MATERNAL-OFFSPRING METABOLICS: FAMILY INTERVENTION TRIAL MOMFIT

Protocol

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1 Introduction

1.1 Study Abstract

The prevalence of obesity has increased dramatically in the United States over the last two decades, with rapidly rising and premature adverse health consequences. Women of reproductive age, especially overweight and obese (OW/OB) minorities and those of low socioeconomic status, are at risk of adverse pregnancy outcomes due to excessive gestational weight gain (GWG) and this further contributes to alarming rates of childhood obesity and diabetes. Preventing excessive GWG could reduce pregnancy complications and improve long term health of women and their offspring. Weight control studies in pregnancy are emerging but most studies have emulated traditional weight control programs through diet counseling or increased activity but with limited evidence of sustained adherence. Novel approaches are needed to limit weight gain to new Institute of Medicine (IOM) goals, and to help OW/OB mothers adhere to recommended diet, physical activity and lifestyle behaviors that they can model for their families. The proposed research will develop and test a new approach to primary and secondary prevention of obesity through a behaviorally adapted, nutrient-dense, energy-balanced lifestyle that can be implemented clinically, assessed objectively and sustained long term through technologically-advanced self-monitoring methods. This randomized controlled clinical trial compares with standard care, as a continuous variable the GWG of OW/OB pregnant women who participate in lifestyle intervention with individualized, motivational coaching and group sessions to develop self-monitoring of recommended diet and physical activity behavior long term. Anthropometric, metabolic, diet, activity and lifestyle outcomes will be assessed prenatally and for at least 12 months post-delivery. The birth outcome, diet, and growth of the infant will also be measured. The Northwestern Department of Obstetrics and Gynecology provides care for over 12,000 ethnically diverse obstetric patients a year, many of whom participate in clinical trials, facilitated by a highly functional obstetric research infrastructure. Our multidisciplinary team, experienced in obstetrics and prevention research, propose innovative technology, personalized nutrient goals and enhanced self-monitoring skills to document whether excess gestational weight gain can be avoided and if new mothers can successfully develop and model energy-balanced diet and lifestyle behaviors for their families, thereby reducing and preventing obesity long term.

1.2 Study Objective

To test, in 300 ethnically diverse OW/OB pregnant women, a behavioral intervention aimed at controlling GWG through recommended diet, activity and lifestyle changes that are to be maintained postpartum.

1.3 Hypothesis

GWG will be less among the Intervention group vs. Usual Care (control) group.

1.4 LIFE MOMS Consortium

This randomized clinical trial is one of the studies conducted by the LIFE-Moms Consortium. The Consortium is a collaborative study group with the goal of testing different behavioral/lifestyle interventions in overweight and obese pregnant women in separate trials while providing for the ability to combine data from the individual trials by harmonizing interventions, trial design elements, study procedures and data collection. Key measures and procedures that will be common to all of the trials are designated as 'Core' and will provide the basis for Consortium wide evaluations. 'Super Shared' measures and procedures are defined as those collected on 4 or more of the LIFE-Moms trials. 'Shared' measures and procedures are defined as those collected on 2-3 of the LIFE-Moms trials.

2 Background

2.1 Incidence and Etiology / Burden of Disease

Significance

Maternal Overweight/Obesity and Adverse Metabolic Outcomes. The prevalence of maternal overweight and obesity has nearly doubled in the United States since 1976 [1]. In 2004-2005, 42% of pregnant women had body mass index (BMI) above 25 versus 23% in 1993 [2]. Gestational weight gain (GWG) over 40 pounds has steadily increased since 1990, and estimated mean postpartum weight retention among women who gained above IOM Guidelines ranges from 10 pounds to over 20 pounds [3]. Excessive GWG increases BMI at subsequent pregnancies with increased long term risk of cardiovascular diseases, cancer and overall metabolic health [3-5]. Adverse maternal-offspring consequences independently associated with excessive GWG include preeclampsia, impaired glucose tolerance, cesarean delivery, large for gestational age (LGA) infants (birthweight $\geq 90^{th}$%ile), and fetal macrosomia (birthweight >4,000gms), as well as obesity in childhood, adolescence, and early adulthood [6-9]. Excessive GWG is also associated with increased systolic blood pressure, levels of C-reactive protein (CRP) and interleukin-6 (IL-6) and decreases in HDL- cholesterol (HDL-C) in offspring [9-15]. The mechanisms underlying this "fetal programming" are unclear, but may include fetal overnutrition from elevated circulating maternal concentrations of glucose and fatty acids, exposure to elevated concentrations of insulin and leptin/adiponectin or other factors affecting the development of the hypothalamic pathways that regulate appetite, body weight, and/or epigenetic effects related to maternal diet [16].

Left uninterrupted, this cycle of perpetual excessive GWG with increasing adverse maternal-offspring consequences could have a devastating public health impact. This prompted the IOM to reexamine and revise the GWG Guidelines in 2009 with limits of 15-25 pounds (7-11.5 kg) in overweight (BMI 25.0-29.9 kg/m^2) and 11-20 pounds (5-9 kg) in obese (BMI $\geq$30.0 kg/m^2) women [3]. Lifestyle modifications which have been proven effective among non-pregnant populations [17, 18] have been applied to prevention of excessive GWG in overweight or normal weight women, and the results have been promising in some [19-21] but not all studies [22, 23]. Research is urgently needed to identify and apply effective approaches to lifestyle modification including electronic, technologically enhanced approaches that can be successfully adapted to OW/OB pregnant women of diverse ethnic, racial and economic backgrounds.

2.2 Potential for Prevention

Studies on Prevention of Excessive GWG: Results and Limitations. Behavioral interventions on diet and increased physical activity in nonpregnant obese adults have successfully achieved weight loss and improved clinical outcomes, such as reduced incidence of type 2 diabetes (T2D); but far less is known about behavioral interventions in pregnant women. Trials conducted to date have yielded mixed results; some but not all intervention trials have succeeded in reducing GWG in OW/OB women [24-27]. Pre-pregnancy BMI, smoking habits, race, income and number of prior pregnancies were all associated with GWG, but not all studies controlled for these factors [22, 24-27]. One randomized controlled trial (RCT) among low income women, intervened with biweekly newsletters, personalized weight gain charts and individualized nutrition counseling and reported decreases in GWG among normal weight but not overweight women [22]. More recent results using a similar intervention also reported improved postpartum weight loss maintenance in both normal weight and OW/OB women [28]. Conversely, intervention with educational radio broadcasts, pamphlets, supermarket tours, cooking demonstrations, exercise groups and individual counseling geared toward healthy diet and exercise during pregnancy was

not associated with significantly reduced GWG compared to the control group [24]. Reduction of GWG in a low income subgroup of normal and OW women was achieved by charting weight gain and providing five 1-page mailings about healthy eating and exercise during pregnancy [25]. A Finnish study that individualized counseling on diet and physical activity following five routine OB clinical visits along with group exercise sessions did not affect excessive GWG but intake of vegetables, fruit and dietary fiber increased [27]. Still another study reported reduced GWG in OB women through weekly 30-minute individual motivational sessions and aqua aerobic classes designed for OB women conducted by nurse midwives [29]. While these studies offer potential promise, well-designed studies with adequate power and standardized methods are needed to enhance adherence to lifestyle interventions and document reductions in excessive GWG in large, ethnically diverse populations and also sustain these behavioral changes postpartum.

Lifestyle Interventions on Diet, Physical Activity and Weight Loss in Non-pregnant Populations: Applications for Prenatal Intervention. Complex interactions between environment, genes and psychological factors occur throughout the lifespan [30]. Virchow called this "disturbances of human culture" [31]. Unfavorable exposures in the modern environment are important considerations in attempting lifestyle change. In non-pregnant OW/OB adults, restricted energy intake and increased energy output are key to achieving weight loss goals [32, 33]. Obesity often reflects an overfed and undernourished paradox with adverse maternal-offspring consequences. Lifestyle interventions to safely reduce GWG must be both nutrient-dense and energy balanced. The Diabetes Prevention Program (DPP) successfully reduced development of diabetes by 58% in non-pregnant OW/OB adults with prediabetes by weight loss through reduced-calorie diet (30% fat, 40% carbohydrate and 30% protein) and increased physical activity (goal of 150 minutes of moderate activity per week) [34, 35]. Originally DPP was individually delivered; later group-based and more cost effective [36, 37]. Likewise, the PREMIER trial focused on reducing blood pressure among free-living individuals through increased physical activity and weight loss through the Dietary Approaches to Stop Hypertension (DASH) study diet with 2,300 mg sodium [38]. Classes taught how to follow the DASH diet and include 180 minutes per week of moderate intensity physical activity through behavior change strategies that enhanced adherence. Self-monitoring using written records, individualized feedback, problem solving and ongoing social support contributed to success. Greater adherence was reported at 6 months versus 18 months, but the 5-6% weight lost by both physical activity only and the exercise plus DASH intervention groups was retained by 75% of these participants (- 4.3 kg vs. -3.8 kg, respectively, versus control, -1.5 kg) long term [18]. Further evidence of the efficacy and safety of this intervention has been reported in a DASH diet trial among adolescents (41). To our knowledge neither the DASH diet nor the multi-component interventions applied within the PREMIER or DPP studies combined with electronic self-monitoring of behavior have been previously tested in OW/OB pregnant or postpartum women.

3 Study Design

3.1 Primary Research Question

Can prenatal diet and lifestyle intervention among overweight/obese pregnant women reduce gestational weight gain? For the purpose of this primary outcome, gestational weight gain is defined as the difference between the maternal weight measured at the 36 week visit and the weight recorded at the Baseline visit.

3.2 Secondary Research Questions

- Will adherence to the DASH diet and lifestyle intervention, in addition to reduced GWG, also produce postpartum weight control and other beneficial outcomes related to the following parameters?
- Will metabolic profiles (blood pressure, anthropometry, fasting glucose, insulin or C-peptide, HbA1c, blood lipids and CRP of mothers and babies be different between the Intervention and Usual Care groups?
- Will prenatal diet and lifestyle intervention in overweight/obese mothers result in fewer complications of pregnancy (preeclampsia, gestational diabetes mellitus (GDM), cesarean birth)?
- Will infants in the Intervention group breastfeed longer, begin solid foods later and have higher quality diets (more fruits, vegetables, dairy, less sugary beverages) than Usual Care group infants at 12 months?
- Is adiposity (percent body fat) and body weight reduced postpartum in mothers and babies in the intervention group compared to Usual Care?
- Do mothers in the Intervention group have higher quality diet (more fruits, vegetables, grams of fiber and nonfat dairy; less saturated fat/trans fat, sugar sweetened beverages) and more minutes of physical activity than mothers in the Usual Care group throughout the study?
- Will diet quality differences be evident as measured by metabolomics assays specifically related to fruit/vegetable and dietary fiber intake as alkylresorcinols (fiber), prolinebetaine (citrus fruit) and S-methly-L-cysteine sulphoxide (cruciferous vegetables in maternal urine and cord blood.
- Are measures of sleep quality and duration, depression and stress, self-efficacy and mindfulness in diet, breastfeeding and physical activity more favorable in the intervention group compared with the Usual Care group?

3.3 Design Summary

A RCT is planned among 300 ethnically diverse OW/OB pregnant women ages 18-45 years to be randomly assigned to the Intervention Group (MOMFIT Lifestyle Change group) or the Usual Care Group (Web-Watcher enhanced Usual Care) group. The MOMFIT behavioral intervention recommends eating the DASH-modified diet and moderate physical activity, primarily walking, adapted through a program of individual visits to tailor calorie/nutrient/activity goals, group coaching sessions, and individualized follow-up contacts. Electronic self-monitoring behavior will be adapted for pregnant/postpartum women via smartphone or Internet access, along with tailored feedback and encouragement from the Lifestyle Coach. Prevention of excessive GWG and achievement of the IOM weight gain goals will be compared between groups, and also whether ongoing adherence to the lifestyle interventions can be sustained through postpartum intervention. Approximately one third of the participants are expected to be minorities and/or from low income backgrounds. In our experience, over

90% of these women have regular computer and/or smartphone access. The primary outcome is gestational weight gain from baseline to near delivery (36 weeks). The secondary outcome is postpartum weight retention between 6 weeks and 12 months postpartum.

3.3.1 Theoretical Framework/Description

The MOMFIT diet and physical activity interventions are adapted from evidence-based studies among free-living individuals involving a nutrient dense, calorie-controlled diet and moderate physical activity (mostly walking) appropriate for pregnancy. This personalized intervention takes small steps over time and includes extended follow-up, relevant educational materials, self-monitoring and skill training to change and sustain new behaviors [18, 39]. This behavioral intervention is derived from social cognitive theory (SCT) [40], self-applied behavior modification techniques, behavioral self-management [41] and the relapse prevention model [42], and utilizes the transtheoretical, or stages-of-change model [43, 44]. SCT emphasizes the importance of an individual's ability to self-manage her behavior by setting appropriate goals, monitoring progress toward the goals and using modeling and observational learning to attain skills necessary to reach goals. With this conceptual framework, interventions are efficacious in producing healthy behavior change by improving individuals' self-efficacy in their abilities to implement such changes. Furthermore, relapse-prevention training provides specific skills to decrease the risk of slips turning into relapse when acquiring and maintaining a new behavior. Motivational interviewing [45] to be utilized by the Lifestyle Coach also provides a useful framework for helping participants make crucial decisions in light of these behavioral theories, while supporting their intrinsic motivation to change. The Lifestyle Coaches trained in this approach [46, 47] will use extended contacts, group interactions, social support, goal setting, self-negotiation and problem solving skills to tailor recommendations via individual visits and follow-up email, text and phone call.

3.4 Study Population and Eligibility Criteria

3.4.1 Source Population

Northwestern Memorial Hospital (NMH) is the primary teaching affiliate for the Northwestern University Feinberg School of Medicine (NUFSM) on the Chicago Campus. Prentice Women's Hospital (PWH) at NMH is one of the largest maternity hospitals in the US with over 12,000 deliveries in 2010, with 54% having BMI > 25. Patients are racially, ethnically and socioeconomically diverse and yet ≥ 90% of all patients, including those attending the Prentice Ambulatory Care (PAC) clinic for patients with public funding, report daily Internet access via personal computer or smartphone. Most receive prenatal care within walking distance of the hospital in the offices of private physicians, many in 680 N. Lake Shore Drive where the Department of Preventive Medicine (DPM) is located. Over 90% of patients initiate prenatal care in the first trimester, enhancing successful clinical research recruitment over the past ten years. The available population is sufficient to provide an ample number of subjects for this and other ongoing antepartum clinical studies.

3.4.2 Inclusion Criteria

-Age 18-45 years

-Singleton viable pregnancy. A twin pregnancy reduced to singleton before 14^0 weeks by project gestational age (see Section 3.4.3 below) is acceptable. An ultrasound must be conducted before randomization that shows a fetal heartbeat; there should be no evidence of more than one fetus on the most recent pre-randomization ultrasound. *

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* Core eligibility criterion for the LIFE-Moms Consortium

-Gestational age at randomization no earlier than 9 weeks 0 days and no later than 15 weeks 6 days based on an algorithm (see Section 3.4.3 below) that compares the LMP date and data from the earliest ultrasound*
-Body mass index between 25-40 kg/m^2 at time of Baseline visit.
-The *last r*eported pre-pregnancy weight will be used by recruiters to determine possible eligibility prior to doctor's appointment. Interested and consented women will have Baseline BMI(first trimester measured weight and height), measured at first clinic visit

3.4.3 Gestational Age Determination

Gestational age is determined as follows, and is denoted "project gestational age". The "project EDC", which is based on the project gestational age, cannot be revised once a determination has been made.

1. The first day of the last menstrual period (LMP) is determined, and a judgment made as to whether or not the patient has a "sure" LMP date.
2. If the LMP date is unsure, the ultrasound measurements obtained at the patient's first dating ultrasound examination are used to determine the project gestational age, by the standard method of ultrasound gestational age determination at that institution.
3. If the LMP date is sure, project gestational age is determined by a comparison between the gestational age by LMP and by the earliest dating ultrasound.
4. If the earliest dating ultrasound confirms the gestational age by LMP within ± 7 days
    - The LMP-derived gestational age is used to determine the project gestational age.
    - If the ultrasound determined gestational age does not confirm the LMP generated gestational age within ± 7 days, the ultrasound is used to determine the project gestational age.

3.4.4 Exclusion Criteria

-IVF conception/ovulation induction w/ gonadotropins
-Weight gain of >15 pounds from reported pre-pregnancy weight to Baseline visit
-Current smoker
-Prior bariatric surgery
-In weight loss program w/in 3 months of conception
-History of alcohol or drug abuse within 5 years
-No access to internet and/or smartphone
-Unable to attend intervention/follow-up visits
-Unwilling/unable to commit to self-monitoring data collection
-Unable to complete intervention program
-Presence of any condition that limits walking or following diet recommendations
-Not fluent in English
-Diagnosis of diabetes prior to pregnancy, or an Hb A1c $\geq$ 6.5 % or other test result suggestive of pre-pregnancy diabetes. All potential participants will have Hb A1c performed prior to randomization.*
-Known fetal anomaly *
-Planned termination of pregnancy*
-History of three or more consecutive first trimester miscarriages*
-Past history of anorexia or bulimia by medical history or patient report. Binge eating disorder (BED) is not an exclusion.*
-Current eating disorder diagnosed by EDE-Q questions 2-4 and confirmed after discussion with the participant by study staff*

-Actively suicidal defined as a value ≥ 2 on the BDI-II question 9*
-Prior or planned (within 1 year of expected delivery) bariatric surgery*
-Current use of one or more of the following medications: *

- Metformin
- Systemic steroids
- Antipsychotic agents (e.g., Abilify, Haldol, Risperdal, Seroquel, Zyprexa)
- Anti-seizure medications or mood stabilizers that would be expected to have a significant impact on body weight (e.g., Depakote, Lamictal, Lithium, Neurontin, Tegretol, Topamax, Keppra)
- Medications for ADHD including amphetamines and methylphenidate

-Continued use of weight loss medication including over the counter (OTC) and dietary supplements for weight loss (e.g., Adipex, Suprenza, Tenuate, Xenical, Alli, conjugated linoleic acid, Hoodia, Green tea extract, Guar gum, HydroxyCut, Sensa, Corti-slim, Chromium, chitosan, Bitter orange) *

-Contraindications to moderate to high intensity physical activity in pregnancy specified in the ACOG Committee Opinion #267, 2002 (reaffirmed 2009) *

- Hemodynamically significant heart disease defined as an AHA class II (short of breath with exercise) or greater
- Restrictive lung disease (e.g. pulmonary fibrosis)
- Poorly controlled hyperthyroidism
- Poorly controlled seizure disorder
- Poorly controlled hypertension defined as a blood pressure ≥ 160/110
- Current extreme sedentary lifestyle (e.g. bed bound)
- Orthopedic limitations to aerobic exercise
- Severe anemia defined as a hemoglobin < 8 or hematocrit <24

-Participation in another interventional study that influences weight control*
-Enrollment in this trial in a previous pregnancy*
-Intention of the participant or of the care provider for the delivery to be outside the LIFE-Moms Consortium hospital*
-Participant's unwillingness or inability to commit to a 1 year follow-up of herself or her child, including planning to move away.*

3.5 Informed Consent Procedures

Written informed consent must be obtained before entry into the study. Full disclosure of the nature and potential risks of participating in the trial is to be made. Patients will also be given the option to consent for long term follow-up (beyond 12 months).

A consent form has been developed according to the requirements of the Northwestern Institutional Review Board (IRB). It contains patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of the institution. A copy of the signed consent form for the study will be provided to the patient.

3.6 Randomization Method and Masking

The randomization will be done using a permuted block design with variable block sizes. In addition to simple randomization this tends to produce groups comparable with respect to known and unknown risk factors and will also ensure that groups are roughly the same size at any point during recruitment which will eliminate the possibility of differential bias due to seasonality. No planned stratification levels are pre-specified. Allocation concealment to the study coordinator will be ensured up to the point of randomization.

Prior to recruitment, a randomization vector (list) reflecting the permuted block design described above is prepared and uploaded to the study tracking system (as a table in an MS Access database). This randomization vector simply gives the random order in which participants are to be placed in either the intervention or control group. When a stratified design is employed, a separate randomization vector is defined for each strata. These vectors are produced via SAS Proc PLAN or with use of random numbers generated in MS Excel depending on the complexity of the study. The randomization table in the Access database is shielded from view by study staff so that it is not possible for staff to view the table during the trial.

As prospective participants are encountered, a recruitment/randomization form in the Access database is opened and populated with status codes indicating study eligibility. Checkboxes and drop down lists are provided for each study component necessary for enrollment into the study (e.g., boxes for completed pre-randomization measures, exclusion criteria, run-in completion, etc. are shown on the recruitment form). The form contains a randomization button: Initially, the button is not enabled, its color is grey, and the button caption is reads "Please Enter All Eligibility Criteria." As participants complete the pre-randomization study components, information is entered into the recruitment screen by study staff. When the information entered indicates that the participant is ineligible to be randomized, the randomization button caption is set to "Ineligible," the button turns red, and it remains un-enabled. When all the information has been entered and the codes indicate that the participant is eligible for randomization, the button text changes to "Eligible, Press to Randomize," the button turns green, and it is enabled by the underlying program.

When the study Coordinator determines that it is time to randomize an eligible participant, the randomization button is pressed and the next sequential entry from the randomization vector is consulted to determine the assignment for that participant. The randomization screen is programmed such that after the button has been pressed once, the trial assignment appears on the button text and it is not possible to press the button again for that participant. The MS Access database employs a username/password scheme such that only staff who are unblinded to trial assignments are able to press the randomization button or view the trial assignments of randomized participants.

4 Study Procedures

4.1 Screening/Recruitment

Recruitment Coordinators (RCs) located in the offices of practices and clinics associated with and delivering at Prentice Women's Hospital will review the charts of patients presenting for a first prenatal visit before 14 weeks' gestation to determine whether eligibility criteria are met.

Research staff will review the inclusion/exclusion criteria against each potential participant's medical and obstetrical history. If no dating ultrasound with evidence of a fetal heartbeat has previously been conducted, one must be conducted and gestational age criteria confirmed before a participant can be randomized.

Weight will be measured without shoes, wearing light clothing on a calibrated beam balance scale and height will be measured with a stadiometer at the baseline visit according to a standardized protocol to confirm the BMI eligibility criteria.

If the potential participant has not had a HbA1c test during the current pregnancy, blood will be collected and tested to ensure eligibility. The patient will be asked questions from the Eating Disorder Examination Questionnaire (EDE-Q) and the Beck Depression Inventory II (BDI-II) will be administered to confirm eligibility in the trial as well as to assess depression.

After completing the Baseline visit and determining eligibility, all participants will undergo assessment of physical activity (Actigraph) and dietary intake (ASA 24) within 2 weeks prior to randomization. Subsequently, participants will be asked to attend the Randomization visit**.** Participants who successfully return the Actigraph and complete the second self-administered ASA24 will be randomized to either the Intervention (MOMFIT Lifestyle Change) group or the Usual Care (Web-Watcher (enhanced Usual Care) group by the Study Coordinator using a randomization code provided by the study statistician. Successful completion of these data collection efforts will constitute a run-in period to determine suitability for randomization.

A follow-up phone call will be made by Research Staff to remind participants to wear the Actigraph and return for the Randomization visit, bringing the Actigraph.

4.1.1 Recruitment Process

If a patient is potentially eligible, she will be approached to determine her interest in learning more about study participation. Patients that are interested in being approached will sign a consent form to have their contact information recorded and provided to the Study Coordinator who will contact and schedule them for the Baseline visit. The Study Coordinator will interface with the recruitment coordinators (RCs) on a regular basis to assure recruitment of 300 multiethnic, eligible women within the first four years of the study.

4.1.2 Recruitment tracking

Screening logs will be kept by all RCs. Data will be entered on all women who were approached by a recruiter to determine initial eligibility for MOMFIT. Women who complete a Contact form will be followed- up on by the coordinator with the intent to screen and schedule. All other women will be documented on the log with status of screening. Information to be collected will include patient initials screening date,screening status, and reason for exclusion. Logs and contact forms will be shared with the Study Coordinator who will follow-up with those who consent to contact with the intent to schedule the Baseline Visit and complete the data collection.

4.1.3 Recruitment of Minorities/ Low SES Participants

Practices associated with Prentice Women's Hospital provide care for women of diverse racial and ethnic backgrounds from the Chicago metropolitan area. Recruitment will also occur in the PAC clinic, which provides care to primarily minority women of low socio-economic status. It is anticipated that recruitment in these different settings will provide for recruitment of a diverse patient population.

4.2 Randomization

Only after a participant returns the actigraphy, completes the second 24 hour recall using ASA24 and the database has recorded that all eligibility criteria are met, will the database provide a randomization button. When the Study Coordinator selects the button, the participant is then randomized. (please see Section 3.6 for further details). Once randomization has been achieved, study measurements at subsequent clinic visits will be conducted by staff who are blinded to the study group assignment. The Study Coordinator is unblinded.

4.3 Baseline procedures

Study Coordinator will initiate a phone, text or email reminder prior to the Baseline visit, which will be conducted with the participant fasting. The Study Coordinator will explain the study and obtain written informed consent among interested participants. Standardized questionnaires (listed in Section 4.4.3) will be administered to ascertain prenatal and demographic data. Height, weight and blood pressure will be measured by trained staff. Eligible women will be asked to conduct a supervised, self-administered 24-hour diet recall (ASA24 online https://asa24beta.westat.com/ResearcherSite.html) and complete sleep/stress/other questionnaires. Assistance will be offered if needed. Women will be instructed how to wear the Actigraph for the subsequent 7 days. Urine and blood will be collected. HbA1c will be measured and storage samples for future measures, including fasting glucose, insulin, adiponectin, IL-6, lipids, CRP and 25-hydroxyvitamin D will be collected. The Randomization visit will be scheduled within 1-2 weeks.

In addition to information collected for eligibility, the following data will be obtained from the participant and chart review:

- Demographic information: maternal date of birth, race and ethnicity, marital status, family size, household type, income, occupational status, TV, telephone and computer ownership, internet/computer access, cell phone usage and technology, maternity leave, education/literacy.
- Paternal demographic information: age at maternal enrollment, race, ethnicity, body type as identified by participant using standard silhouettes
- Medical history: self-reported pre-pregnancy weight, underlying medical conditions, current medications; family history of diabetes and hypertension
- Obstetrical history: to include gravidity, parity, and a description of previous births (year, birth weight, gestational age at delivery, weight gain, gestational diabetes, preeclampsia, birth trauma. A Modified-Pregnancy-Unique Quantification of Emesis and Nausea Index (PUQE) questionnaire, which assesses the severity of nausea and vomiting of pregnancy, will be given at baseline.
- Social history: alcohol use, tobacco use

Blood Pressure (BP). Seated BP will be measured after a 5 minute rest according to a standardized protocol.

Maternal physical activity. The *ActiGraph GT3X+* accelerometer will be used to measure maternal activity and sleep objectively during gestation for seven days. The monitor records time varying accelerations ranging in magnitude from +/- 6 g's. The accelerometer output is sampled by a twelve-bit Analog to Digital Convertor and the raw acceleration is then stored in flash memory for future analysis. The GT3X+ is small and lightweight (19g) and can be worn at the hip, wrist, or ankle. The LIFE-Moms consortium will use wrist-placement to minimize participant inconvenience and to better measure sleep.

Questionnaires

- *Household food insecurity* will be measured with the first two questions of the USDA Food Security Module subscale
- *Sleep :* A sleep questionnaire, devised by NuMom2B Sections A,C,E,and F, a cohort study of pregnant women and their infants, including questions regarding sleep schedule, quantity, quality, habits and disorders and sleepiness
- *Frequency of weighing.* Participants will be asked to indicate how frequently they had weighed themselves during the past month using a 7-point scale ranging from *several times a day* to *never*.(1,2)
- *Maternal Sedentary Behavior* will be measured with Item 39 from the Nurse's Health Study II Questionnaire (http://www.channing.harvard.edu/nhs/questionnaires/pdfs/NHSII/2009.pdf). This item includes 5 questions that ask respondents to rate the average hours per week over the past year that they engaged in certain sedentary behaviors.

  Health Survey (SF-12) The SF-12 is a 12-item self-report measure of quality of life. It was derived from the original 36-item measure, and taps a variety of domains including physical functioning, bodily pain, general health, vitality, social functioning, physical and emotional functioning, and mental health functioning. The SF-12 also provides two composite indices of physical health and mental health.

Maternal blood and urine. All samples will be collected in the morning following an overnight fast. A total of seventy -one (71) mL of blood will be collected with thirty-one (31) mL of blood going to the NIDDK Repository and 40 mL to be stored locally.

For the NIDDK Repository:
A total of thirty-one (31) mL of blood will be collected with approximately 15 mL used to obtain archived samples of serum and plasma, 8.5 mL for DNA extraction, 2.5 mL for RNA extraction and 5 mL to measure a metabolic panel comprised of glucose, insulin, lipid panel and C-reactive protein. A total of five (5) mL of urine will be collected. All samples will be shipped and stored at the NIDDK Repository.

For Northwestern Repository:
Locally, a total of forty (40) mL of blood will be collected with 10mL blood to be used for DNA extraction for three epigenetic factors, i.e., histone modification cell specific DNA methylation(CD4+ T cell),, and miRNA. Samples required include additional 2,5ml Paxgene tube for miRNA and gene expression measurement; 4 ml for CD4+ T cell separation, and 3.5ml for histone modification.

For metabolomics measures, 10 mL blood will be stored for future analyses of short chain fatty acids, bile acids, alkylresorcinols (fibre), prolinebetaine (citrus fruit) and S-methyl-L-cysteine sulphoxide (cruciferous vegetables) using a combination of UPLC-MS and NMRmethods.

Another 20mL blood will be stored in a -80 degree freezer to be used for lipid panel, insulin, glucose, C-peptide, C-Reactive Protein (CRP), leptin, adiponectin, vitamin D, n-3 fatty acids and other nutrients.

Hair and Toenail Specimens. For baby, we plan to collect a small sample (a few strands less than one half inch long) of hair at the last visit (at 12 months). For mothers, we will collect a very small sample of toe nails (self-collected with a small nail clipper) at baseline and at the last visit. these two tissues will be used to measure *environmental metals, including cadmium (Cd), lead (Pb), arsenic (As), mercury (Hg), copper (Cu), and chromium (Cr).*

4.4. Infant Blood Collection Procedures

5/1/2015: The original proposal called for optional venous blood draw in the 12 month toddler in the final visit. Of the more than 50 visits already completed, no mothers have granted permission for

Venous blood draw. When asked, these mothers indicated that they would have agreed to a finger stick but not a venous sample. Simultaneously we have become aware of the rapidly growing interest in dried blood spots (DBS) as a viable alternative with ever increasing evidence of accuracy in numerous biomarkers of interest. This approach is highly cost effective, amenable to long term storage and is generally less burdensome than venous blood draw. The LIFE-Moms Data Safety and Monitoring Board has granted approval to this approach. Effective 5-11-2015

Infant blood will be collected via a finger prick on babies at their one year visit. A trained technician will prick the middle or ring finger (just off the center of the tip of the finger) with a sterile, single-use micro-lancet. The micro-lancet delivers a controlled, uniform puncture that stimulates capillary blood flow but minimizes pain and injury. Up to5 blood drops will be placed on a filter paper (ie Whatmam #903). All samples will be kept locally for site specific testing (MOMFIT)

4.4.1 Intervention

Control Group Description:

The Control Group in this study is an enhanced Usual Care group. For purposes of potentially improving recruitment, this is called the Web-Watcher group, since the Usual Care involvement will primarily be based on clinical visits and referral to the MOMFIT website that is password protected . The Usual Care group will attend the baseline and all data collection visits (**Table 3**) conducted by trained research staff blinded to the group assignments. They will be informed of their group assignment at the Randomization Visit and for retention purposes will be offered l web-based intervention consisting of publically available websites that will be conveniently organized and targeted to pregnant women as listed in Table 1. This approach will help encourage and maintain involvement of these participants in the study but differentiate the potential influence of the study intervention versus the usual care provided by their OB or other clinical provider.

The interventions planned in both groups are presented in Table 1 as follows:

Table 1. Description of the Interventions

	Usual Care	Intervention
Diet	Web-based access and printed pamphlet on the ChooseMyPlate.gov/ Dietary Guidelines 2010	Calorie-controlled, individually tailored DASH diet for pregnancy and lactation.

	recommendations for pregnancy/lactation; other relevant pregnancy websites and access to password protected MOMFIT website	Breastfeeding encouraged preferably exclusively for 4-6 months, with gradual introduction of "Baby-DASH" –type diet
Physical Activity	US Dietary Guidelines Website includes activity recommendations	ACOG recommendations: ≥30 minutes of moderate-intensity activity 5-7x/week; we will emphasize walking and gradually increase
Self-Monitoring	None required	Daily diet & activity ; weekly self-reported weights via LoseIt! Website/App
Group Sessions	Invited to groups (2 prenatal; 2 postpartum) covering infant CPR, care for newborns and transitions to motherhood offered by the hospital	7 group sessions: 6 prenatal; 1 postpartum
Individual Visits	None provided	5 Individual Visits conducted by study nutritionists (3 prenatal; 2 postpartum) to individualize calorie/dietary/physical activity goals, encourage breast feeding
Phone Coaching	None provided	Weekly for the first 6 weeks of intervention; monthly or more frequently as needed through 11 months postpartum
Electronic Contact	MOMFIT Website access: this group will have access to PDFs on childcare related topics that will be drawn from publicly available source No additional emails, phone or electronic contacts	MOMFIT Website Weekly emails/texts regarding electronic self-monitoring of diet/ weight/ physical activity plus an online privatized social support system for 24 months Educational modules (PDFs) emailed 7x prenatally; 8 x post-partum

Intervention Descriptions. As indicated above, the Web-based (Enhanced Usual Care Group will be provided with minimal intervention as listed in Table 1.

Lifestyle Change Group (Diet Intervention Group): Nutritional Quality/Calorie Goals**.** Energy needs in pregnancy and breastfeeding are based on the following Institute of Medicine formula for normal weight adult females:

Energy needs (calories**) = 354 – (6.91 × age [y]) + PA × (9.36 × weight [kg] + 726 × height [m]) + addition for pregnancy/breastfeeding [3]**

Where PA is the physical activity coefficient:
1) PA = 1.00 if PAL is ≤ 30 min/day
2) PA = 1.14 if PAL is 30 to 60 min/day
3) PA = 1.27 if PAL is 60 min/day or more

During the Individual Visits, each participant will have her own energy needs calculated and her daily dietary calorie goals will be reviewed as indicated in **Table 2**. For weight control purposes in these overweight/obese women, MOMFIT will minimize increases in energy intake. This intentional energy deficit is calculated to enhance energy balance without compromising nutrient density. In order to reduce weight gain but achieve nutrient adequacy, we will recommend 75% and 50% of the calorie goals for overweight and obese participants, respectively as presented in Table 2. Careful monitoring for safety and prevention of weight loss during pregnancy will occur via weekly contacts. Weight gain or loss of 1 pound or more within one week will be further reviewed with the mother.

Table 2. Calorie needs during pregnancy and lactation for nonobese women compared with recommendations to accompany reduced weight gain goal for overweight/obese MOMFIT participants

Trimester or phase	Pregnancy and Lactation	IOM Addition Normal Weight	MOMFIT Addition Overweight	MOMFIT Addition Obese
IOM Weight Gain Goals (lbs) *		**25-35**	**15-25**	**11-20**
1st trimester	Prenatal (kcal)	0	0	0
2nd trimester	Prenatal (kcal)	340	255	170
3rd trimester	Prenatal (kcal)	452	339	226
1st 6 mos.	Breast milk only, no formula (kcal)	330	248	165
1st 6 mos.	At least half breast milk, plus some formula (kcal)	70	53	35
1st 6 mos.	Some breast milk, mostly formula (kcal)	0	0	0
2nd 6 mos.	Breast milk only, no formula (kcal)	400	300	200
2nd 6 mos.	At least half breast milk, plus some formula (kcal)	200	150	100
2nd 6 mos.	Some breast milk, mostly formula (kcal)	0	0	0

* reference [3]

Physical Activity Component of MOMFIT Intervention. (LC) Participants will be informed that the American College of Obstetricians and Gynecologists (ACOG), the CDC, and other national guidelines all agree participation in recreational and physical activities are safe during and after pregnancy. They will be encouraged to eventually engage in 30 minutes or more of moderate-intensity activity, primarily walking, on all or most days of the week. Contraindications for exercise will be reviewed in determining eligibility and throughout the study. Since participants will likely be sedentary at baseline, we will gradually increase walking time if necessary, starting with 10 minutes and advancing step-wise in increments of five minutes over the course of pregnancy.

Sleep and Stress. The benefits of sleep are increasingly well documented for pregnant, as well as non-pregnant individuals, and measures of stress have been correlated with both obesity and adverse pregnancy outcomes. While a formal sleep intervention is beyond the scope of this study, MOMFIT intervention participants will be encouraged to sleep on average 7-8 hours/ night. Strategies to improve sleep habits of offspring will be discussed during the postpartum intervention. Data on sleep and stress will be collected at baseline, 24-28 weeks, 36 weeks, and 6 weeks and 12 months postpartum.

Individual Visits. Immediately after randomization, participants assigned to the Intervention / Lifestyle Change group (LC) will be scheduled at their convenience for an individual visit with the intervention dietitian. For some participants this will occur that day, but for those who cannot stay we will find another day as soon as possible. Goals tailored to individual needs for calorie intake, diet and physical activity will be calculated prior to this visit. Prior to this visit, preferably the randomization visit, participants will be instructed on how to use a web-based program for self-monitoring their diet and pedometer for tracking their daily steps. This will involve viewing a brief DVD that will illustrate this system and how to access it via internet or smartphone app. Food models will be shown to illustrate desired portion sizes.

An overview of the DASH diet and its target food groups will also be discussed along with the importance of daily physical activity. The first individual visit will conclude with the participants establishing goals using the SMART (Specific, Measurable, Attainable, Realistic and Timely) goal method.

Participants will be scheduled for five individual visits with the intervention dietitian, three conducted during the prenatal period and two postpartum. If needed, additional individual sessions, either over the phone or in person, will be arranged by the study Coach (see intervention contact schedule).

Group contacts. In-person group sessions will be held seven times from the second trimester through 11 months postpartum to provide ongoing nutrition, behavior and activity education for weight management, as well as peer support. Session topics are listed on the intervention contact schedule.

We will develop our own website for purposes of engaging in ongoing discussion with our participants. In this password-protected online social support group, participants will be encouraged to share concerns, ideas or support on an ongoing basis throughout the 24 month intervention. This type of electronic social support is offered as a convenient and real-world approach to in-person social support for strengthening participants' motivation to meet study lifestyle goals. Study coaches will monitor these chat groups discussions periodically to determine its utilization and appropriateness of its content.

Phone Contacts. Each participant in the Lifestyle Change group will be assigned to a study coach (behaviorist &/or registered dietitian trained in Motivational Interviewing (MI)) during the 24 month intervention. The study coach will call participants initially weekly and then less often as the intervention progresses (see intervention contact schedule). During these 10-15 minute calls, the study coaches will follow a standard outline and use MI counseling skills to help participants overcome barriers to meeting their diet, weight and activity goals. A brief discussion of the most recent electronic educational materials emailed to participants will also be conducted. An outline of each coaching call is described below.

MOMFIT Phone Coaching Outline. The following is an example of the script that will be followed by the Study Coaches in making weekly phone contact with the Intervention participants:

1. Hi. Can you please recall for me what your daily calorie goal is? Weight goal?
2. Weight:
    a. Current
    b. Weight change since last call based on home weight or last office visit.
3. Self-monitoring adherence:
    a. Self-monitored ____days out of 7 days
    b. Have you experienced any changes in your routine that may have affected your self-monitoring this past___?
4. Daily Calorie Goal:
    a. # days met calorie goal over past _____
    b. # days >300 calories over daily goal____
5. DASH diet goals
    a. Can you recall what your daily fat/fiber goals are?
    b. # servings FV for past____
    c. # servings low fat dairy for past____
    d. # servings whole grains for past___
    e. Can you tell me what foods you're eating that don't fit into your MOMFIT DASH diet goals?

6. Exercise
    a. Can you recall what your daily PA goal is?
    b. # minutes of PA _____ per day/week
7. SMART goal setting and recommendations with reinforcement of the benefits of breastfeeding and encouragement to practice lifestyle role modeling for the benefit of both mother and family

Electronic Contacts.

Intervention website: Our password-protected study intervention web site will house educational materials addressing diet, physical activity and behavior change for weight management as well as breast feeding, infant nutrition and other post-partum issues related to study lifestyle goals. A variety of formats will be used on the study web site to convey this information. This includes web content (HTML), PDFs (available for download), message boards, short videos and podcasts.

MOMFIT Intervention Facebook Account: In response to participants' requests for an intervention social media forum to provide timely information related to the adoption of a healthy lifestyle, MOMFIT will offer a **private** Facebook page, inviting only intervention participants to join.

The purpose of this online forum is to provide timely information that motivates/reinforces' participants' adherence to the MOMFIT lifestyle goals. Timely articles/research briefs discussing nutrition, exercise and other healthy lifestyle topics, appropriate recipes, food product reviews, parenting information and infant nutrition updates will be posted on this social media site. Additionally, announcements of upcoming study group sessions will also be posted.

The study intervention director will be responsible for posting information and making other necessary maintenance updates for this Facebook page. Participants will not be allowed to post information on the MOMFIT Facebook page in order to keep this format confidential. This Facebook page will also not be used for recruitment.

Monthly Electronic Materials: Per the intervention contact schedule, participants in the Lifestyle Change group will also receive monthly educational materials addressing a specific nutrition and behavior topic (PDFs) sent to their email accounts. These electronic lifestyle education modules build on the information presented in group sessions and augment participants' knowledge and skill training of relevant nutrition and behaviors. These PDFs will also be archived on the study intervention web site.

Based on recent diet and activity, study coaches will either email or text (per participant's preference) reminders, tips, feedback on a weekly basis. These electronic contacts are designed to keep the participants accountable and motivated to record their diet & activity daily and weights weekly using their online account. For example, participants will receive electronic reminders to record their diet if no activity was observed in the past 48 hours. The study nutritionists (registered dietitians) will also periodically monitor participants online accounts for nutritional adequacy and unusual weight changes and then report this information to the assigned study coach.

Self-Monitoring. Study participants are required to record their dietary intake and physical activity online on a daily basis. Additionally, weekly self-reported weights are also logged into participants'account. Study coaches will, in turn, tailor their electronic contacts and phone coaching based on participants' recent self-monitoring activity to help participants' meet their lifestyle goals.

Postpartum Intervention. An individual visit will occur soon after delivery for the Lifestyle Change group. New calorie goals promoting weight loss (1-2 lbs. per week), DASH diet review in the context of nutrition supporting lactation, importance of hydration for breastfeeding and physical activity for new moms will be addressed. SMART goals will be established for weight loss, physical activity and breastfeeding. Participants will be reminded that breastfeeding helps with energy expenditure and with careful attention to diet and physical activity, weight loss and maintenance can be enhanced. Postpartum intervention will incorporate infant intervention that promotes ideally, exclusive breastfeeding for the first six months if possible, if not breastfeeding supplemented with formula for the first six months and delayed introduction of solid foods until 6 months. We will approach introduction of solids with care to address nutrient quality and proper quantity for age

Each month, participants in the Lifestyle Change group will also receive modules (PDFs) addressing infant and maternal nutrition, behavioral skills supporting weight loss and increased physical activity and exercise guidelines also promoting weight loss. These will be emailed to the participants on a monthly basis and will be archived on the study intervention web site. Additionally, intervention participants will receive monthly phone calls from their study coach to discuss the highlights of these educational materials (PDFs) as well as review the participant's goals/barriers related to meeting target weight, DASH food groups and exercise targets.

Five months post-partum, participants in the Lifestyle Change group will attend a group session to discuss how transitioning from breastfeeding to solids affects mom's energy needs and infant nutrition. Due to the complexity of this topic, group session was deemed the best type of delivery of this material.

At six months postpartum, participants in the Lifestyle Change group will receive their final individual visit. Weight loss progress report, infant feeding issues, exercising with baby and other factors influencing new moms will be addressed. SMART goals will also be established at this time.

4.4.2 Standardization of Intervention Delivery

The Intervention will be delivered by experienced Registered Dietitians who are already trained in Motivational Interviewing and group facilitation who will lead the group intervention sessions and conference calls. Refresher training in motivational interviewing will be developed and delivered by the Intervention Director prior to initiation of the intervention. Additionally, behaviorists or dietitians trained in Motivational Interviewing will provide ongoing phone and other electronic counseling to the intervention participants as preferred. Intervention sessions and phone coaching calls will be recorded and randomly reviewed to ensure fidelity of treatment.

4.4.3 Procedures and Visit Schedule

Standardized data collection visits and timing for both the intervention and the control groups are presented in **Table 3.**

Glucose tolerance will be measured by a 75 gm 2 hour oral glucose tolerance test at 24,0-27,6 weeks at our clinic if it is not ordered as part of the regular visit with the OB.

Infant anthopometric measurements. Length obtained on a hard-surface infant measuring board, weight, head circumference and skinfold thickness measurements will be performed by a trained research team member at approximately 24 hours to 1 week of life. Length, weight, and skinfold thickness will also be performed by a trained research team member at approximately 48-56 weeks of life. Infant growth will be plotted on the Fenton growth chart for preterm infants who have not yet reached their project estimated date of confinement (EDC) and the WHO growth chart for preterm infants who have reached their project EDC and term infants. Length or weight-for-length at the 5th percentile or less at any visit, or length or weight-for-length that has crossed two or more percentile lines downward, requires that the mother be informed and that it is recommended that she have the infant seen by a health care provider for

further evaluation. An in-person training will be conducted for the infant skinfold, head circumference, and length measurements to standardize procedures across sites.
Infant Blood Collection. A venous sample will be drawn on at 52 weeks of age (range 48-56 weeks). Approximately 4 ml of blood will be collected as a super shared measure (part of the study wide consortium), The child will sit on the mothers lap, facing the phlebotomist. A trained study phlebotomist will draw only one tube to be used to shared with the study repository. Mothers who have agreed and signed the initial consent will be approached. The blood draw will only occur if mom is still willing.

TABLE 3: Data Collection Visits for Both Groups

	VISITS							
Measures		**Prenatal**				**Postpartum**		
Week of Pregnancy	**Screening 8- 15.3 wks**	**Baseline 9-15.4 wks**	**Random-ization 9-15.6wks**	**24-28 weeks***	**35-37 wks**	**Delivery**	**6 weeks**	**12 months**
Visit Location	**OB Office**	**DPM Clinic**	**DPM Clinic**	**DPM Clinic**	**DPM Clinic**	**Prentice Hospital**	**DPM Clinic**	**DPM Clinic**
Consent	**x**	**x**						
Self-reported pregravid weight	**x**							
Height (Mom)		**x**						
Weight (Mom)		**x**		**x**	**x**		**x**	**x**
Blood pressure		**x**		**x**	**x**		**x**	**x**
Waist and Hip circumference							**x**	**x**
Blood: 8 Hr Fast for storage (glucose, insulin, CRP, IL-6 and adiponectin, lipid panel, vitamin D and metabolomics)		**x**		**(**routine; OGTT at OB visit)***	**x**		**x**	**x**
HbA1c		**x**					**x**	**x**
Spot Urine		**x**		**x**	**x**		**x**	**x**
First Diet recall (ASA 24)		**x**			**x**		**x**	**x**
Second diet recall (ASA24)*			**x**		**x**		**x**	**x**
Actigraph		**x**	**Returned**		**x**		**x**	**x**
Cord blood collection						**x**		
Weight (Baby)						**x**	**x**	**x**
Length (Baby)						**x**	**x**	**x**
Skinfold , baby						**x**		**x**
Head circumference						**x**		
PEA POD						**X**		
BodPod (Mom)							**x**	**x**

Breastmilk (as relevant)							x	x
Sleep/Stress Behavioral Data Collection **		x		x	x		x	x
Infant feeding & activity					X		x	X
Blood: Infant, at 12 months as consented								X
Infant stool sample, as consented						x	x	x

*Two 24 Hour recalls will be completed. The first is completed at the clinic for 4 of the 5 clinic visits (not 24-28 wks), The second recall will be completed within 2 weeks of the first one.
** Detailed survey data collection listed below in Table 4 (see below).
***2hr OGTT collected at DPM clinic is not ordered at routine OB visit

As part of the LIFE Moms Steering Committee the following blood collection amounts have been established.

Blood Collection Amounts: Core and Shared

Center		Pre-randomization		35-37 weeks		1 year postpartum		48-56 wk	Infant blood draw
		Volume (ml)	Labs Planned	Volume (ml)	Labs planned	Volume (ml)	Labs planned	Volumn (ml)	Labs planned
	Site protocol	40	Archive	40	Archive	40	Archive	1-5 drops of blood	Archive
	Repository	31		31		31		0	
	TOTAL	71		71		71		4	

Site specific IRB restrictions on the volume of blood drawn: Not to exceed 500 ml in 8 weeks for non-pregnant women. No specific guidelines given for limits during pregnancy.

Epigenetic studies. Some of the blood collected as part of the site protocol specified above will be used for epigenetic studies. In addition to studying DNA methylation, blood will be used to evaluate histone modification and miRNA. These epigenetic studies will also be performed on cord blood and infant blood taken at the 12 month visit.

In addition, maternal hair and toenail samples will be used to measure environmental metals, including cadmium (Cd), lead (Pb), arsenic (As), mercury (Hg), copper (Cu), and chromium (Cr) in future studies. Hair sample from baby at 12 months and toenail clippings from mother at baseline and 12 months will also be taken for similar studies.

Metabolomic Studies. Metabolomics allows for parallel assessment of a broad range of metabolites and has been shown to have a great benefit for classifying phenotypes and investigation of physiologic status even in the newborn [48]. This study offers an exciting possibility of comparing potential metabolic benefits in utero from maternal energy balance and nutrient density aimed at prevention of excessive GWG. The opportunity to compare spot urines and cord blood from neonates born to OW/OB mothers who adhered to the diet/activity intervention versus OW/OB controls will offer exciting possibilities regarding primary prevention of obesity in utero. Briefly, samples will be collected according to in-house protocols, immediately frozen and stored at -80°C pending analysis. For each urine, maternal serum and cord blood serum sample, 600 MHz ^{1}H NMR spectra will be acquired using standard in-house protocol [49]. For serum samples additional pulse programs will be applied to focus on the lipoprotein components

(diffusion editing) and the low molecular weight components (Carr-Purcell-Meiboom-Gill pulse sequence) respectively. Ultra-performance liquid chromatography (UPLC)-MS profiling will be used in general screening mode using in-house methods [50]. Targeted analysis will be conducted for alkylresorcinols (fibre), prolinebetaine (citrus fruit) and S-methyl-L-cysteine sulphoxide (cruciferous vegetables) using a combination of UPLC-MS and NMRmethods. Data will be analyzed using multivariate statistical tools including linear projection methods and cluster analyses in order to identify candidate metabolic biomarkers associated with obesity or intervention. Candidate metabolic biomarkers of obesity in pregnant mothers at baseline and 36 weeks will be identified using available databases, by further analytical experiments such as 2-dimensional NMR pulse sequences including homo and heteronuclear correlation spectroscopy, LC-NMR-MS etc and by statistical correlation spectroscopy methods [48]. Several mathematical strategies will be applied to achieve higher sensitivity in detecting panels of inter-related biomarker candidates associated with maternal weight gain, maternal BMI and infant birthweight and adiposity. These methods will accommodate the specific challenges posed by spectral data including low sample:variable ratio, colinearity of predictor variables, confounding factors or co-morbidities correlated with both predictor and outcome variables etc. A flexible framework based on generalized linear models will be implemented to identify univariate and multivariate relationships of predictor variables with outcomes while statistically accounting for potential confounding effects observed in human studies. The choice of a model will be considered based on the probability distribution of a clinical outcome and both Bayesian and conventional maximum likelihood inferences will be made.

In addition to the ASA24 nutrient data, diet quality differences will be measured by metabolomic assays specifically related to fruit/vegetable and dietary fiber intake as alkylresorcinols (fiber), prolinebetaine (citrus fruit) and S-methly-L-cysteine sulphoxide (cruciferous vegetables in maternal urine and cord blood.

Weight will be measured without shoes, wearing light clothing on a calibrated beam balance scale at the Baseline visit, and at 24-28 week, and 35-37 weeks prenatal visits and the 6 week and 12 month postpartum visits.
Waist and Hip Circumference will be measured using standardized methods at the 6 week and 12 month postpartum visits for the mothers.
Height will be measured with a stadiometer at the Baseline visit only, according to the CARDIA standardized protocol.
Blood Pressure. (BP) will be measured at each clinic visit (Table 3), baseline, 24-28 weeks, 35-37 weeks, 6 weeks and 12 months postpartum**.** Seated BP will be measured after a 5 minute rest according to a standardized protocol. Systolic and diastolic (5^{th} phase) BP will be measured three times, one minute apart, using an Omron® automated BP device. Participants with DBP $\geq$ 100 mmHg or SBP $\geq$ 180 will be referred for medical attention immediately.
Phlebotomy. Fasting (8hr) samples of serum and plasma will be collected for storage at baseline, 35-37 weeks, 6 weeks and 12 months postpartum. If needed a 2hr OGTT will be done on participants with a fasting, 1hour and 2 hour blood draw. This would be in lieu of the 1 hour at their OB/GYN.

At the Baseline visit, HbA1c will be analyzed for eligibility. All other blood will be stored for future analysis of glucose, insulin, HbA1c, CRP, lipid panel (total cholesterol, triglycerides, HDL-C, calculated LDL-C), vitamin D and other potential biomarkers. Some of these markers (lipids) are altered by pregnancy but these will be used to compare groups. All samples will be promptly placed in melting ice and centrifuged (2500 for 20/min) within 2 hours of collection. This volume of blood drawn is safe in pregnancy. The changes in glucose from baseline to 24-28 and 36 weeks and the frequency of GDM in the two groups provide secondary endpoints/outcomes.
Spot urine for mothers will be collected at all data collection visits and stored for purposes of metabolomic measures to be assessed as exploratory aims and provide possible preliminary data regarding possible diet-influenced changes observed between groups.

Breastmilk will be collected among participants who choose to breastfeed at the 6 week and 12 months postpartum visits for purposes of comparing in both groups, the nutrient quality of the mothers' diet with the nutrients measured in breast milk, and also the nutrients measured in the cordblood and infant's blood. Samples of 50-150 mL (approximately 1.5-4.5 fl oz) of early (6week) and mature (12 month) breastmild will be collected and stored in the Northwestern repository.

Diet Data Assessment. Self-reported 24-hour recalls will be completed at the Baseline and 36-38 weeks prior to delivery, and at 6-weeks and 12 months postpartum as the outcome measure of dietary adherence. These diet recalls will be performed with the NCI's ASA24 online system.

Assessment of Physical Activity: Actigraphy (Actigraph GT3X). Accelerometers objectively monitor intensity and duration of activity and measures will be collected at the same clinical visit periods listed in Table 3 (baseline, 36-38 weeks, 6 weeks and 12 months postpartum). Accelerometers can record participant data in 1-minute intervals, continuously for 7-11 days and provide the number of minutes/hour spent in sedentary, light, moderate, hard and very hard activity. We will use the Actigraph GT3X monitor and the cut-points for sedentary and light intensity activity as described in the literature: sedentary behavior (1-100 counts/min), light intensity activity (101-1952 counts/min), moderate intensity (1,953-5,724 counts/min), hard intensity (5725-9498 counts/min), and very hard intensity (greater than 9498 counts/min). Participants will wear the accelerometer for 7 days , allowing us to capture both week and weekend activity.

Sleep/Stress/Other Data/Process Data Collection. Demographics including marital status, residence type, household composition, educational attainment, current employment status and access to grocery stores versus supermarkets will be assessed at Baseline only. Smoking and other lifestyle behaviors, as well as hours and quality of sleep and perceived stress, will be assessed from validated questionnaires. In addition, the following validated questionnaires will be collected:

Additional Psychosocial Assessment Measures. The following questionnaires will be collected during the time periods identified.

Table 4. Northwestern - LIFE-Moms Survey / SHARED measures and time points

Survey / Questionnaires	**9,0-15,6 Baseline**	**24-28 wks**	**35-37 wks**	**6 weeks post delivery**	**12 months post delivery**
Maternal demographics	X			X	X
PANES	X	X	X		X
BDI-II	X	X	X	X	X
Sleep questionnaire from* NuMoM2b ** (Everything but Section B Qs 7,8,9)	X	X	X	X	X
NHS for Sedentary Behavior	X	X	X	X	X
Frequency of self-weighing	X	X	X	X	X
Eating Disorder Questionnaire	X	X	X		X

Mindful Eating Questionnaire	X	X	X	X	
SF-12 – Quality of Life questionnaire	X	X	X		X
Breastfeeding Questionnaire					X
Milestone Questionnaire					X
Infant Feeding Questionnaire		X	X	X	X
Infant Sedentary Behaviors					X
Hospitalization Questionnaire (mother and infant)		X	X	X	X
Weight Management Support Inventory	X	X	X	X	X
Exercise Self-Efficacy Scale	X	X	X	X	X
Weight Efficacy Lifestyle Questionnaire	X	X	X	X	X
Satisfaction Questionnaire					X

Psychosocial Measures: MOMFIT will collect CORE and SHARED Assessment Data as follows:

Maternal Demographics

PANES [51] Physical Activity Neighborhood Environment Scale (PANES) : Physical environment can effect community access/interest in pursuing physical activity PANES is a validated questionnaire with 17 items that can help identify the ease of access to neighborhood resources and physical activity.

BDI-II The relation between obesity and depression is reciprocal; being obese predicts higher levels of depression and depressed individuals are more likely to be overweight [52]. Additionally, woman who are overweight prior to pregnancy are at higher risk for increased depression during pregnancy [53]. The BDI-II [54] is a 21-item self-report inventory assessing the severity of depressive symptoms. Each item is rated on a 4-point scale from 0 (low severity of symptom) to 3 (high severity of symptom). The maximum total score is 63. Symptoms assessed include sadness, pessimism, loss of pleasure, changes in sleep and appetite, and other DSM-IV-TR symptoms of Major Depressive Disorder. The BDI-II has demonstrated high reliability across populations (α=.81 for nonpsychiatric patients and α=.86 for psychiatric patients). Concurrent validity of the BDI to other measures of depression is also high ($r = .72$ and $r = .73$ for psychiatric and nonpsychiatric patients, respectively). The BDI is able to discriminate between clinical and nonclinical levels of depression, can differentiate depression subtypes, and can discriminate depression from anxiety [55].

Sleep Questionnaire

The **NuMoM2b project is a prospective cohort study of a racially/ethnically/geographically diverse population of 10,000 nulliparous women with singleton gestations. The women will undergo intensive research assessments during the course of their pregnancies to study the mechanisms for and prediction of adverse pregnancy outcomes such as preterm birth, preeclampsia, and fetal growth restriction in their first pregnancy. With funding from Office of Research in Women's Health, biomarkers reflecting the maternal-placental-fetal endocrine milieu related to stress will be analyzed from the bio-specimens being collected from 10,000 women. As part of the parent study, various questionnaires assessing psychosocial status during pregnancy are being administered during pregnancy. The combination of race/ethnic-specific profiles of genetic variation, perceived stress and

resilience factors (psychosocial environment) as well as biomarker differences will likely account, in part, for racial/ethnic disparities in the risk of preterm birth.

Frequency of weighing. Participants will be asked to indicate how frequently they had weighed themselves during the past month using a 7-point scale ranging from *several times a day* to *never [56, 57]*. These ratings will be recoded so that higher numbers represent more frequent self-weighing. In addition, scores on the scale will be used to form a dichotomous variable indicating whether or not the participants weighed themselves daily (including several and 1 time a day) or less often. Self-weighing will be assessed at study entry, gestation week 26, gestation week 35 and postpartum week 52.

Example:
Over the past month, how often did you weigh yourself? This does not include getting weighed at the doctor's office.

Several times a day
One time each ay
Several times a week
One time a week
Less than once a week
Less than once a month
Never weighed myself

Eating Disorder Questionnaire: Includes only 3 questions that access eating behavior.

Mindful Eating Questionnaire (MEQ). The construct of mindfulness refers to a nonjudgmental awareness of physical and emotional sensations associated with eating that, if recognized may help a person identify and respond appropriately to satiety [59-62]. A 28 item scale was developed and validated by Framson, et al [63]as an initial step towards characterizing and measuring mindful eating. It addresses disinhibition, awareness, external cues, emotional responses and distraction but is distinct from cognitive restraint. LIFE Moms can assess and differentiate over time whether the role of mindful eating plays a role in facilitating adherence to an energy balanced diet.

SF-12 Health Survey (SF-12) [64]. The SF-12 is a 12-item self-report measure of quality of life. It was derived from the original 36-item measure, and taps a variety of domains including physical functioning, bodily pain, general health, vitality, social functioning, physical and emotional functioning, and mental health functioning. The SF-12 also provides two composite indices of physical health and mental health. *Estimated completion time: 5 minutes*

Breastfeeding will be measured using three questions adapted from the Southampton Women's Survey [65] and CDC Infant Feeding Practices study [66]. The questions assess initiation and duration of breastfeeding [66], duration of exclusive breastfeeding [65], and timing of introduction of water and complementary fluids [65]. The questions will be administered between postpartum weeks 48 and 56. Breastfeeding status will be confirmed at the 6 week post-partum visit.

Infant Food Intake The infant Food Frequency Questionnaire by LIFE-MOMS (FFQ). Long-form is a dietary assessment instrument to characterize infants' food intake during the first year of life. The long FFQ was assembled by Life-Moms based on a published shorter version, expanding the 19 categories to include 54 food items with a brief description on how these were prepared and/or their source (e.g., raw, canned, etc.). Previous infant studies were used to identify these food items, with particular emphasis to include typical Hispanic foods. It also includes information on supplements use. A food database will be

created to calculate nutrient intake for the long FFQ. The long FFQ is interviewer or self-administered and is a pen-and-paper or a web-based instrument.

Infant Feeding Styles will be assessed at 35 weeks gestation and 6 and 12 months postpartum. The 22 item questionnaire, adapted from Thompson et al. [67], assess Restrictive Feeding Style (3 items - item #: 7, 9, 15), Pressuring/Overfeeding Style (7 items - item #: 1, 2, 4, 6, 10, 11, 14), Responsive Feeding Style (1 item - item #: 5), and Beliefs in the Benefits of Breastfeeding (5 items - item #: 3, 8, 12, 13, 16).

Weight Management Support Inventory [69]. The WMSI is a 26-item self-report measure assessing social support for weight management. It assesses how frequently and how helpful specific supportive behaviors are in regard to managing weight. The WMSI has 4 subscales (emotional support, instrumental support, information support, and appraisal support). Internal consistency for the overall measure is .90. Subscale Cronbach's alphas are as follows: emotional support (6 items) $\alpha = .75$, instrumental support (7 items) $\alpha = .69$, informational support (7 items) $\alpha = .85$, and appraisal support (6 items) $\alpha = .85$.

Exercise Self-Efficacy [71]. This 18-item measure assesses the degree of self-confidence in one's ability to participate in exercise under a variety of challenging conditions. Participants are asked to respond to each item using a 5-point Likert scale that ranges from 1 (not at all confident) to 5 (completely confident). *Estimated completion time: 7 minutes*

Weight Efficacy Lifestyle Questionnaire (WEL) [72]. The WEL is a 20-item self-report measure that assesses individuals' self-efficacy for engaging in dietary behaviors that support weight management. Items evaluate self-efficacy under the following situations: negative emotions, availability, social pressure, physical discomfort, and positive activities. *Estimated completion time: 7 minutes*

Hospitalization form: This form will be used to identify any hospitalizations between clinic visits. We will begin capturing this data at all post-randomization visits. It will provide data on the mother pre-delivery and then both mother and baby postpartum.

Satisfaction Questionnaire. Participants will be asked to complete a questionnaire that relates to their experiences with the MOMFIT study. Specifically, this will involve various aspects of the intervention and their overall enjoyment with the study.

Cord Blood Collection

Cord blood samples are collected under either "ideal" or "standard" collection procedures. For both procedures, collection should occur within 30 minutes of delivery. The "ideal" requires collection by venipuncture and processing within 30 minutes of delivery. Under "standard" collection, samples are collected by venipuncture (preferred) or by allowing the blood to drip in the tubes, and refrigerated for later processing within 24 hours of delivery. The collection will include a total of 48 ml of blood from the cord. Samples will be processed and stored; the types of specimens that will be collected and stored are: serum, EDTA plasma, sodium fluoride for glucose testing, PAXgene for DNA, and PAXgene for RNA.

Placenta Collection

The placenta should be immediately put in a placenta bucket after delivery and placed in a refrigerator (4°C) until it is processed for samples. The placenta should not be washed at any time and saline (unless sterile) should not be added to the bucket. Placenta samples are collected under either "ideal" or "standard" collection procedures. The "ideal" requires collection and processing within 4 hours of

delivery. Under "standard" collection, samples are collected and processed within 12 hours of delivery on weekdays and within 60 hours for deliveries on weekends. Collection will include 3 sections (basal plate, villous tissue, chorionic plate) from four sample sites of the placenta. In cases where the placenta is ordered to go to pathology, research staff may take the samples they need before it is sent to pathology. All placentas will be weighed.
If the placenta does not require a local pathology examination and can be released immediately after birth, the fresh placenta should be collected directly from the hospital labor and delivery unit if they are available to do so. If the placenta is sent to pathology before research staff can obtain the samples needed for the study, staff should contact the pathology department and make arrangements to pick up the placenta once they are finished with their analyses. All samples may be obtained once the pathology department is finished with the placenta, even if it has been longer than 12 hours. These should be collected from areas without gross pathology.

Postpartum anthropometric and other Clinical Data Collection: Adiposity and Body Composition Measurements.
Newborn; Infant anthropometric measurements. Length obtained on a hard-surface infant measuring board, weight, head circumference and skin fold thickness measurements will be performed by a trained research team member at approximately 24 hours to 1 week of life. Length, weight, and skinfold thickness will also be performed by a trained research team member at approximately 48-56 weeks of life. An in-person training will be conducted for the infant skinfold, head circumference, and length measurements to standardize procedures across sites
We will use the PEA POD system to measure fat mass. It will be performed by a research team member at approximately 24- hours to one week of life. Briefly, the PEA POD Air Displacement Plethysmography System is calibrated by menu-operated system. A wig-cap is placed on the baby, and the baby is measured nude, first weighed, and then placed in the transparent test chamber for 2 minutes for volume measurements. The system accommodates all infant behaviors. Body volume and mass are utilized to calculate body density, and predictive equations are then used to determine body composition, including fat mass.

Collection of Infant Stool sample: Microbiome. A separate, optional consent will be presented by MOMFIT staff after the birth of the baby. A small sample of stool will be collected initially at the hospital and later by moms prior to clinic visits at 6 weeks and 12 months post-partum.

Postpartum Women. The BOD POD will be used to measure adiposity 6 weeks and 12 months post-partum. A body-clinging bathing suit and cap are worn. Two measures are taken (total time <15 min) by trained personnel using specified procedures and averaged to get the % body fat outcome measure. At 6 weeks and 12 months postpartum, waist and hip circumferences will be measured (in cm),using standardized methods.

Infant; 12 month old. The 12 month study visit will also be performed by a trained research team member at 48-56 weeks of life. Length will be measured on a hard-surface measuring board and weight will be measured on a calibrated scale. Length, weight and skinfold thickness will also be performed by a trained research team member at approximately 48-56 weeks of life. An in-person training will be conducted for the infant skinfold, head circumference, and length measurements to standardize procedures across sites

4.5 Patient Management and Follow-up
The Study Coordinator will continually be in touch with all participants in both groups. Scheduling of data collection visits will be an ongoing process with reminder calls/texts prior to each scheduled visit.

Participants in the Lifestyle Change group will further be followed by the nutritionist who will interact in person during individual and group sessions. In addition the Study coaches will be in touch weekly through electronic self-monitoring with feedback dialogue.

4.5.1 Retention Strategies

Consent to be contacted throughout the study and beyond will be collected from all mothers in both groups. We anticipate the possibility of continued follow-up upon completion of this important study. Our experience in previous clinical trials with over 90% retention has demonstrated that building personal relationships with participants, regardless of group assignment, is the single most important factor in enhancing retention. We plan to assure that every participant feels special by treating her with friendliness and genuine interest. Our clinic staff is well versed in this approach. Use of Internet access has been successfully employed in other studies. We will establish a MOMFIT website and have password protected access for both groups. Web-Watcher (Enhanced Usual Care) participants will have access to PDFs on childcare related topics that will be drawn from publicly available sources. Birthday and holiday cards will be provided for both groups as well as a study newsletter available online.. Each week participants in the Lifestyle Change group will be contacted with a "how is it going?" message. At the time of delivery, a baby gift card will be personally delivered to all new mothers in both groups with well wishes, the opportunity to meet the new baby and provide ongoing encouragement.

4.5.2 Strategies to Promote Adherence

Electronic self-monitoring is the primary strategy for promoting adherence to weight management behaviors (i.e., self-monitoring diet, physical activity, weight). An online weight management program that provides online tools to self-monitor diet, physical activity and weight will be adapted for use. Individualized goals for dietary intake (calories, fat), and physical activity will be established at the outset of the intervention. Goals for self-monitoring of diet and activity behaviors will also be established. Dietary self-monitoring adherence will be defined as recording 2/3 meals per day on 5/7 days per week. Physical activity self-monitoring adherence will be defined as recording minutes of moderate-vigorous intensity activity on 5/7 days per week. Progress toward goals will be reviewed with participants on a weekly basis. Behavioral coaches will provide ongoing surveillance of self-monitoring behaviors (diet and physical activity), and will provide coaching as needed. Participants will be encouraged to weigh themselves daily or at least weekly. Weight will be coach-monitored at each intervention visit to provide ongoing surveillance. Communication about adherence will occur in person during study related clinic visits, by telephone, or by email. Goals will be reviewed with participants using a motivational interviewing framework to support and encourage autonomy and intrinsic motivation for healthy changes in diet and activity behaviors.

4.6 Safety Monitoring / Adverse Event Reporting

Per the RFA, we propose to review all outcome data for monitoring adverse outcomes. We will collaborate with the central Data and Safety Monitoring Board (DSMB) on all aspects of data review. We will also name an obstetrician not connected with the study as the Safety Officer to review adverse events within one week of their occurrence for any link to the study protocol.

The following findings would generate a safety alert and specific action if noted during any study visit:

1. Weight loss from enrollment weight during pregnancy
    - Alert values will be weight loss of 4% or greater of enrollment weight for women who were overweight at enrollment and loss of 6% or greater of enrollment weight for women who were obese at enrollment.

- For the first weight loss alert, the research staff will notify the patient, discuss her energy balance activities, provide weight management counseling, and modify the intervention if appropriate. Participants with a first alert for weight loss will return for a repeat weight within 2 weeks. Repeat weights should be collected at the same location at which the original safety alert weight was collected.
- If the weight loss is the same or greater upon reassessment, the patient's prenatal care provider should be contacted by research staff and additional modifications to the intervention may be indicated (i.e. decrease exercise, increase caloric intake). If the weight upon reassessment is no longer at alert values, the participant will continue current study activity.

2. High Blood pressure

- If measured blood pressure is ≥ 160/110, i.e. systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg, study staff will call the participant's prenatal care provider immediately and have a plan in place before the patient is allowed to leave.
- If measured blood pressure is ≥ 140/90, i.e. systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, study staff will instruct participants to contact their provider regarding the elevated measure to arrange appropriate follow-up. Additionally, study staff will notify the prenatal care provider by phone before the end of the study visit.
- At least one blood pressure reading must meet criteria when two readings are taken, and at least two blood pressure readings must meet criteria when three readings are taken.

3. Contraindications to moderate to high-intensity physical activity during pregnancy

If any of the following conditions are reported, study staff will notify the PI and interventionist(s) that the participant has developed a contraindication to moderate to high-intensity physical activity in pregnancy. The physical activity component(s) of the intervention may need to be modified. All moderate to high-intensity physical activity must be stopped and not resumed until after delivery. Participants may potentially continue low-intensity physical activity at the PI's discretion. The presence of any of the conditions below does not require a change in any dietary component(s) of the intervention. Participants for whom a change to the physical activity component(s) of the intervention is indicated should not be considered withdrawn from the study.

<u>Contraindications</u> to moderate to high-intensity physical activity <u>during pregnancy:</u>

- Incompetent cervix/cerclage
- Persistent 2nd or 3rd trimester bleeding
- Placenta previa after 26 weeks' gestation
- Premature labor that requires hospitalization and treatment with medications to stop contractions
- Ruptured membranes
- Preeclampsia / gestational hypertension
- Severe anemia defined as a hemoglobin < 8 or hematocrit < 24
- IUGR defined as <5th percentile with abnormal Umbilical Artery Doppler studies

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4. High score on the Beck Depression Inventory II

- Actively suicidal
    - BDI-II question 9 value of 2 or 3 (regardless of BDI-II total score) requires notification of the Principal Investigator (PI) or a designated clinician with

appropriate training in mental health assessment. The research staff should wait with the patient until the PI or clinician has the opportunity to assess the participant. The PI or designated clinician should assess the patient for risk of imminent harm and contact emergency services if needed. If the PI or designated clinician is not immediately available, notify emergency services according to local standards. Research staff should wait with the participant until emergency services has assumed care. The participant's prenatal care provider should be informed within 2 business days.

- Severe depression
    - BDI-II score of 29-63 (and BDI-II question 9 value of 0 or 1) requires that research staff inform the participant about her elevated score and notify the PI or designated clinician who should assess the patient for safety and/or possible psychiatric referral. If the PI or designated clinician is not immediately available, the participant may leave unattended, but the PI/ designated clinician should contact the participant within 24 hours to assess her for risk of imminent harm and should contact emergency services if needed. The participant should be told to expect such contact from study personnel. The patient's prenatal care provider also should be informed within 2 business days.
- Moderate depression
    - BDI-II score of 20-28 (and BDI-II question 9 value of 0 or 1) requires that the participant be informed and that it is recommended she see her physician for further evaluation. Sites may provide participants with materials on available mental health resources.

5. Incidental findings

   For imaging studies and all lab studies *except* the OGTT: When incidental findings on imaging studies or out of range values on lab tests are obtained by study personnel, the participant will be notified and a copy of the report sent to her physician. For lab tests, this pertains only to those tests for which results are obtained in real-time.

   For study-collected OGTTs: As often as possible, the OGTT's will be collected as part of routine care at the participants doctor's office, if this is not an option, and as a retention strategy, we will perform this assessment as part of the 24 week visit and share the results with the patient and doctor.

   No safety alert or action is required, for out of range values, when study OGTT results are obtained by review of results generated in the course of routine clinical care.

6. If study personnel suspect that an infant/child enrolled in the study is being abused or neglected they will notify the local child protective services office, law enforcement agency, or other local authority. This requirement applies to all sites, with or without a Certificate of Confidentiality.
7. Infant growth
    - Infant length or weight-for-length assessed at the 12 month core visit that is at the 5th percentile or less according to the WHO growth standard requires that the mother be informed and that it is recommended that she have the infant seen by a health care provider for further evaluation.

- At the 6 week visit, infant growth *will* be plotted on the WHO growth chart. Length or weight-for-length at the 5th percentile or less at any visit, OR length or weight-for-length that has crossed two or more percentile lines downward, requires that the mother be informed and that it is recommended that she have the infant seen by a health care provider for further evaluation.

4.6.1 Potential Risks

The risks of phlebotomy include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection. Risks from the questionnaires include discomfort and emotional upset. There could also be some minor pain or discomfort from a pinch from the calipers used for assessment of body fat.

The limitation of caloric intake and gestational weight gain has the potential to lead to weight loss during the pregnancy. The effects of weight loss in this population are unknown, but could increase the risk of fetal growth restrictions. Patients who loose in excess of 5% of their weight at the Baseline visit will have their diet reassessed to reassure adequate caloric intake.

4.6.2 Definitions of Adverse Events (AE) /Serious Adverse Events (SAE)

An **adverse event** is any untoward medical occurrence associated with participation in the study, including but limited to:

- Musculoskeletal injury that requires medical attention
- Fetal growth restriction (<5th percentile with abnormal umbilical artery Dopplers)
- Small for gestational age infant (birth weight <5th percentile)
- Unanticipated untoward medical events that are not plausibly pregnancy related and may be study related

A **serious adverse event** (SAE) is defined as an untoward medical occurrence, whether associated with study participation or not, that results in one of the following:

- Death
  - Maternal death
  - Fetal or infant death, including miscarriage, therapeutic abortion because of increasing signs of maternal or fetal compromise, and stillbirth.
- Life-threatening event
  - Life threatening events in the mother, fetus, neonate or infant are defined as those that in the view of the research staff and PI put the individual patient at imminent substantial risk of dying, or if continued participation in the study might have resulted in death.
- Hospitalization (initial or prolonged)
  - Maternal hospitalization or acute outpatient evaluation (e.g. in an emergency room or labor and delivery triage unit) alone is not sufficient to qualify as a serious adverse event. Hospitalization or acute outpatient evaluation for the following would not be considered a serious adverse event: term delivery, preterm premature rupture of membranes (pPROM), pyelonephritis, bedrest, contractions, ruling in or out preeclampsia, and preterm labor. \
  - Preterm delivery prior to 32 wks gestation is reported as a serious adverse event.
  - Any infant or child hospitalization after neonatal discharge and during the infant's participation in this trial is reported as a serious adverse event.
  - Any medical or surgical procedure performed (e.g., surgery, transfusion) itself is not the adverse event; instead, the condition that leads to the procedure is the adverse event.
- Disability or permanent damage

    - If the adverse event resulted in a substantial disruption of the mother or infant's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life. The recommendation for bedrest does not constitute an SAE.
- Congenital anomaly /birth defect
- Medical Intervention to prevent permanent impairment or damage

Other serious important medical events also qualify. When an event does not fit the other outcomes, but may jeopardize the patient and may require medical or surgical intervention or treatment to prevent one of the other outcomes, this should also be reported as an SAE.

4.6.3 Surveillance and Reporting Procedures

Serious adverse events should be telephoned, faxed, or emailed within 24 hours of ascertainment by the center PI or study coordinator to the NIDDK program official. Because a written record of notification is required, telephone notifications must be followed with written documentation that the NIDDK has been informed. The NIDDK program official will immediately share reports with the DSMB chairperson. Together they will decide if the entire DSMB should be notified in real time or if the report can be reviewed as part of the cumulative safety reports at the next semi-annual meeting of the DSMB. The initial notification should be followed by a written adverse event form completed by the PI at the reporting center and forwarded to the NIDDK and the RCU within 3 days of ascertainment of the event. The RCU will inform the Data and Safety Monitoring Board of adverse events experienced by study participants in the semi-annual meeting reports.

4.6.4 Safety Monitoring Plan

Participants with elevated depressive symptoms will be informed of the possibility that they are depressed and referred to their OBGYN or a mental health provider for further evaluation and treatment. If a participant reports suicide intent, she will be evaluated immediately and appropriate intervention initiated (e.g., staff accompany subject to the emergency room, immediate psychiatric consultation). After the depression has been evaluated and treated, a determination about the safety of continued participation in the study will be made. The OBGYN and any mental health professional involved in the participant's care should help with this determination.

4.6.5 Rules for Participant Termination

Participants may withdraw from the study at any time. Permission will be sought to continue to collect outcome data for use in the analysis. Patients who incur a pregnancy loss after randomization or preterm delivery will also be included in the analysis, with the last weight obtained at a study visit or a clinical visit used for the primary outcome.

4.7 Study Outcome Measures and Ascertainment

4.7.1 Primary Outcome

The primary outcome is GWG as assessed continuously by the difference between the maternal weight measured at the 36 week visit and the baseline visit.

4.7.2 Maternal Secondary Outcomes

a) gestational diabetes

b) preeclampsia
c) cesarean delivery
d) shoulder dystocia
e) weight, adiposity, BP, fasting glucose, lipids, C-reactive protein, vitamin D, leptin, adiponectin
f) Homeostatic Model Assessment (HOMA) score, a measure of insulin resistance (with the assistance of a computer program available online from the University of Oxford Diabetes Trial Unit)
g) diet quality (diet and metabolomics assessment)
h) physical activity
i) sleep quality and duration
j) measures of stress and self-efficacy

4.7.3 Fetal and Neonatal Secondary Outcomes

a) birth weight
b) newborn length
c) % body fat measured by ADP
d) cord blood/ C-peptide
e) hypoglycemia
f) NICU admission, length of stay
g) birth trauma

4.7.4 Infant Secondary Outcomes

a) weight
b) length
c) sum of skinfolds
d) duration of breastfeeding
e) infant age at which solid foods were introduced
f) diet quality
g) physical activity

4.7.5 Methods to Minimize Ascertainment Bias

Pre-pregnancy weight will be determined prior to randomization, and data collection visits will be conducted by trained staff, blinded to group allocation.

Participants randomized to the Usual Care group will receive educational advice to follow the guidelines established by the USDA MyPlate.gov diet recommendations for pregnancy and lactation, as well as the US Dietary Guidelines, 2010. Usual Care participants will be invited to attend group sessions offered quarterly at the hospital during the study period that provide general well care for new moms and their babies but do not include detailed information or behavioral intervention regarding diet, physical activity or GWG. The Usual Care Group will also receive weekly electronic newsletters developed by Prentice Hospital that provide general information about pregnancy, infant care and transitioning into motherhood.

The Usual Care group will attend the baseline and all data collection visits (**Table 3**) conducted by trained research staff blinded to the group assignments. This approach will maintain separation of the study and the clinical follow-up.

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

Studies have shown typical standard deviations (SD) of 15 lbs (6.8 kg) when assessing gestational weight gain. Additionally, studies have demonstrated that approximately 35% of overweight and obese women will gain more than current IOM recommended weight. Studies examining postpartum weight loss have typical SDs of 12 lbs (5.5 kg).

5.2 Sample Size and Power

The proposed total sample size for MOMFIT is 300 women, with 150 randomized to Active Intervention and 150 to the Control Group. Because this study compares two randomized groups, power is based on an independent 2-sample t-test using a two-sided type I error rate (α) of 0.05. Assuming a SD of 15lbs (6.8kg) of GWG, a sample size of 143 women per group is sufficient to attrition to provide 80% power to detect a difference of 5 lbs (2.4 kg) between groups. A difference of 5 lbs was chosen to be clinically significant. It is expected that there will be no more than 5% attrition from randomization through 36 weeks and delivery; thus a total sample size of three hundred patients was chosen.

The anticipation is for no more than 10% attrition for secondary outcomes measured at delivery, and no more than a 20% attrition rate from randomization to 12 month postpartum. **Table 5** shows the specific aims, attrition, and effect sizes detectible for secondary outcomes with 80% power for a sample size of 300 women based on two-sided t-tests and Chi-square tests of association (α=0.05).

Table 5. Effect Sizes Detectable with 80% Power

Aim	attrition	control mean(SD) or percentage	intervention mean (SD) or percentage
Achievement of IOM guidelines	5%	35%	51.2%
Metabolic profiles (delivery)	10%	Effect size = 0.35	
Metabolic profiles (12 m. postpartum)	20%	Effect size = 0.37	
Infant metabolic profiles	10%	Effect size = 0.35	
Infant weight for length (≥95%)	10%	15%	4.9%
Complication rates (delivery)*	10%	11%	2.8%
Postpartum weight loss from 36 week visit weight	20%	13 lbs (12lbs)	17.4lbs (12 lbs)

* composite composed of preeclampsia, shoulder dystocia, or birth injury

5.3 Interim Monitoring Plan

The DSMB for the Consortium will have overall responsibility for monitoring the emerging results. For this and other trials conducted by the Consortium members, the focus of the DSMB will be on safety issues, recruitment, retention, protocol adherence and data quality and timeliness. The DSMB will meet at least twice each year and more frequently if needed.

Since the enrollment period is relatively short and planned analyses will be conducted by the Consortium, using outcome data from all of the centers, no interim monitoring for efficacy will be undertaken. Thus no group sequential stopping rules are specified. Any explicit stopping rules for harm will be determined by the DSMB. In addition, futility as defined by low conditional power to show a benefit given the outcome data to date will not be assessed. However, recruitment will be monitored by the DSMB and the recommendations of the group will be sought if accrual is falling below the goal needed to complete the project by the conclusion of funding.

For each meeting, a formal detailed statistical report will address all aspects of the trial, including baseline variables, outcome variables, compliance with the protocol, data quality, loss to follow-up (primary outcome missing), and protocol violations (such as randomization of ineligible patients). Outcomes will be reported in a cohort of patients randomized before a given date. All adverse events reported to date will be included, with an indicator showing new events since the previous meeting. Adverse events may be reported to some or all of the DSMB members on a more frequent basis if applicable, as requested by the DSMB.

Only outcome variables primarily assessed for safety reasons will be reported by treatment group, including inadequate weight gain for mother and infant. The DSMB will not be masked to group, unless specifically requested.

The DSMB will also consider new information from external sources such as the results of other randomized trials and results of meta-analyses of similar interventions. If this new information is judged relevant to all patients, the DSMB may recommend changes to the protocol or to the consent form.

5.4 Analysis Plan

All statistical analyses will be based upon the total cohort of patients randomized into the trial. Although data on some patients may be missing, all relevant data available from each patient will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of the adherence to the intervention.
The primary analysis will consist of a simple comparison of GWG using an independent t-test. While this is a longitudinal study, and taking advantage of second trimester weights would be a more powerful analysis, there is currently no indication that the pattern of weight gain (whether excess weight gain occurs in the second trimester or third) is associated with worse outcomes. As the intent of this trial is to limit GWG, the analysis is designed to specifically address the comparison of mean weight gain in the two groups. Mean and standard deviation of weight gain will be reported. If the groups are found to differ on a pre-treatment factor known to be a factor related to weight gain, the statistical analysis will adjust for these differences using a multiple linear regression model. Additionally, adjusted means and confidence intervals will be presented after adjusting for factors such as age, pre-pregnancy BMI, and race.

5.4.1 Methodology

In general, analyses of data will be conducted to address the primary and secondary research questions of the trial, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study. Specifically when comparing groups multiple linear or logistic models will be fit. A further exploration of weight gain and retention will be examined using mixed models to determine if the patterns of weight gain and loss are similar across the two groups.

5.4.2 Racial/Ethnic Subgroup Analysis

A priori the study is designed to control for race/ethnicity, not to examine differences in race/ethnicity or test for differences between randomized groups within race/ethnicity subgroups. However, exploratory analyses will be run to determine if any differences that are seen are consistent within race/ethnicity groups.

5.4.3 Handling Missing or Incomplete Data

Every effort will be made to minimize missing or incomplete data. Due to the nature of the study, there will be incomplete data that will be needed to address via statistical modeling. Specifically, we do not expect linear imputation to adequately address missing GWG for women who experience pre-term labor. In these cases, we will examine sensitivity to several assumptions via multiple imputation methods which will include weight gain at 24-28 weeks and through delivery, pregnancy complications and gestational age at delivery.

The first strategy will be to prevent the occurrence of missing outcome data. Missing pregnancy outcome data (including maternal weight gain) as well as missing neonatal outcomes derived from the medical charts are expected to be very low. Women who plan to deliver at a hospital outside of the study center will be excluded before randomization. All women will be required to sign a medical records release for themselves and their newborn prior to randomization in case delivery does occur elsewhere. Multiple methods for contacting women will be sought at the initial interviews, including contact information for friends and relatives. Loss to follow up and missing and incomplete data will be monitored closely by the Design, Data Quality and Data Analysis Committee of the Consortium, as well as the DSMB, to solve potential issues of missing data before there is a substantial impact on the results.

For data collected as responses to questionnaires, all forms will be reviewed for completeness before the participant leaves the study visit. Data entry will be accomplished quickly so that missing values may still be retrieved. For weight gain and related outcome variables in particular, if the study measured weight from the scheduled third trimester study visit at 35-36 weeks is not available, the closest maternity care provider visit weight (preferably on or before 36 weeks) will be used. This last weight will be corrected for length of gestation. If a loss occurs after randomization but before any further weight measurements are performed, a value of zero will be used for the primary outcome.

Under intention-to-treat principles, all participants will be included in the analysis. Missing data related to the primary outcome will be evaluated to assess whether the missing mechanism may be ignorable or non-ignorable [74-76]. If the missing data mechanism is judged to be ignorable, where appropriate, analyses involving mixed models may be used such that all existing values are analyzed, and no observations are deleted due to missing values. Alternatively multiple imputation may be carried out to create several complete data sets. For each complete data set, overall tests of interest for the outcome will be conducted and the results of each combined to create a single test result. For completeness, a pattern-missing analysis should be conducted to investigate non-ignorable missingness. If the missing data mechanism is likely to be non-ignorable, multiple imputations can be conducted using a version of the approximate Bayesian bootstrap based on distance-based selection criteria [77]. Sensitivity analyses under various assumptions regarding the missing data will be conducted to confirm the robustness of the results.

5.4.4 Handling Early Termination/Censoring

Patients can choose to withdraw from the study at any time. If they do so prior to 36 weeks' gestation, the last weight collected at a study visit or clinical visit will be used for the primary analysis after adjustment of gestational age. Patients who incur a pregnancy loss after randomization or preterm delivery will also be included in the analysis, with similar handling of the last weight obtained at a study visit or a clinical visit. Patients will still be included in the intent to treat analysis if they develop

gestational diabetes or contraindications to exercise. If there is a fetal, infant or maternal demise, the surviving member of the dyad should be asked to return for the core 12 month postpartum if willing.

5.5 Analysis Plan

The primary outcome analysis should not adjust the treatment effect for gestational age at delivery.

6 Data Collection

6.1 Data Collection Forms

Data forms will be developed in conjunction with the RCU. These forms will capture all data elements described in this protocol at each study visit and from the hospitalization for delivery. They will include information from both the mother and baby in a format compatible with transmission to the RCU for those elements to be managed centrally.

6.2 Data Entry and Management System

Study data will be collected and managed using MIDAS and a custom MS Access database, hosted at NU. All common measurements will be entered in MIDAS as directed by the LIFE-Moms Design, Data Quality, and Analysis Committee. Site-specific data will be entered into MS_Access. Other electronically obtained data (e.g. Actigraph, LOSE-IT, etc) will be uploaded to this system. The MS Access database is located on FSMFILES which is a secure HIPPA compliant server provided by FSM. The database developer will design, develop and maintain the interface and electronic data collection forms contain within the MS Access application. Reports will be periodically generated for tracking and validating participant information. Confidentiality of the data will be strictly maintained. All paper forms will be kept in locked cabinets, with no access to outside sources. Data for each participant will be stored in the database by participant ID. The database is password protected and data file access is restricted to the approved personnel list.

6.2.1 Quality Control

NU is committed to the security of all data in its care and the protection of the human subjects represented by that data. This commitment is manifest in the organization's physical facilities, information systems, information management protocols, and staff training.

6.2.2 Confidentiality and Data Security

NU and the Department of Obstetrics and Gynecology are committed to information security for all the projects in which they are engaged. Due to the sensitive nature of subjects' health information, Northwestern University is prepared to take any steps deemed necessary to ensure the security of the project. We look forward to working with the NICHD or their designated representatives to review our current security practices and correct any identified deficiencies.

6.2.3 Sharing of Data for Common Measures

All core and super shared data will be entered directly into a MySQL database maintained by the RCU either through direct data entry using the RCU's web-based data management system (MIDAS) or by file upload via secure FTP. The RCU is responsible for quality control of the database and will generate data queries both at the point of entry and in batch, as well as additional checks for data consistency within or across forms.

At the completion of the project, all core and super shared data will be transferred by the RCU to the NIDDK Repository. In doing so measures will be taken to protect patient confidentiality, including replacing the patient ID, scrambling records out of order, removing dates and replacing them with days elapsed since randomization, and recoding variables with low frequencies into categories, or combining categorical variables.

6.3 Performance Monitoring

We will institute ongoing data analysis for local/shared data collection and include quality control assessment based on 10% duplicate data collection as much as possible without overly burdening the participants.

6.3.1 Assessment of Participant Adherence

Weekly, the Study Coach and/or nutritionist will drop in on the Lose-it software to determine adherence to tracking of diet and determine adherence to the DASH diet. This involves careful assessment of the participant's activity during the previous week and the self-monitoring of dietary intake. Comparison of intake with the recommended DASH diet goals will be assessed weekly. The Lifestyle Coach will conduct a standardized telephone interview with each intervention participant that will ask her to state the calorie goals, the self-weighing behavior, the physical activity/walking minutes and general sense of commitment to the study.

Should any deviation be noted, the Intervention Director/Nutritionist will follow up with these participants to further discuss possible barriers to meeting nutrient needs and other pre-established lifestyle activity goals.

6.3.2 Assessment of Intervention Fidelity/Consistency

We plan to use a video to introduce the use of Lose-it so that this important aspect of the intervention will be standardized. We will also initiate ongoing reminders on the website.

The majority of the group intervention sessions will be led by the same nutritionist, with input from a behaviorist as needed. We will train all our interventionists prior to the launch of the intervention effort. This will primarily involve our Intervention Director/Nutritionist, Coordinator/Nutritionist, both of whom are very skilled in Motivational Intervention, as well as our Behaviorist Lifestyle Coach.

7 Study Administration

7.1 Organization and Funding

The study is funded by NHLBI as part of the Lifestyle Interventions in Overweight and Obese Pregnant Women Consortium, known as Lifestyle Interventions for Expectant Moms or 'LIFE-Moms'. The Consortium is funded primarily by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); but also by the National Heart, Lung, and Blood Institute (NHLBI), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Center for Complementary and Alternative Medicine (NCCAM), with additional support from the Office of Research on Women's Health (ORWH) and Office of Behavioral and Social Science Research (OBSSR).

7.1.1 Clinical Center and Collaborating Units

Clinical Center. This clinical center is one of seven clinical centers in the Consortium. A multidisciplinary team of investigators at each clinical center is conducting a randomized clinical trial designed to test a lifestyle intervention to control gestational weight gain and/or influence maternal metabolic profiles. The clinical center teams are each represented by their respective Principal Investigators (PIs).

Research Coordinating Unit. The Research Coordinating Unit is a single organization responsible for facilitating collaboration and coordination of research activities. The PIs of the RCU lead a team of biostatisticians, epidemiologists, technical and research staff. The goals of the RCU are as follows:

- Promote collaboration and communication across the clinical centers, among the investigators, and with NIH
- Plan, arrange, and facilitate meetings of the Steering Committee, its subcommittees, and DSMB
- Facilitate the development of standardized variable definitions and core measures and methods
- Facilitate data sharing where appropriate
- Provide support for analysis of data for manuscripts that are common across studies

7.1.2 Overall Consortium Organization

The Consortium is a collaboration between the seven clinical centers, the Research Coordinating Unit and the funding Institutes and Centers of NIH above. Funding is awarded to each clinical center and the RCU under the cooperative agreement mechanism, thus there is substantial NIH programmatic involvement in all aspects of the Consortium.

Although each clinical center is conducting a separate trial, the goal of the collaboration is to maximize the value of the separate trials by identifying core measures to be collected across all studies, ensuring consistency of procedures, definitions and data collection, harmonizing design elements of the trials and the proposed interventions, and jointly monitoring progress and solving problems as the trials progress. This will facilitate the ability to combine the data and resources to different approaches when there is not enough evidence to test one single approach in a multi-center trial. The organization of the group is built around these goals.

7.1.3 NIH

Each of the Funding Institutes is represented in the Consortium by one or more Project Scientists. NIDDK is additionally represented by the Program Scientist and Program Official, who take a leadership role in the overall project for scientific, funding and policy issues.

7.2 Committees

7.2.1 Steering Committee

The Steering Committee is the governing body for the Consortium and is composed of the Principal Investigator(s) of each clinical center and of the RCU, in addition to the NIH Project Scientists. The Steering Committee has primary responsibility to design research activities, establish priorities, develop common protocols and manuals, questionnaires and other data recording forms, establish and maintain quality control among awardees, review progress, monitor patient accrual, coordinate and standardize data management, and cooperate on the publication of results. Major scientific decisions regarding the core data will be determined by the Steering Committee

Two co-Chairs have been appointed by NIH from among the members of the Steering Committee. Each clinical center, the RCU, and the NIH has one vote. In general, the Steering Committee will meet in-person twice each year, and more frequently by teleconference.

Executive Committee. This subgroup of the Steering Committee consists of the NIDDK program Scientist, the NIDDK Program Official, the NICHD Project Scientist, the RCU Principal Investigator(s) and the co-Chairs of the Steering Committee. This committee meets more frequently than the Steering Committee. The purpose of the Executive Committee is to discuss emerging issues, and to recommend solutions and policies to be put before the Steering Committee for discussion and vote.

7.2.2 Standing Committee

Four standing committees have been established as follows:

Recruitment & Retention Committee. This committee will develop plans to track recruitment and retention across all clinical sites. Other activities may include: developing recruitment and retention tracking tools, creating a recruitment and retention report, providing a mechanism to share the best practices and lessons learned about recruitment strategies, and monitoring/trouble-shooting study-specific recruitment issues.

Ancillary Studies Committee. This committee is charged with developing a policy for submission/evaluation of ancillary proposals for external funding to use core study data and/or biospecimens. The committee will review ancillary study proposals and make recommendations to the Steering Committee.

Publications & Presentations Committee. This group will develop a policy for publications and presentations specific to core measures and analyses and oversee all publications and presentations that emanate from the Consortium as a whole. The Committee is also charged with identifying opportunities for other Consortium-wide publications

Safety Committee. The Safety Committee includes expertise in relevant disciplines, including obstetrics and pediatrics. This committee is charged with establishing common definitions for safety-related events and methods for ascertaining and reporting such events as required by local IRBs and the funding institutes. The committee is charged with recommending definitions of safety-related exclusion criteria, adverse events and serious adverse events, alert values for participant assessments, and tracking medication use. The Safety Committee will make recommendations to the Steering Committee and develop training procedures as appropriate. The Safety Committee will also review all adverse events reported on a regular basis. Data will be tabulated by the RCU for distribution to the committee.

7.2.3 Subcommittees

Subcommittees and working groups of the subcommittees are formed as needed to determine core and shared measures and procedures, and how data and resources derived from core measures and procedures will be processed, analyzed or used. Examples are the Design, Data Quality and Analysis Committee, the Biospecimens Committee and the Data Management Committee. Subcommittees may become inactive once their goals have been accomplished.

At a minimum, a representative from each clinical center, NIH and the RCU will sit on each subcommittee. Every PI is expected to serve on at least one subcommittee (or standing committee), but clinic investigators/staff are also eligible. Individuals may serve on more than one committee

7.2.4 Data and Safety Monitoring Committee

The DSMB, a group of individuals not affiliated with any of the participating institutions in the Consortium, was established by NIDDK. Before this and the other trials in the Consortium can begin, the protocols must be approved by the committee. Any subsequent major changes to a study's protocol must also be approved by the DSMB.

The DSMB for the Consortium will have overall responsibility for monitoring the progress of all LIFE-Moms studies. The focus of the DSMB will be on safety issues, recruitment, retention, protocol adherence and data quality and timeliness. The DSMB will meet at least twice each year and more frequently if needed. Recommendations by the committee can include protocol modification or early termination for unexpected safety problems. Recommendations are made to the NIH and disseminated to the Steering Committee.

8 Study Timetable

8.1 Study Timeline

Year of Study	*Year 01*				*Year 02*				*Year 03*				*Year 04*				*Year 05*				*Year 06*				*year7*			
	2011-2012				*2012-2013*				*2013-2014*				*2014-2015*				*2015-2016*				*2016-2017*				*17-18*			
Quarters*	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Officially funded	x																											
Work began		x																										
First LIFE-MOMS Steering Committee Meeting (1/24/12 & 1/25/12)		x																										
Second LIFE-MOMS Steering Committee Meeting (3/29 & 3/30/12)			x																									
Protocol Development		x	x	x																								
Forms Development			x	x	x																							
Manual of Operations Development				x	x																							
Staff training				x																								
Recruitment					x	x	x	x	x	x	x	x	x	X	X	x												
Randomization						x	x	x	x	x	x	x	x	x	X	x	x											
Data Collection						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	XXXX							
Prenatal Intervention						x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Periodic Clinical Visits						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	XXXX							
MOMFIT Babies are Born								x	x	x	x	x	x	x	x	x	x	x	x	x								
Postpartum Intervention									x	x	x	x	x	x	x	x	x	x	x	x	XXXX							
Final Data Collection													x	x	x	x	x	x	x	x								
Complete Data Analyses																	x	x	x	x		X	X		X	X		
Metabolomics Assays and Analyses															x	x	x	x	x	x	X	X	XX		XX			

*Quarter 1 = September to November
Quarter 2 = December to February
Quarter 3 = March – May
Quarter 4 = June – August

** At this time it has not yet been determined whether there will be additional funding provided to complete the full 12 months post-partum intervention for all babies of mothers recruited past 9/31/15.

8.1.1 Training and Certification

Study-specific training will take place regarding clinical measures and survey measures as appropriate for core measures to be standardized for the overall study as well as shared or individual measures for this center. The Study Coordinator will be the master trainer for all measures and she will train on these aspects with study staff as appropriate.

NU requires that all investigators and members responsible for the design and/or conduct of research provide evidence of adequate training in order to maintain IRB approval of a study. The names of the individuals who will be involved in conduct of the research have been provided. They have all completed the course required by Northwestern University for those who will participate in human subjects research, namely, the **CITI web-based course in human subject protection** and the NU HIPPA training course (www.research.northwestern.edu/research/oprs/irb/education/HIPAA_Presentation_2006.ppt.).

8.1.2 Recruitment and Data Collection Period

Recruitment will begin in November 2012 (Quarter 4 of Year 1), with the final recruitment targeted as late as September of 2014 (Quarter 3 of Year 3). Per recruitment goals established by the NIDDK and agreed upon by the consortium, this study has the following recruitment goals:

Mid-April 2013 (25% through recruitment period), randomize 30 women.
October 2013 (50% through recruitment) randomize 105 women (cumulative).
Mid-March 2014 (75% through recruitment) randomize 200 women.
September 2014 (100% through recruitment) randomize 300 women.

Data collection will continue 20 months past the last randomization (through the intervention during 8 months to delivery and 12 months post-partum), and is thus targeted for completion May 2016 (Quarter 2 of Year 5).

8.1.3 *Final Analysis*

Data cleaning will be done throughout the data collection period (Quarter 4 of Year 1 through Quarter 2 of Year 5) and will be completed by July 2016 (month 7 of Year 5). As data for the primary aim analysis will be available by May of 2015 (Year 4), preliminary analysis can be completed by the beginning of Year 5. Preliminary analyses for all aims will be completed by September of 2016 with the remaining three months dedicated to secondary analyses and manuscript preparation.

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Glossary

MOMFIT – Maternal-Offspring Metabolics: Family Intervention Trial

OW/OB - overweight and obese

GWG – gestational weight gain

IOM- Institute of Medicine

BMI – body mass index

LGA – large for gestational age

CRP - C-reactive protein

IL-6 - interleukin-6

HDL-C - HDL- cholesterol

T2D – type 2 diabetes

RCT - randomized controlled trial

DPP - Diabetes Prevention Program

DASH – Dietary Approaches to Stop Hypertension

GDM - gestational diabetes mellitus

SCT - social cognitive theory

NMH - Northwestern Memorial Hospital

NUFSM - Northwestern University Feinberg School of Medicine

PWH - Prentice Women's Hospital

PAC - Prentice Ambulatory Care

DPM –Department of Preventive Medicine

LMP - last menstrual period

BED - Binge eating disorder

OTC - over the counter

IRB - Institutional Review Board

RCs - Recruitment Coordinators

ACOG - American College of Obstetricians and Gynecologists

CDC – Center for Disease Control

CK - Calorie King

SMART - Specific, Measurable, Attainable, Realistic and Timely [goals]

MI - Motivational Interviewing

UPLC - Ultra-performance liquid chromatography

BP - Blood Pressure

FFQ - Food Frequency Questionnaire

DSMB - Data and Safety Monitoring Board

PI - Principal Investigator

HOMA - Homeostatic Model Assessment

HC – Head circumference