for comparing models with different parameters and account for goodness/lack of fit of a model and include a penalty for additional parameters to penalize overfitting.

Next, this effort uses a non-randomized study design which improves the external validity since it reduces the reactive effects of the experimental procedure. However, such designs may be more sensitive to internal validity problems like selection.[88] It is possible that the observed difference between the study groups is attributable to characteristic differences between groups rather than the intervention (in this case, meal delivery). Comparative effectiveness studies however seek to estimate the potential causal effect of an intervention on the outcome, un-confounded by the differences between the study groups.[89] To achieve a balance between the study groups, several efforts use regression based parametric adjustment measures which are sensitive to model misspecification.[89]

Propensity scores are another widely used measure to achieve balance or matching between the study groups.[90,91] These model the probability of being assigned to the given treatment conditional on observed baseline covariates obtained via measures including, matching, inverse probability treatment weighting (IPTW), stratification, and covariate adjustment.[90] While matching based measures have been extended to the three-group setting through nearest neighbor matching algorithm, these often lead to study participants being excluded when a match is not available. This may potentially bias the effect estimates.[90,91]

This effort therefore proposes to use IPTW, a non-parametric balancing strategy to achieve balance between the study groups. Using the weighted data, we will then model the causal parameter as the inverse of the conditional probability of receiving the treatment given the observed covariates, a technique that provides asymptotically unbiased estimates and uses data on all available study participants.[92] Through this procedure, we will be able to generate a pseudo-population in which baseline covariates will be independent of the study group status, a property that IPTW mimic of randomization procedures. IPTW generation: For the *i*th study subject, the IPTW will be estimated = Zi/ei + (1- Zi)/1- ei where Zi indicates the subject's treatment group and ei indicates the probability of being in the given group using a logistic regression model, adjusted for specific socio-demographic, general health, and pregnancy-related covariates, identified a-priori, using Directed Acyclic Graphs.[93] The generated weights will then be stabilized as needed because they may be inaccurate or unstable for subjects with a very low probability of being in the study group that they are in.[94] Next, to balance the bias-variance tradeoff, given the potential high variance in the generated IPTW, sensitivity analyses will be conducted and the effect of progressive truncation of the weights on the estimates will be assessed. As an additional sensitivity analysis, we will also compare the estimates obtained from weighted mixed models with an unweighted traditional mixed model, adjusted for the following covariates: days between first and last prenatal care visit weight measurements, age, race, parity, and BMI at first prenatal care visit.

Note that, similar IPTW based mixed models will be used to then model the secondary binary outcome of interest, i.e. proportion of women with excessive GWG. These models will be built to estimate risk ratios (using a log link), instead of estimating odds ratios (using a logit link). This is because odds ratios are hard to comprehend directly and are usually interpreted as being equivalent to the relative risk. Additionally, they tend to be farther away from the null because of how they are calculated.[95] However, if the model does not converges using the log link, the logit link will be used.

Mixed models, accounting for random effect of participant ID similar to those described earlier will be used to model the outcomes for Aim 3, using appropriate links and distributions. For example, stress measured as a continuous variable will be modelled using linear mixed models with an identity link and normal distribution (if normality assumptions hold). For the primary analyses, we will again model the outcomes at the end and control for the baseline levels as an exposure to account for regression to mean, while also accounting for the following covariates: 1) demographics (e.g., age, race, household income); 2) parity; 3) maternal or fetal health conditions diagnosed during pregnancy (e.g., preeclampsia, gestational diabetes). As additional sensitivity analyses, we will compare these estimates with those obtained by modeling the change scores (post-pre intervention scores), given the potential confounders.

8.3.4 SAFETY ANALYSES

Rates and severity of adverse events will be summarized using descriptive statistics.

8.3.5 BASELINE DESCRIPTIVE STATISTICS

At baseline, descriptive statistics will be used to summarize demographic characteristics and outcome measures.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have

the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy are strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Medicine, Division of General Internal Medicine and Population Science research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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