DATA AND SAFETY MONITORING BOARD PROTOCOL AND REPORT

(Revised July 18, 2014)

e-MOMS of Rochester

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Section 1: Abstract

This proposal aims to expand the understanding of how to slow the accumulation of weight in childbearing women by developing, implementing and evaluating electronically-mediated patient intervention programs for pregnant and postpartum women. The goals of the interventions are to decrease the prevalence of excessive pregnancy weight gain and to decrease weight retention in the first year postpartum in a socio-economically and racially/ethnically diverse sample of both higher and lower income (<185% of the poverty line) women who enter pregnancy with normal (18.5-24.9) and overweight plus obese, class 1 (25.0-34.9) body mass indices (BMI). In phase 1, two programs of electronically-mediated patient interventions (e-interventions) will be refined, developed, and beta-tested. In phase 2, a randomized controlled trial will be undertaken to evaluate the efficacy of the pregnancy e-intervention alone and the combined pregnancy and postpartum e-interventions. About 1,600 women will be randomized in the first 20 weeks of pregnancy to one of three groups: Intervention Group 1 will receive the electronically-mediated patient intervention program only during pregnancy (e-intervention 1). Intervention Group 2 will receive e-intervention 1 plus an electronically-mediated intervention for 12 months postpartum (e-intervention 2). Control women will receive non-weight related content at the project website. The primary hypotheses are as follows: H1: The proportion of women in the combined Intervention Groups 1 and 2 (receive same intervention during pregnancy) who gain more weight in pregnancy than is recommended by the IOM will be 10 percentage points lower than the proportion of women in the Control Group who gain excessively (45% vs. 55%). H2a: The Control Group will have an at least 5 pound greater weight retention at 12 months postpartum than Intervention Group 1 (intervention during pregnancy only). H2b: The Control Group will have an at least 5 pound greater weight retention at 12 months postpartum than Intervention Group 2 (intervention during pregnancy and postpartum). Secondary research questions address additional treatment group contrasts, other weight outcomes and time points (e.g; 18 months postpartum), genetic susceptibility and behavioral mediators of any intervention effect.

Section 2: Specific Aims

Primary Aims

This proposal aims to expand the understanding of how to slow the accumulation of weight in childbearing women by developing, implementing and evaluating electronically-mediated behavioral intervention programs for pregnant and postpartum women. The goals of the interventions are to decrease the prevalence of excessive pregnancy weight gain and to decrease weight retention in the first year postpartum in socio-economically and racially/ethnically diverse sample of both higher and lower income (<185% of the poverty line) women who enter pregnancy with normal (18.5-24.9) and overweight plus obese, class 1 (25.0-34.9) body mass indices (BMI).

In phase 1 of this project, two programs of electronically-mediated behavioral interventions (**e**-interventions) that encourage women to gain an amount of weight during pregnancy that is within the ranges recommended in 2009 by the IOM and to adopt a healthy lifestyle to minimize postpartum weight retention will be refined, developed, and tested. For the intervention during pregnancy, we will adapt and refine a patient education program that was previously demonstrated to be efficacious in reducing the prevalence of excessive gestational weight gain in a low income, rural white population in upstate New York (1, 2). In phase 2, a randomized controlled trial will be undertaken to evaluate the efficacy of the pregnancy e-intervention and the combined pregnancy and postpartum **e**-interventions. As they enter prenatal care in the first 20 weeks of gestation, recruited, eligible women will be randomly assigned to one of three groups: Intervention Group 1 will receive the electronically-mediated behavioral intervention program only during pregnancy (**e**-intervention 1). Intervention Group 2 will receive **e**-intervention 1 plus an electronically-mediated intervention for 12 months postpartum (**e**-intervention 2). Control women will receive access to non-weight related content at the project website.

The **primary hypotheses** for the randomized controlled trial are as follows:

H1: The proportion of women in the combined Intervention Groups 1 and 2 (receive same intervention during pregnancy) who gain more weight in pregnancy than is recommended by the IOM will be 10 percentage points lower than the proportion of women in the Control Group who gain excessively (45% vs. 55%).
H2a: The Control Group will have an at least 5 pound greater weight retention at 12 months postpartum than Intervention Group 1 (intervention during pregnancy only).

H2b: The Control Group will have an at least 5 pound greater weight retention at 12 months postpartum than Intervention Group 2 (intervention during pregnancy and postpartum).

Secondary Aims

Additional analyses will be conducted on research questions pertaining to additional treatment group contrasts, other weight outcomes and time points, genetic susceptibility to excessive gestational weight gain and postpartum weight retention and behavioral mediators of intervention effects.

First, we hypothesize that Intervention Group 1 will have a higher postpartum weight retention than Intervention Group 2.

Second, we hypothesize that the interventions will have a larger effect on each of the major study endpoints listed above in higher income compared to lower income and in normal weight compared to overweight/obese women.

Third, we hypothesize that treatment group differences at 6 and 12 months postpartum will be in the same direction but of greater magnitude than those seen at 18 months postpartum.

Fourth, we hypothesize that the intervention will have larger effect on both gestational weight gain and postpartum weight retention among women who do not have the genetic susceptibility.

Fifth, we hypothesize that food intake and physical activity will mediate any effect of the intervention on risk of excessive gestational weight gain and postpartum weight retention. And finally, we hypothesize there will be a 3-way interaction between the intervention, genetic susceptibility, and physical activity in predicting excessive gestational weight gain and postpartum weight retention.

Section 3: Background

Childbearing is associated with excessive weight gain. Childbearing, generally indicated by parity (the number of live births a woman has experienced), has been found to be positively associated with weight gain beyond that of aging (2-7).

Gestational weight gain is related to postpartum weight retention. A high level of gestational (pregnancy) weight gain including gaining above the upper limit of the Institute of Medicine (IOM) gestational weight gain range is consistently and positively related to high levels of weight retention in the post-pregnancy (postpartum) period and thus contributes to the development of obesity in women (8-14). Reviews by Gunderson and Abrams (15), Lederman (16), Parker (17), and Cromwell (18) confirm that women gaining more than the recommended amount of weight during pregnancy are at high risk for retaining weight postpartum and becoming obese. Two recent long-term follow-up studies document the negative impact of excessive gestational weight gain on body weight 8 to 15 years after pregnancy (14, 19).

Gaining more than the recommended amount of weight in pregnancy and postpartum weight retention are common. The most recent data available indicate that 46% of pregnant women in the US gain more weight in pregnancy than is recommended by the IOM (20). Public health objectives for 2010 call for the following: Objective 16-12: Increase the proportion of mothers who achieve a weight gain consistent with the IOM guidelines during their pregnancies (21). Gaining more weight in pregnancy than is currently recommended by the IOM and postpartum weight retention are very prevalent in low-income women of all racial and ethnic groups. However, few current studies examine these issues in socio-economically and racially/ethnically diverse urban samples of women. One study by Lederman, Alfasi, and Deckelbaum (22) collected information on body weight on 47 low income, non smoking, women

aged 18-36 years, self-identified as black (17 also self-identified as Hispanic). About 2/3 of women in the total sample and 100% of the overweight (high BMI) women gained more than the recommended amount of weight during pregnancy. At 2 months postpartum, the women were on average 18 pounds heavier than they were prior to pregnancy. No additional maternal weight was lost from 2 to 6 months postpartum.

Another relevant study was reported Boardley and colleagues (23). They examined Black and White postpartum women participating in the WIC Program in South Carolina. They found that black women retained more weight than white women and they went further to try to explain the mechanisms. They found that Black women reported consuming significantly more energy (2039 versus 1552 kcals), a higher percent of calories from fat in the diet (41% vs. 38%), and engaged in significantly lower levels of physical activity in both the prenatal and postpartum periods. Thus diet and physical activity appear to be important components of preventing excessive gestational weight gain and postpartum weight retention in the population of interest for this project.

Gestational weight gain can be altered through intervention, although there are few studies on the topic. In 2008, Olson (24) reviewed the literature on clinical intervention studies aimed at achieving a healthy weight gain in pregnancy and identified 5 published intervention studies with outcome data. Three focus on non-obese pregnant women and two focus on obese pregnant women. Two are from the US and three are from Scandinavia. She concluded, "Interventions to promote healthy weight gains have demonstrated efficacy in subgroups of women, including low-income women with normal and overweight BMI in the United States and obese women in Scandinavia" (24). A 2010 meta-analysis of four randomized controlled trials and five non-randomized trials on effects of diet and physical activity counseling in pregnancy found lower gestational weight gain in the intervention groups with a standardized mean difference of –0.22 units (95% CI: -0.38, -0.05) (25).

Postpartum interventions are likely to add to the effects of intervention in pregnancy. Overall, the major reviews of the literature on postpartum weight reduction, including a Cochrane review, come to the same conclusion: Interventions focused on physical activity and diet in the postpartum period result in greater weight loss than usual care (26). Kuhlmann et al. (27) point out that no intervention studies have been done that follow women from pregnancy through the postpartum period, so it is an open question whether postpartum interventions will add to the effect of interventions implemented during pregnancy.

Interventions implemented in the postpartum period have unique challenges. While the postpartum interventions included in the Cochrane review had significant effects on weight, several showed fairly high dropout rates: 31% in Leermakers et al (28) and 42% in O'Toole et al. (29). Both authors discuss the challenge of maintaining active participation in the intervention as being a unique challenge of intervention in this time period of women's lives. In addition, there is evidence that women of different socioeconomic status (SES), and potentially race/ethnicity, differ in terms of the amount of postpartum weight retention and in the pattern of postpartum weight loss and gain. In a recent study from the UK, Shrewsbury et al. (30) showed median weight retention at 8 months was significantly higher in medium and lower SES women than in higher income women (3.2 kg vs. 1.8 kg, $p = 0.008$). Walker (31) found that in a sample of women in Texas, low-income, ethnic minority women do not experience weight losses after the initial fluid-related losses in the first 6 weeks postpartum. Many postpartum women have a strong desire to lose weight as substantiated by Krummel (32) who found 55% of lower income postpartum women in WIC were at the action stage for weight loss. But fewer than 30% were at this stage for engaging in actual weight loss behaviors. Thus high sample attrition, the variation in the phenomena by SES, and low interest in the behavior changes needed to achieve a healthy weight must be addressed in any intervention developed for women at this life stage. Sleep deprivation, the resumption of smoking, and postpartum depression are additional realities that must be considered in designing interventions.

Some important elements of postpartum intervention have been identified by women. Investigators have identified lack of time, limited financial resources, absence of mothers and female relatives and friends to provide support, low self esteem and postpartum depression as barriers to weight loss and participating in weight loss programs (33-35). The characteristics women indicate they would like to see in healthy weight programs include physical activity,

opportunities for social interaction (camaraderie with other women), child care, self-help approaches to diet, inclusion of family members, and location in the neighborhood (33, 34, 36).

Biological factors (genetic susceptibility) may modify the impact of interventions on the outcomes of excessive pregnancy and postpartum weight gain. The *GNB*3 825T allele has been associated with increased gestational weight gain (GWG) (37), postpartum weight retention (38), and low birth weight (LBW) (39). The 825T allele has a high prevalence in the African-American population world-wide (>70%) and is present to a lesser extent in the Caucasians(40). The G protein β_3 subunit C825T polymorphism has also been associated with hypertension (41-43), obesity (44-46), and the metabolic syndrome (46).

There appears to be an interaction of this SNP with physical activity in the non-pregnant population (38, 45). Women homozygous for the 825T allele are more likely to retain weight in the first year postpartum when physical activity level is low (< 1 hour/week), compared with women with a higher physical activity level (> 1 hour/week) (38). Only this one study has examined postpartum women (postpartum was designated as any time within 12 months of delivery) and method of physical activity measurement was not reported (38). As a result, the strength of the interaction cannot be determined. A recent cross-sectional study that examined the C825T allele in relation to physical activity reports that there was not an independent association of the T allele with obesity. There was however, a significant interaction between the 825T allele and physical activity in predicting obesity in African Americans (45). Physically active African-Americans experienced a 20% reduction in obesity for each T allele and conversely, in those with low levels of physical activity, there was a 23% increase in obesity prevalence. This relationship was not evident in Caucasians.

Behavior factors (diet and physical activity) may mediate the effect of the intervention on weight. At least theoretically, energy intake (from diet) and energy output (one component of which is physical activity) should be related to gestational weight gain and postpartum weight retention. Olson and Strawderman (47) showed that women who reported eating much more food in pregnancy and being less physically active in pregnancy compared to pre-pregnancy were 2.35 and 1.68 times, respectively, more likely to gain above the IOM recommended range in pregnancy than women who did not exhibit these behaviors. During the postpartum period, women who exercised often (daily) were only 0.22 times as likely to retain 10 or more pounds at one year postpartum than women who exercised less often. Women who reported eating more in the first year postpartum compared to pregnancy were nearly 3.5 times more likely to retain 10 or more pounds (48). These relatively simple and crude measures appear to work reasonably well in predicting the two weight outcomes in regression models, but they are not very helpful in understanding the degree of behavioral change an intervention must produce to achieve a certain level of the desired outcomes. For this, more quantitative measures of dietary intake and physical activity are needed.

Web-based approaches to health interventions have much to offer. In a recent review on Internet methods for delivering health interventions, Strecher (49) states: "Emerging communication technologies allow us to potentially reach more individuals with effective health-related advice and information at very low cost." He notes that more than 78% of adults in the US now have access to the Web, including 61% of those with incomes less than $30,000. Another study in Michigan found 65% of low-income females between the ages of 18 and 50 years, most of whom were mothers, had a computer in the house and 75% had access to the Internet (50).

Women in one study preferred getting nutrition information from the Web over print and games. This source of information performed better than print and games in terms of immediate knowledge outcomes, but not in terms of knowledge retention (50). A meta-analysis of 22 published articles compared behavior change interventions using Web-based versus non-Web based approaches (51). The comparison of effect sizes showed better outcomes in areas such as increased exercise, increased knowledge of nutritional status and asthma treatment, increased participation in health care, slower health decline, improved body shape perception and 18-month weight loss maintenance. Several published studies on Web-based weight loss, management and/or maintenance programs show positive results (52-55). One of the very positive aspects of an ongoing randomized controlled trial of a Web-based approach to long term weight loss

maintenance is that 80% of participants were still using the project Web-based program after 12 months. E-mail and telephone prompts helped in maintaining use of the Web-site (56).

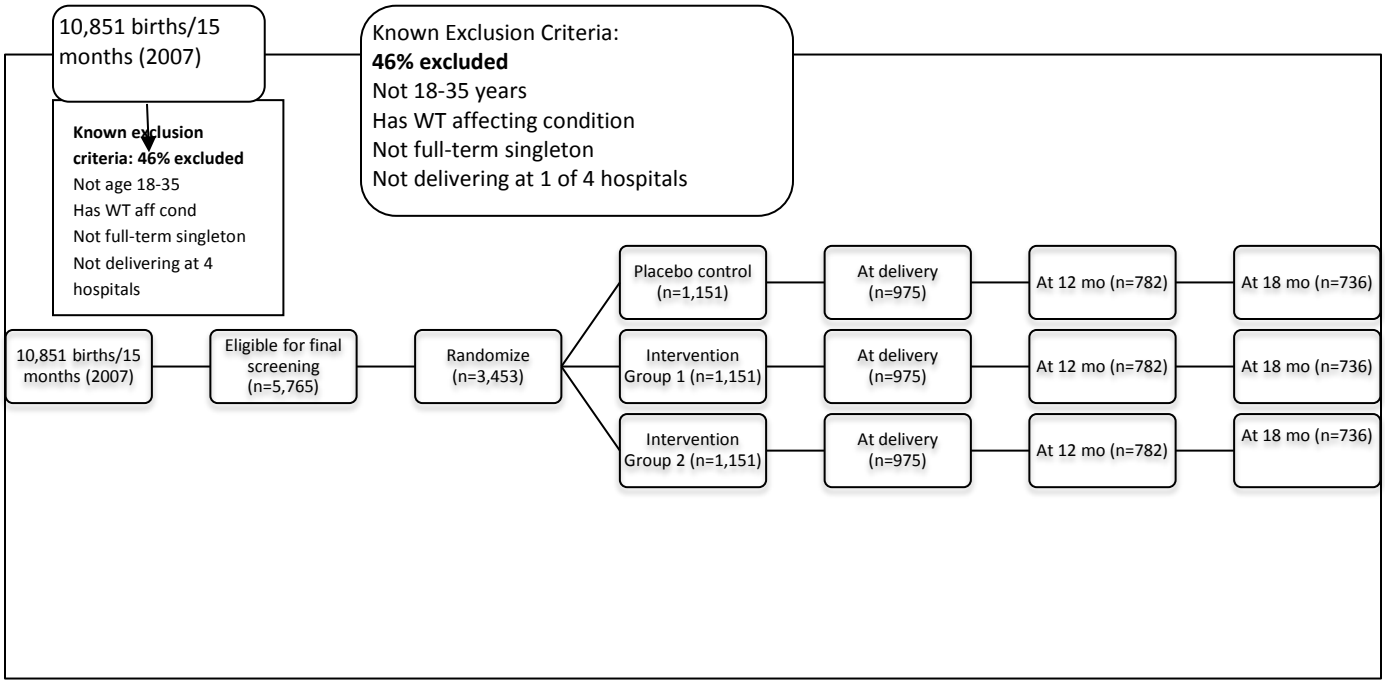
The relatively new field of *Persuasive Technology* provides insight into how to approach electronic technology-based behavioral interventions. Subtle psychological influences (intrinsic motivation) and social influences built into computer systems that people use on a regular basis can have effective and lasting impacts on behavior (57, 58).

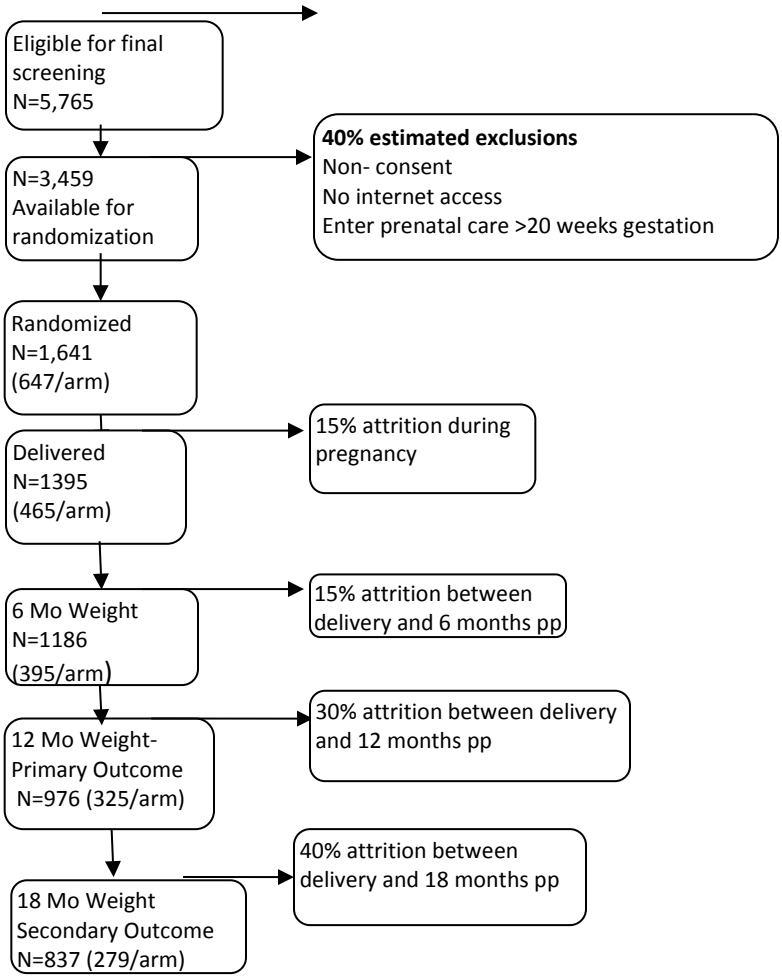
Numerous studies have expounded on the benefits of social support for health. We rely on research in social psychology, social marketing and persuasive technology for direction in how to design an application that will yield the benefits of social support and social connectedness, yet work within the constraints of current electronic technology. Work in social presence and awareness has shown that individuals exhibit greater feelings of social connectedness just by using an online system that keeps them aware of the others around them (58). The concepts of social comparison (57) and social cognitive theory (59) can be applied to suggest that by sharing the experiences together, individuals in general will perform better in desired targeted behaviors.

Section 4: Overview of Design

We will conduct a double masked, randomized control efficacy trial with a parallel group design in which the individual is the unit of randomization and analysis. Pregnant women in the first 20 weeks of pregnancy will be randomized to 3 arms: Control arm; e-intervention 1 during pregnancy alone (Intervention Group 1); and e-intervention 1 during pregnancy plus e-intervention 2 postpartum (Intervention Group 2). The study design and available sample size are depicted in Figure 1 below.

Figure 1. Randomized Controlled Trial Design and Estimated Available Sample Size





Section 5: Study Population and Eligibility

Study population

Based on the number of total births in Monroe County (the county in which Rochester, NY is located) from the Vital Statistics for the State of NY in 2007, we expect 10,851 births during the 15 months of accrual. Based on data from the 2007 Finger Lakes Perinatal Data System (FLPDS), there were 5,765 term singleton births in Monroe County in 15 months to women aged 18 to 35 with BMI 18.5 to <35.0 without weight affecting medical conditions at the 4 hospitals in Rochester, NY. Thus, we expect to have 5,765 women who are eligible for final screening and entry into the study, and of those, 40% will not consent or meet eligibility criteria determined by final screening resulting in 3,459 women available for randomization. Sample size estimates require randomizing 1,641 women to 3 treatment groups (Figure 1). Further discussion of the sample sizes at various time points in the study is included in Section 12.

Table 1: Eligibility Criteria

e-Moms of Rochester Study Eligibility Criteria
Inclusion Criteria
1) Age 18 – 35 at the time of enrollment
2) Consented at or before 20 weeks gestation
3) Intending to be available for a 24 months intervention
4) Plan to deliver in one of the 4 hospitals in Rochester, NY (the study area)
5) Plan to carry the pregnancy to term
6) Plan to keep the baby
7) Read and understand English
8) Has a valid e-mail address
Exclusion criteria
Study Specific
1) BMI < 18.5 kg/m^2 and $\geq$ 35.0 kg/m$^{2.}$
2) Multiple gestation. If multiple gestation is diagnosed after enrollment participant will be terminated from the study (reasons for termination will be included in the consent form)
3) Medical conditions prior to pregnancy which could influence weight loss or gain: cystic fibrosis, hyperthyroidism, renal insufficiency[1], proteinuria[1], cerebral palsy, lupus erythematosus; rheumatoid arthritis, Crohns disease (severity and other autoimmune diseases evaluated case by case), ulcerative colitis, maternal congenital heart disease (patients are often underweight); hypertension treated with medication[2,]
4) Psychiatric medication associated with major weight gain or loss (e.g.; Lithium & Divalproex)
5) Having had three or more consecutive miscarriages (spontaneous abortions)
Common Criteria
6) *Household member on study staff
7) *Past or planned (within the next 24 months) weight loss surgery (e.g. gastric bypass, lap band, or liposuction); current participation in a commercial weight loss program (e.g. Weight Watcher's, Jenny Craig); currently enrolled or planned to enroll in a weight loss or another weight gain prevention study
8) *Participants will be excluded during screening if they report regular use of systemic steroids, prescription weight loss drugs, and/or diabetes medications (oral or injected- insulin, metformin, byetta, TZDs, other). "Regular use" is defined as "taking this medication most days of the week for the previous month"
9) *Current treatment for eating disorder
10) *Positive screening for bulimia
11) *Cardiovascular event (heart attack, stroke, episode of heart failure, or revascularization procedure) within the last 6 months. Revascularization is defined as bypass surgery or stints

12) *Mental or psychiatric condition that precludes giving informed consent and completing questionnaires
13) *Current treatment for malignancy (other than non-melanoma skin cancer and CIN cervix) or on remission for less than 5 years
14) *Blood pressure criterion- See footnote 2
[1]Because they cause edema even when treated. Most of the other severe kidney disorders will be in dialysis.
[2]Our blood pressure indicator is hypertension treated with medication at baseline.
*These exclusion criteria are common to EARLY trials.

Section 6: Recruitment

Recruitment Sources

Community at Large: A major public awareness campaign will be rolled out shortly before recruitment begins. The University of Rochester e-Moms study staff will work closely with University of Rochester Public Relations in designing press releases to the public about the study. University of Rochester Public Relations will also work with other organizations to target various communities and to promote the study in organizational newsletters and local publications. In addition, mass mailings to Monroe County women ages 18-35 years have been added as an additional recruitment strategy.

Practices/Clinics: The University of Rochester e-Moms of Rochester study staff have contacted all ObGyn private practices and clinics in Monroe County whose deliveries take place in one of the four major hospitals in Rochester; University of Rochester Medical Center (3 private medical practices with multiple offices and 3 hospital affiliated clinics), Highland Hospital (13 practices some with multiple offices and 2 clinics), Rochester General Hospital (7 practices some with multiple offices and 3 clinics) and Unity Health (5 practices and 1 clinic). The e-Moms of Rochester staff will measure maternal postpartum weights at their child's pediatrician's office in cooperation with The Greater Rochester Pediatric Based Research Network (GR-PBRN) that includes over 40 pediatric practices and 14 family medicine practices. additional information is in the appendix related to the number of Ob/Gyn practices at each stage in the process. e-Moms of Rochester brochures for patients and practices/clinics are included in the Appendix.

The study staff has explained what is necessary from each practice/clinic to assist with recruitment. Memoranda of agreement have been signed for all participating practices and clinics. Each practice will receive an incentive (e.g. lunches, monetary incentive) for their participation in the study.

Recruiter number rationale

: We have five recruiters and each recruiter will approach 3.8 or 4 women each weekday for screening. Each recruiter will consent 2.3 or 2-3 women per weekday. These figures will give the expected enrollment numbers discussed in the Study Population section.

Plans for Recruiting Subjects: To best accommodate Ob/Gyn clinics and private practices and recruit women directly from the community, three types of recruitment plans have been created. Each Ob/Gyn site will pick the recruitment plan that works best for their office.

Recruitment Plan 1 This plan will recruit using study staff to conduct both the pre and final screening of potential subjects and will not involve nursing staff at the practice/clinic.

Recruitment Plan 2 This plan will recruit using practice/clinic nursing staff to prescreen. Prescreening forms will be faxed to study office for study staff to then conduct final screening.

Recruitment Plan 3 This plan will recruit participants using an online screening. Pregnant women who learn about the study through posters and brochures in community locations (e.g.; WIC offices), in their own Ob practices, or through press releases can opt to learn more about the project and complete the screening online. All printed materials and publicity will have the web address and instructions to utilize this option.

Recruitment Process

Depending on the type of recruitment plan 1, 2 or 3, the recruitment process will differ initially. Potential subjects will be contacted in person by recruiter (recruitment plan 1), over the phone or email contact by recruiter (recruitment plan 2), or via posters and brochures in waiting rooms that direct women to screen online (recruitment plan 3). Study subjects will complete all of the same pre-screening and final screening questions regardless of their recruitment plan. The online recruitment that a recruiter uses has the same decision tree as the online screener that a potential participant completes on her own. Similarly, the consent form that is administered is the same regardless of recruitment plan. Study subjects will be given up to $140 based on the number of surveys completed, as incentive for their participation.

Moderation of Online Recruitment

In order for a subject who is deemed eligible based on the online screening to give consent and be randomized to the e-Moms of Rochester Study, an online enrollment moderator (study personnel) must review and approve each subject. The online moderator will review basic participant characteristics to determine whether a subject should be approved and offered consent into the study. The online moderator will review the following variables on the potential subject: e-mail address, telephone number, mailing address, practice providing prenatal care, IP address, date of birth, estimated delivery date (EDD), height, weight, insurance provider, time and date of completion of online screening, and response to the question "how did you hear about this study?" The online moderator will review these variables within 24 hours and if there are any suspicions about the validity of the potential subject's responses (i.e. similarity to other subjects enrolled or in process of being enrolled, or validity of the claim of pregnancy), then the subject will be contacted via telephone and asked to verify her identity and the information she provided on the screening form.

If the answers to these questions differ from what was answered in the screening tool, the online moderator will deny the request to enter into the study. If a subject who has provided questionable responses does not return a telephone call within 7 days, or the telephone number provided is not valid, the online moderator will deny the request to enter the study. A potential subject who has been denied entry through the process described above can request to meet face-to-face with a recruiter in order to re-enter the study. If a potential participant is moderated and enters the study, she will receive an e-mail indicating for her to complete enrollment and the link to continue the consent process will be provided.

Recruitment Tracking

The study team will track all aspects of recruitment on an electronic hand held device, which is also used for recruiting, screening, consent, and randomization. The tracking tool is in a database that is accessed through the internet. Study personnel have access to the database on a wireless handheld device and on a computer. For additional information on the security of the website see Section 14: Data Management.

All Potential subjects who complete a prescreen will be tracked. Of those who fail prescreen, the reason for the failed prescreen will be tracked (criteria based on age, gestation age, BMI and interested in participating). Potential subjects who complete final screen will be tracked along with reasons of ineligibility after final screen. Refer to eligibility criteria in Section 5. Study staff will also track expected recruitment compared to actual recruitment.

Inclusion of Women and Minorities

The targeted enrollment includes pregnant women who are 18-35 years of age, including all racial/ethnic groups that obtain obstetrical care in Rochester, NY. All pregnant women 18-35 years of age who receive prenatal care at the practice sites of the four Rochester, NY hospitals and meet the stated criteria will be offered enrollment. The population under study is limited to pregnant women.

The project will recruit participants among clinic/private practices in Monroe County ensuring a representation of racial/ethnic minorities that mimic the population of the area. At the same time, the project will be aided by the Center of Community Health (CCH) at the University of Rochester part of the Clinical and Translational Sciences Institute (CTSI) Community Engagement Core. The CCH has established contacts and procedures to reach minority populations through the African American and Latino Health Coalition. In addition, the CCH Community Advisory Council will advise the project on strategies to reach minority populations. Council members include representatives of community organizations and the Monroe County Department of Health. Our minority recruitment target will reflect the 2007 proportions among the eligible sample as documented in the Monroe County data from the Perinatal Data System: 67% White Non-Hispanic, 19% Black Non-Hispanic, 9% Hispanic, and others 5%.

Section 7: Data Collection and Measurements

Data Collection Contacts

The major variables related to the specific aims of this study, and the common elements for all the EARLY Trials are listed in Table 2, column 1. They are organized by meaningful categories with common elements marked with an *. The sources of the data for the variables are shown in column 2. The timing of the measurements are organized by EARLY Trial measurement time points and the project specific time points, as indicated in the rows at the top of the table. We have made every effort to harmonize the e-Moms data collection time points with the Early Trial time points, while not overburdening new mothers during the time around delivery (the puerperium). Prenatal I (baseline) is before 20 weeks gestation and the prenatal II time point is between 32 and 36 weeks gestation. A darkened cell indicates that data will be collected at that time.

Table 2: Variables, sources and timing of measurements

EARLY Trials Time Points		**Baseline**	**Six Months**			**12 Months**	**18 Months**	**24 Months**
e-Moms Trial Time Points		**Prenatal I**	**Prenatal II**	**Delivery**	**6 Week**	**6 Month**	**12 Month**	**18 Month**
		Pregnancy	**Puerperium**			**Postpartum**		
Variables	**Source of data**							
Outcomes								
Maternal Weight (pregnancy) *	Chart review							
Maternal Weight (postpartum) *+	Measured by study staff							
Height (for calculation of BMI)	Measured							
Independent (treatment variable)								
Treatment group	Assigned							
Sociodemographic Variables								
Age, marital status, work status, education, hh size, income *	Online questionnaire							
Race/ethnicity *	Online questionnaire							
Medicaid eligibility-	Chart review							
Neighborhood environment *	Online questionnaire							
Maternal/Infant Health								
Infant birthweight and gestational age	Chart review							
Parity	Chart review							
Glucose screen (test, values, dates); GDM diagnosis	Chart review							
Hypertension diagnosis, BP values	Chart review							
Urinary protein	Chart review							
Infant health	Online questionnaire							
Behavioral Variables								
Cigarette smoking *	Online questionnaire							
Alcohol *	Online questionnaire							
Sleep *	Online questionnaire							
Breastfeeding	Online questionnaire							
Physical activity (PPAQ)	Online questionnaire							
Physical activity (Paffenbarger) *	Online questionnaire							
Sedentary behavior (CARDIA) *								
Energy intake; diet quality (ASA-24) *	Online questionnaire							
Eating behaviors and patterns *	Online questionnaire							
Weight management *	Online questionnaire							
Psychosocial Variables								
Depressive symptoms *	Online questionnaire							
P.partum depression (Edinburgh)	Online questionnaire							
Social support	Online questionnaire							
Perceived stress (Cohen), Affect	Online questionnaire							
Behavioral intentions, self-efficacy, barriers, beliefs, attitudes	Online questionnaire							
Process Variables								

Frequency of visits to website pages, goals set, content viewed, content posted	Website log of activity & custom reports							
Biological Variables								
Genomic DNA	Saliva sample							
Other								
Clinic	Design feature							
Adverse events*	Online questionnaire							
Prescription medications*	Online questionnaire							

[+] Maternal postpartum weights will be measured through May 31, 2014. Some 24 month weights will not be measured.

Boxes with this pattern are variables for which a subset of the common element questions will be used.

Boxes with this pattern are constructs in the common elements that will be queried with questions that are more appropriate for women in the immediate post-birth period.

The table below summarizes the active period for collecting online surveys at each of the major collection points. At least 6 separate attempts will be made to obtain the information using online pop-ups, email and /or text message reminders, postcard reminders, phone reminders and possibly telephone interviews. Finally, Cornell University Survey Research Institute will conduct a telephone survey if all previous efforts to collect the online surveys fail at Prenatal 1 and 2 and at 6 and 12 months postpartum. A similar scheme will be followed postpartum to measure maternal weights at pediatric well-child visits or other locations according to participant preference and need (e.g. at participants' homes or other location at U or R Center for Clinical Research).

Table 3: Time Windows for Online Data Collection

Time Point:	**Prenatal I**	**Prenatal II**	**6 weeks PPM***	**6 months PPM**	**12 months PPM**	**18 months PPM**	
Last Contact/ Timed out	28 weeks gestation	Delivery	12 weeks PPM		9 months PPM	15 months PPM	21 months PPM
Online Survey	Randomization-196 days into pregnancy	224 days into pregnancy-delivery	42-84 days from delivery		168-252 days from delivery	336-420 days from delivery	504-588 days from delivery
Weight Visit	n/a	n/a	n/a		152-244 days from delivery	320-412 days from delivery	489-588 days from delivery
Active Period	>= 8 weeks	+/- 8 weeks	6 weeks		14 weeks	14 weeks	14 weeks

* PPM=postpartum

Measurements

Weight Variables and Outcomes: Body weight will be measured with available scales at the first prenatal visit by practice/clinic staff following the EARLY Trial-developed protocol. Postpartum weights will be taken at pediatricians' offices or alternative locations (see protocol below). Protocols for weight and height measurements will be posted at the nurse's stations. Initial weight in early pregnancy will be used to calculate ***body mass index (BMI).*** The primary weight outcome variables are: 1) **e*xcessive gestational weight gain***; 2) **mean p*ostpartum weight retention at 12 months.*** Weight at ***6 and 18 months*** postpartum are secondary outcomes. Each of these is described in detail in **Section 13: Analysis Plan.**

Measurement of Maternal Postpartum Weights at 6-12-18 months

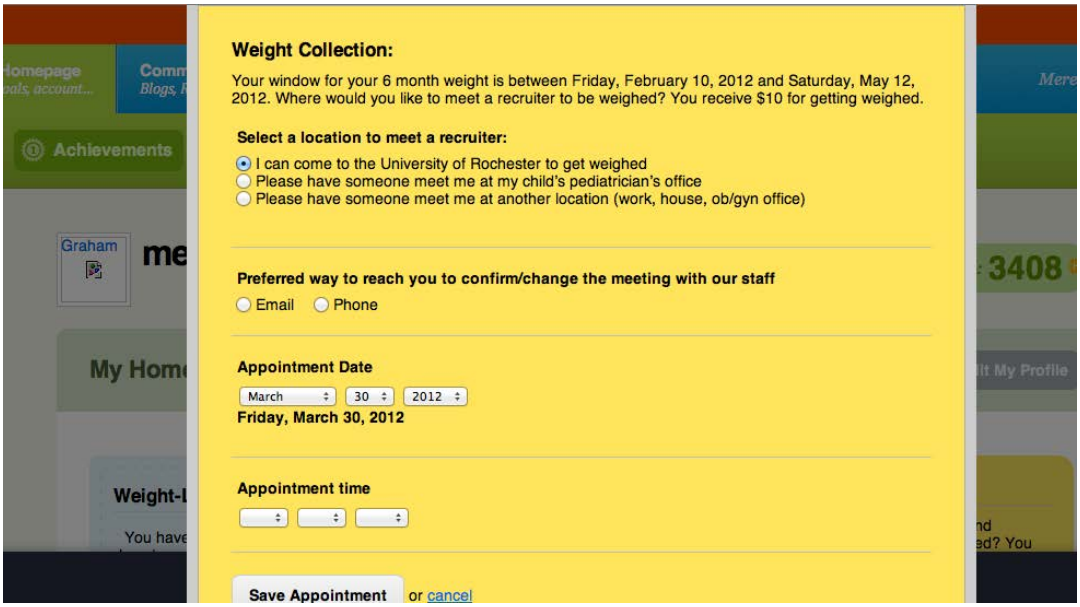
Weights are measured at the pediatric and family practice offices in the Rochester area at the time participants take

their children to well-baby check appointments. In addition, weights are measured at alternative sites in the community and/or a woman's home for those women who miss their children's well-baby checkups.

- Participants provide the name of their pediatrician/pediatric practice via the following procedures:
    - Women will be asked to indicate their pediatrician on the Prenatal II questionnaire (32-36 weeks pregnancy).
    - At 2 weeks postpartum, an email is sent to all research participants asking them to logon to the postpartum website where as part of the set-up process they are asked to provide the name of the pediatrician and/or practice.
    - A question on the 6 weeks PPM online questionnaire ask for the name of the pediatrician and/or practice. (By 6 weeks, participants should have established pediatric care for their children.)

When the weight collection window opens the following text is displayed to a subject: Your window for your (6 month, 12 month OR 18 month) weight is between ____ and ___*" Where would you like to meet a recruiter to be weighed? You receive $10 for getting weighed. This should only take between 5-10 minutes".* An example is shown below.

Figure 2. Weight Collection Appointment Prompt.



Then the subject is e-mailed:

Participant e-mail: We have received your request for an appointment to be weighed and our study staff will confirm this appointment within 3 business days.

2. Using the event reminder preferences that a subject has set for text or e-mail, or if none, then an e-mail is sent, there is a reminder sent to the subject one day before the weight collection appointment reminding her:
Dear XX,
This is a reminder that you are scheduled to meet with an e-Moms of Rochester study staff member tomorrow at (time) at (location). Please let us know via telephone at **585-273-5554** or via signmeup@emomsroc.org if you are unable to make this appointment and we will re-schedule.
See you soon!
e-Moms Roc

3. For subjects that have not yet indicated a "meet me at my appointment" AND have not filled out the pop-out form above, here is the schedule to prompt them to enter that information:

a. Day of window opening (Week 1 out of 12): email to participant that she is now in window and does not have an appointment
b. Week 2: email to participant
c. Week 4: email to participant
d. Week 6-12: weekly email reminders to participant (slightly different reminder sent for weeks 6-12)

- Women will be measured as per the EARLY studies protocol for measurement of weight and height within a 3-month window of each postpartum time point (height will be only measured once, typically at the 6-months well-baby check appointment).
- Trained study staff will measure weight and height (following EARLY trials protocols).
- Study staff will use portable auto-calibrating scales, and a field stadiometer or stadiometers in physician offices. Study staff will measure maternal weight in a private space at the pediatric office and enter the weight (and height when applicable) directly into the database from their hand held device. In case another non-study scale is used, the weight collection tool allows staff to indicate if the weight was measured on a UR study scale or another scale.

Pediatric offices

Collaborations with pediatric practices are facilitated through the Greater Rochester Practice-Based Research Network (PBRN). A letter of support with a description of the procedures has been signed by this group on behalf of all members. Pediatric Practices that do not belong to the PBRN will be contacted individually if a participant informs the project she has selected a non-PBRN practice. Before weight collection visits, a member of the study team contacts the pediatric office to let them know of the upcoming visit.

Back up plan to measure weights

For any reason for which the measurement cannot be obtained at the pediatric appointment, study staff will schedule a measurement appointment directly with the participant to obtain her weight at a location convenient to the participant. A minimum of 3 attempts will be made to secure maternal weights using this approach. Weights taken outside the 3-month time window, but before the next measurement time point will be imputed to the nearest time point.

The following locations are available for weight measurements:

1. Clinical Science and Translation Research Building located in the city of Rochester. This building has facilities for clinical research studies.
2. Red Creek: ObGyn clinic affiliated with SMH located in a southeast suburb
3. Center for Community Health: The center has offices for clinical practices and is located in downtown Rochester.
4. WIC clinics: These three clinics also have private offices for clinical purposes and are located in different areas in the city of Rochester.
5. The Towne House: This is a University of Rochester site that has available rooms for meeting study subjects.
6. Participants' homes.

Sociodemographic Variables: Data on **maternal age, marital status, work status, years of education, household income and composition and maternal race/ethnicity** will be collected as common elements through the online survey. Self –reported **Income eligibility for Medicaid** will be used to define a woman as low-income for the purpose of random assignment to treatment group within BMI and income subgroups. Final income status will be confirmed by the medical practices and hospital clinics that receive payment for services and the information is included in the medical record, which will be the source of the information.

Maternal and Infant Health Variables: **Infant birth weight, gestational age and parity** will be abstracted from the medical record. Blood glucose values from the currently used **50 gram glucose challenge** test administered routinely at 26-28 weeks gestation (earlier among women with prior history of gestational diabetes), the diagnosis of **gestational diabetes mellitus (GDM)** for those women who fail the glucose screen and thus are given a glucose tolerance test will also be obtained from the medical record. An indicator variable will be created for the type of glucose screening test administered. **Blood pressure values and urinary protein values**, as well as a diagnosis of gestational hypertension will be abstracted from the medical record and used according to EARLY Trial cut points. **Infant health conditions** will be assessed through online questionnaires using questions from our previous Bassett Mothers Health Projects (BMHP).

Behavioral Variables*:* Cigarette smoking, **alcohol, and amount of sleep** will be assessed in the online questionnaire using the common elements questions at all EARLY trial defined measurement time points. Pre-pregnancy and during pregnancy smoking and alcohol consumption habits will also be abstracted from the medical record. Cigarette smoking and sleep will also be assessed at 6 weeks postpartum to accurately capture the dynamics of these two variables. **Duration of any breastfeeding and duration of exclusive breastfeeding** will be assessed using the questions from BMHP. **Dietary intake of energy** and expenditure of energy through **physical activity** (PA) are the hypothesized mediators of any effect of the intervention on weight outcomes. We will measure energy intake using the ASA-24 with measurements for 2 days (1 weekday and 1 weekend day) as agreed upon by the majority of the EARLY studies. In addition we will measure eating behaviors and patterns that the literature demonstrates are associated with energy intake and/or dietary quality using the common element questions. Physical activity will be measured during pregnancy and the postpartum period using the Pregnancy Physical Activity Questionnaire (PPAQ), which has been validated for use in pregnancy by Chasan-Taber (60)and the Paffenbarger (EARLY trials common element). Sedentary behavior will be measured using a revised CARDIA measure. Weight management practices will be assessed as a common element.

Psychosocial Variables*:* We see several of the psychosocial variables as potentially modifying the effect of the intervention on behavioral and weight outcomes and thus we will measure them. **Depression** will be measured using Center for Epidemiologic Studies Depression Scale (CES-D) from the common elements. **Postpartum depression** will be assessed by the Edinburgh Postnatal Depression Scale (EPDS). First, participants will answer the EPDS-3 three-item scale at 6 weeks and 6 months postpartum (61). Those who score ≥ 10 for the EPDS-3 will be administered the additional 7 questions of the EPDS (62, 63). Responses to the full EPDS with a score of 10 or greater and/or ≥ 1 to the question about suicidal thoughts will receive a letter referring participants to their obstetrician for potential postpartum depression. **Social support** from family and friends will be assessed using questions with previously demonstrated validity in pregnant women. **Perceived stress** will be measured using Cohen's tool and **positive and negative affect** will be measured using the International Positive and Negative Affect Schedule Short Form. For another set of the psychosocial variables we will measure, we hypothesize these variables will serve as mediators of any intervention effect on behavior and psychosocial outcomes. These variables (**behavioral intentions, self-efficacy, skills, perceived barriers, beliefs and attitudes)** are drawn from Fishbein and Yzer's Integrative Model of Behavioral Prediction (one of the theoretical foundations of the intervention) and will be measured using item formulations related to this theory and the Theory of Reasoned Action (a related theory).

Process Variables: We have a much longer list of what will be measured than can be listed in the table. Because our intervention is only online, we can tap into a number of different measures of the frequency, intensity and type of use of intervention features.

Biological Variables: We hypothesize that the effect of the intervention could be modified by **Genetic variables.** Two major GNB3 haplotypes have been identified that consist of additional polymorphisms that are in linkage disequilibrium with the C825T allele. These haplotypes potentially differ in generation of an enhanced cellular signal transduction. Carriers of the 825T allele simultaneously contain more than one defined alteration on the GNB3 gene. The effects of

the T haplotype on phenotype have not been examined to date in large samples. In this proposal, we will have a large sample to study these polymorphisms. Genomic DNA will be obtained using oragene saliva collection kits collected upon participant enrollment. A total amount of 2-4 ml of saliva will be collected in a self-administered collection vial in the presence of the study recruiter. The saliva sample will be labeled with participant ID number only and taken to the genomic center for processing and storage for genotyping. DNA PCR will be performed and used to identify genotypes for the C825T polymorphism. All laboratory work will be conducted in the Functional Genomics Center using standard procedures.

Retention Strategies for Data Collection

1. Subjects will provide contact information including: telephone number(s), e-mail address and mailing address upon entry into the study. Subjects will be able to update their contact information and preferences via the website and study staff will be able to update subject contact information.
2. In order to enhance the completion of online questionnaires, we use a multi-modal follow-up for data collection. Study staff contact participants via e-mail, text, postcard, telephone call, and mail. In addition, participants have the option to complete survey by telephone if a questionnaire hasn't been completed online.
3. Financial incentives of up to $140 over the duration of the study will be given to participants for the completion of online questionnaires. A set amount is earned for the completion of each survey and that is shown to the participant on their e-Moms Roc dashboard. Participants can cash-in at any point in time using our gift card store that is part of the website. Thus we are allowing participants to chose when they'd like a gift card and to where they'd like a gift card. At the end of a participant's participation, an email reminder is sent to cash out within 30 days and if earnings are not cashed out that a check will be mailed to the address on file.
4. Our online surveys are designed to allow women to save and return to the survey at a later point in time.
5. Subjects are e-mailed a congratulations card at the time of delivery, as well as holiday and birthday cards throughout the study.
6. The study website indicates the surveys, food recalls and weights that need to be taken as well as when they need to be completed.
7. Participants that complete all study data collection activities are entered into a drawing for $150.

Section 8: Quality Assurance and Control

Study Staff Training (recruiters)

All recruiters will be trained in the following procedures by a variety of overlapping methodologies. These procedures will be written up as individual protocols with suggested scripts for each step in the process of recruiting, consenting, DNA collection, and provision of necessary documents to participants. Recruiters will be required to: 1) read all procedural protocols and scripts, 2) practice the protocols with other study team members to attain proficiency, 3) demonstrate proficiency of carrying out all procedures and protocols to principal investigator before any contact with potential participants and on a yearly basis. In addition, the project coordinator (or other designated team member) will randomly observe recruiters carrying out these procedures/protocols in the field. Retraining of recruiters will be done on an as needed basis. Regular updates and training will occur on a yearly basis with all recruiters. Finally, all study staff will be required to provide documentation of successful completion of the Human Subjects Protection Program (HSPP) course provided through the University of Rochester website and renewed every 3 years. Record of successful completion of the course and HSPP will be kept on file in study offices.

Staff Training for Adverse Events Assessment and Reporting

Staff members will be instructed by the principal investigator and one of the clinicians (who are trained by the EARLY Trials safety webinar) in the purpose of collecting data on adverse events, definitions of adverse events, expected

and unexpected serious adverse events (SAE), and interim events. They will be shown the medical adverse events forms, when to refer a form to the study clinician for the determination of an adverse event, and how to proceed when they learn of an interim adverse event.

After formal instruction, staff members will be presented with test online medical event forms for them to resolve. They will be presented with the online medical event form in which no events were reported, others with medical events during pregnancy and postpartum, some will be SAE and some will not, and they will be trained in reporting interim adverse events. Staff members will be asked what procedure they will follow and answers will be discussed. Staff members will be instructed to always consult with principal investigator and/or study clinicians in case of doubt.

Training for prenatal, delivery, and 6-week postpartum records data abstraction

Data abstractors will be trained in abstracting the prenatal medical record and delivery data from the hospital record. Procedures will include: review medical abstraction form and data dictionary; coding of data; clues to find variables not found in the standard location in the charts; discussion of errors in data abstraction; practiced data abstraction under the trainers' supervision; abstract diagnosed health conditions during pregnancy, notes from the social worker, and new medications from the prenatal/delivery/6-week postpartum charts progress notes in abstracting the prenatal medical record and delivery record at the hospital.

Although records are similar for all hospitals, once abstractors are trained, investigators and the study coordinator will test prenatal medical charts and delivery records from the other hospitals to evaluate data abstraction. Similar procedures will be followed to train abstractors. Six weeks postpartum data will be found in electronic medical records for clinics affiliated with Strong Memorial (SMH) and Highland Hospital (HH). All other 6-week postpartum data are in electronic medical records or paper medical records located in medical practices and clinics.

Reliability of data abstraction

Every abstracted chart will be reviewed by a second member of the research team. Inter-rater reliability of data abstraction will be checked by randomly selecting 5% of the prenatal/delivery charts across hospitals, practices and data abstractors. A different data abstractor will abstract data to an electronic chart audit form. Reliability will be checked and If the data abstracted match is less than 95%: 1) Disagreement will be resolved by a senior project coordinator or an investigator and the original chart audit form will be corrected; and 2) A refresher training session for the data abstractors will be held (protocol as above).

Online survey data quality

Online surveys developed by our vendors will be programmed to incorporate real time data quality prompts approximating what might occur during a face-to- face interview. If a subject enters a value, which is clearly impossible, a message will appear in red text asking the subject to re-enter the value. If a subject enters a value, which ***may*** be incorrect, a message will appear on the screen asking the subject just to verify that the response was what they meant to enter. For example, the Paffenbarger Exercise Habits Questionnaire Guide states that item 3a "Number of days in the past week with brisk walking >10 minutes" must be an integer between 0 and 7. The online survey will only offer these choices for responses. Item 3b is the average minutes per day of brisk walking. The guide specifies that a total of >300 min of brisk walking per week should be queried. If the multiplication of days per week times average minutes per day exceeds 300 minutes per week, a message will appear asking the respondent to re-check these values. Online surveys will automatically present skip patterns for the subject so that they only see and respond to the items that apply to them based on prior responses. Unanswered questions are coded differently than skipped questions due to a skip pattern. This study will ask for self-reported adverse events online. Should any event be entered by a subject that could possibly be a serious adverse event (hospitalization or related medical complication), a list of events reported by ID will appear

on the SRI adverse events review webpage for the study coordinator and/or medical officer to review. The online survey system incorporates several other features to maintain data quality. The data will be exported directly from the survey system in a format that includes an integrated data dictionary with response option coding and variable labels (RCU names and codes for all common elements). A codebook is automatically generated with all data exports. Finally, one-way frequency tables are available to investigators in real time to monitor the data collection process.

Section 9: Randomization and Masking

We are proposing to conduct a randomized control efficacy trial with a parallel group design in which the individual is the unit of randomization and analysis. Pregnant women in the first 20 weeks of pregnancy will be randomized within 4 BMI x income strata to 3 arms: Control arm; e-intervention 1 during pregnancy alone (Intervention Group 1); and e-intervention1 during pregnancy plus e-intervention 2 postpartum (Intervention Group 2). The main characteristics of the design proposed are:

Double masked: Randomization will be done after consent is obtained. Study recruiters will enter participant data in the study registration webpage where randomization will take place and not be visible to the study recruiter. Clinic staff will not deliver the intervention strategies and therefore will not be aware of the assignment. The placebo control website has non-weight related information.

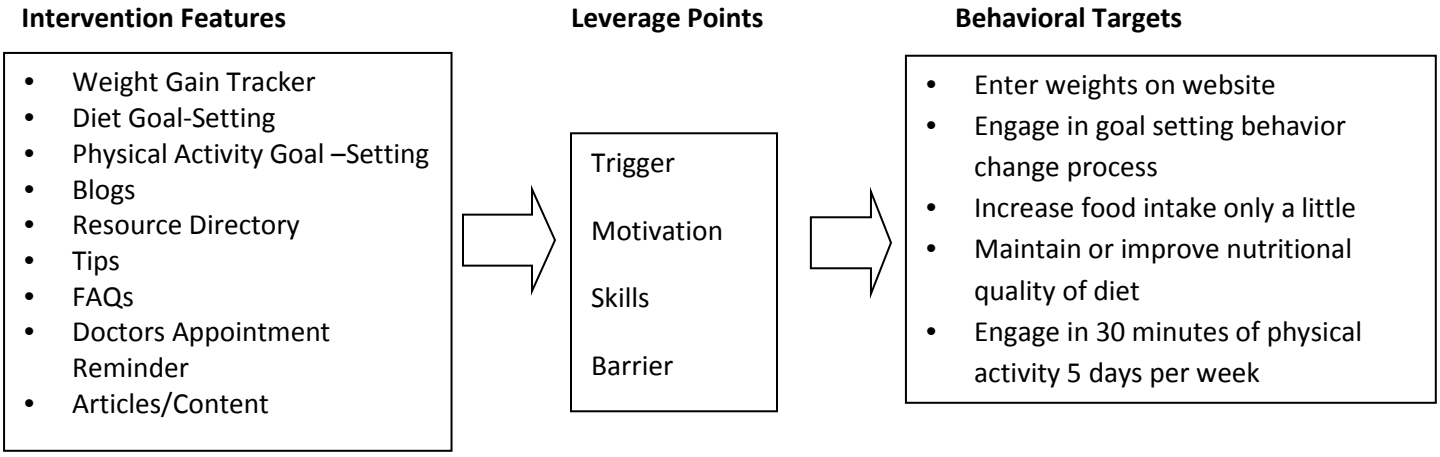
Random assignment to intervention and control conditions within strata: To ensure that treatment groups are balanced with respect to BMI and income, random assignment will be done within 4 early pregnancy BMI x income groups. We will have two early pregnancy BMI groups, normal (18.5-<25.0) and overweight + obese class I (25.0-<35.0) and two income groups, higher and lower income (Medicaid eligible with household income <185% of the poverty line).
Unit of randomization and analysis: Women will be randomized to intervention and control conditions and are the unit of analysis. Recruitment will be done within clinics and the resulting possibility of correlation of clinic with outcomes will be addressed in the proposed analyses.

Section 10: Intervention

Overview

This project will use two electronically-mediated behavioral interventions to encourage women to gain an appropriate amount of weight during pregnancy (e-intervention 1) and to follow a healthy lifestyle postpartum to minimize postpartum weight retention (e-intervention 2). The electronic media are an interactive project website and cell phones. Figure 2 shows the target behaviors, proximal leverage points for promoting behavior change, and the main features of e-intervention 1.

Figure 3. e-intervention for pregnancy



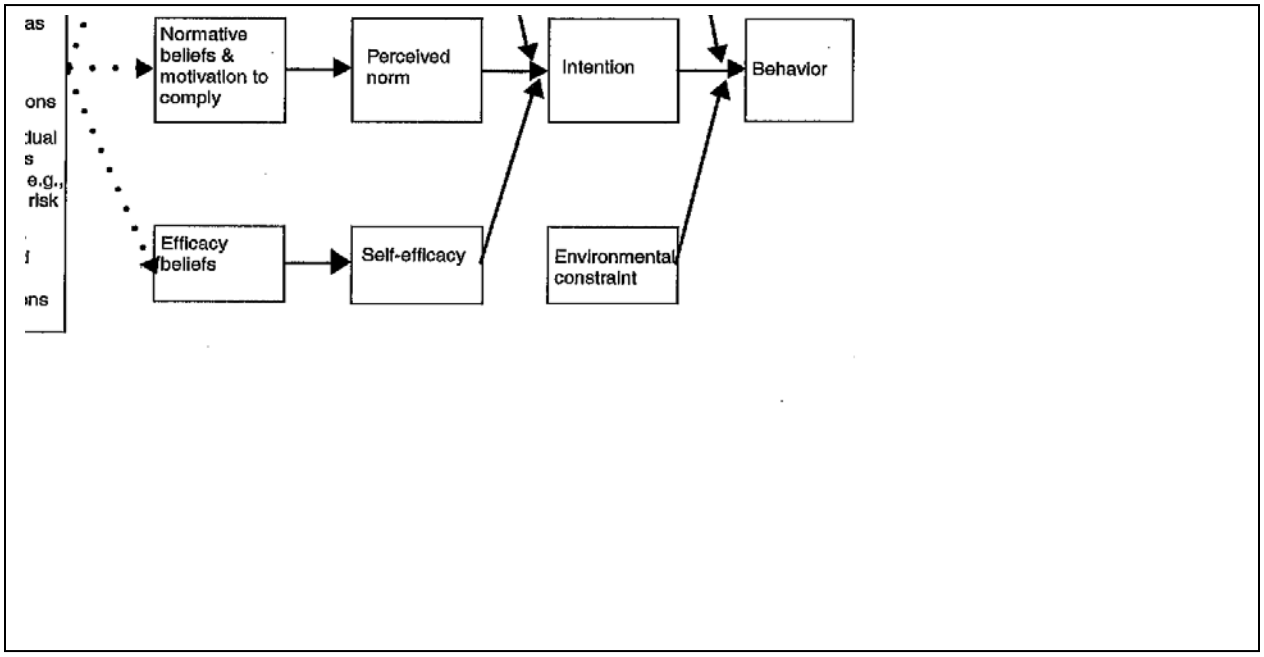
e-intervention 2 will have similar behavioral targets to e-intervention 1. The intervention features will be similar, but expanded to include a more extensive social component including social networking, resource sharing, blogs and a healthy behavior sharing tool. (More detailed descriptions of the interventions follow the section on theory.)

We think that each intervention feature will work through specific leverage points to move women closer to their behavioral targets. Some leverage points will be more important than others for achieving change in different behaviors. For example, we think that the ***Doctors Appointment Reminders*** will be important ***Triggers*** for getting women to ***enter their weights on the website***. We think that the ***Diet Goal Setting*** will be important in building the ***Skills*** to ***increase food intake only a little.***

Theoretical Rationale/Model Underlying the Interventions

The two primary theoretical perspectives that have informed the design of the intervention are Fishbein and Yzer's (64) Integrative Model of Behavioral Prediction shown below in Figure 3 and Fogg's Behavior Model for Persuasive Design (57). Fogg, drawing on many different theories from psychology and other social sciences, asserts that for a target behavior to happen, a person must have sufficient motivation, sufficient ability, and an effective trigger. The strength of his perspective is the linking of these predictors of behavior to features of electronic communication technology. Fishbein and Yzer's (64) proximal predictors of a behavior (shown in the Figure 3 below) are very similar to Fogg's: skills, intention (a product of motivation), and environmental constraints (which we call barriers in figure 2). Intervention features are designed to affect predictors of leverage points (eg. attitudes), as well as, the leverage points themselves. So as an example of the former, we think that the ***Articles*** and ***Tips*** will affect ***Behavioral Beliefs and Outcome Evaluations*** that will help women form **Attitudes** and **Intentions** to perform a behavior such as, ***engage in physical activity five times a week***.

Figure 4. Fishbein and Yzer's Integrative Model of Behavioral Prediction



In terms of building skills for changing diet and physical activity-related behaviors, we will draw on a guided goal setting in which women assess their current behaviors, set goals for change, and then engage in self-monitoring. We are using fairly simple assessment tools, not the tools for collecting research data, and giving women a fair amount of choice in selecting the areas for behavior change. As part of this process, we encourage women to think specifically about the barriers they are likely to face in achieving their goals and to think about multiple strategies for achieving success. This approached is modeled after Glasgow (65-67).

Description of the Interventions

Control Group

A placebo intervention using the same electronic media will be designed for the control group. The content will be non-weight related. During pregnancy, the content will be related to getting ready for having a baby. In the postpartum phase the content might focus on infant development and safe non-weight topics such as sleeping position. In each of the sections below, tools and content that will be available to control group are indicated by an *.

e-Intervention 1: Pregnancy Intervention

For each phase of the randomized controlled trial, there are several behavioral targets that the intervention features are designed to facilitate participants reaching. Below are the behavioral targets for Intervention Groups 1 and 2 during pregnancy:

- Pregnant women will enter their weights into the project website "gain tracker" coinciding with their OB visits.
- Pregnant women will take action in the areas of diet or physical activity when inappropriate weight gain happens.
- Pregnant women will increase their caloric food intake by the recommended amount during the second and third trimesters of pregnancy.

- Pregnant women will improve or maintain the nutritional quality of their diets by consuming 5 servings of fruits and vegetables per day; avoid eating excess sugar, fat, and emotional eating;
- Pregnant women will engage in 30 minutes of moderately vigorous physical activity on at least 5 days per week.

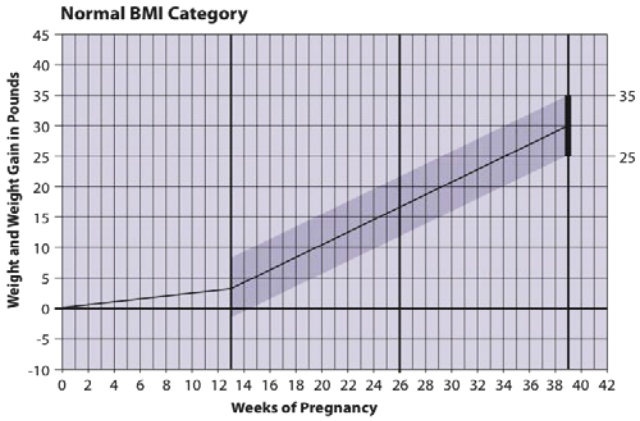
Intervention Features

All of the intervention features described below are only available to logged in users of the e-Moms of Rochester website that are in Intervention Groups 1 and 2 of the study.

Weight Gain Tracker

The weight gain tracker uses the pre-pregnancy BMI collected at recruitment to determine a woman's weight gain recommendation (68) and when the participant visits the intervention site she will see a graph for all 40 weeks of pregnancy with the weight range that she should gain over time (see Normal BMI example below).

Figure 5: Weight Gain Tracker



Women will have ability to enter their weight via text message or directly using a web form. Each weight that is entered will be plotted on their personal graph and she will see her weight gain plotted throughout their pregnancy.

The weight gain tracker and doctor appointment reminder features of e-Moms Roc will be linked for participants in Intervention Groups 1 and 2. For instance, just before the time of a scheduled doctor's appointment a text will be sent to a participant to remind her to text back her weight. If a participant is gaining out of her recommended range (either above or below) then prompts or nudges to the diet or physical activity goal-setting tools will be triggered. Participants that utilize the weight gain tracker will be awarded a virtual badge based on their utilization of the tool.

Diet Goal-Setting

Below are the steps that will be part of the diet goal-setting feature in e-Moms Roc:

Step 1: Participant completes a dietary assessment. The dietary assessment includes questions from Rapid Eating Assessment for Participants-Shortened Version (REAP-S) (69) and from the Eating Stimulus Index (68) for emotional eating and dietary restraint questions. A total of 23 questions are asked in the dietary assessment.

Step 2: The e-Moms Roc website calculates issue area scores from related questions in the assessment. An issue area is identified for a participant if the average score from related questions is 2.5 or more. There are ten potential issues areas that a participant can work on:

1. Eating out frequently

2. Eating high-fat foods
3. Eating and drinking too much
4. Not eating enough whole grains
5. Not eating enough fruit
6. Not eating enough vegetables
7. Not eating enough calcium-rich foods
8. Eating high sugar foods
9. Eating low-nutrient density foods
10. Emotional eating

Step 3: The intervention site will display feedback such as: "Congratulations! You're (issues area(s) with lowest scores)! (Sentence why that issue area is healthy/helpful). However, (number of areas to work on) area(s) to work on is/are (issues areas with scores greater than 2.5 in descending order). (Issue areas with scores greater than 2.5) may be leading you to gain weight too quickly (if nudged from weight gain tracker) or may lead you to gain more than (user's target weight gain range), your target weight gain range."

Step 4: Based on the issue areas displayed in the feedback section, a participant then selects one issue area to work on. Within that issue area multiple pre-written goals are displayed and participant selects a goal to try.

Step 5: The e-Moms Roc website will then display the common barriers for the particular goal area that was selected and will also display strategies that may address barriers/help achieve goal. Participants will also have the option of entering other barriers and/or strategies.

Step 6: The general goal area that was selected allows for the participants to specify the number of times or proportion of times that she will do the behavior or discontinue doing the behavior. In this step, the site will display suggestions for setting the number or proportion for a goal and deadline timeline. Then a participant will set an achievable number or proportion for the goal and timeline using a behavior to monitor template (see Figure 5 below).

Figure 6: Diet-Goal Setting: Issue Area, Goal, Barriers, Content, Strategies and Self-Monitoring

Issue Area	**Goal Area**	**Barriers**	**Related Content**	**Strategies**	**Behavior to Monitor**	**Self-Monitoring**
Eating high-fat foods	Decrease the # of times/week that you eat high fat processed meats like salami, bologna and hot dogs.	-Not the person that shops or prepares food. -Local food environment. -Food preferences -Social influences (partner/family) -Cost	-Formation of food preferences -Effects of high fat and high sodium diet -Nutrition comparison between leaner processed meats and higher fat meats -Impact of food avail.	-Try this instead of that -Locations and descriptions of low-fat sandwich options -Use low-fat processed meats rather than high-fat processed meats.	-Set max number of times per week that you eat high fat processed meats likes salami, bologna, and hot dogs.	-Web or Printout—Check off from list which high fat processed meats you ate and fill in number of times eaten per week/day? For printout users, have blank box next to each meat to tally number of times eaten. Weekly prompt on dashboard to enter total number of times of all high fat process meats eaten. -Text or Email or Dashboard--Respond to prompt, "How many times did you eat high fat processed meats this week/day?"

Step 7: Based on the goal area selected, different self-monitoring options will be displayed and then a participant will select a self-monitoring option.

Step 8: A list of potential rewards for achieving goals will be displayed on the website and the participant will select what reward they'd like if/when she achieves her goal.

Step 9: An action plan will be displayed for the participant to print or simply review. She will then be directed to content related to her goal and also to her selected self-monitoring templates.

Physical Activity Goal-Setting

Below are the steps that will be part of the physical activity goal-setting feature on e-Moms Roc:

Step 1: Participants will review the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recommendations for physical activity during pregnancy(71)

Step 2: Participants will assess their physical activity. First, a participant will assess whether or not she has been told by her prenatal care provider that she should avoid physical activity and/or has contraindications for physical activity. Second she will assess whether she was sedentary before getting pregnant using a validated question from Pregnancy Risk Assessment Monitoring System (PRAMS). If a participant is not sedentary, the next question assesses what types of activity she is currently engaged in.

Step 3: The intervention website displays feedback to the participants based upon her assessment.

-If a woman has contraindications for PA during pregnancy, this will be reported back to her and she will be advised/reminded to avoid PA during pregnancy.

-If a woman is sedentary, then walking, swimming, cycling and aerobics can be recommended and a woman will be directed to move through the remainder of the physical activity goal-setting tool.

-If a woman is not sedentary, but isn't meeting the recommendation, then she will be prompted to move through the physical activity goal-setting tool.

-If a woman is adequately active, she will be congratulated then shown our self-monitoring tools as well as content for continuing physical activity through pregnancy. She will be prompted to return at the start of her next trimester.

Step 4: The e-Moms Roc site will display the appropriate goal areas to a woman divided by sedentary and insufficiently active. The actual tool shows a subset of the activities listed from the Paffenberger (72), which indexes 70 activities, 52 of which are acceptable for pregnant women that are not sedentary and 27 of which are acceptable even for sedentary pregnant women. In the table below, selected examples are shown.

Below are examples given of activity types divided by sedentary and insufficiently active from the ACOG Bulletin (70):

Sedentary Woman	**Insufficiently Active Woman**
Walking	Walking
Swimming	Swimming/Water aerobics
Low-impact/Prenatal Aerobics	Low-impact/Prenatal Aerobics
Bicycling	Bicycling
Prenatal Yoga	Prenatal Yoga
Active transport	Active transport
	Running
	Weight lifting
	Cross-country skiing/ Snow shoeing

Step 5: Potential barriers to physical activity will be assessed. Barriers that have been identified in the quiz will be displayed to a participant along with potential strategies for overcoming barriers/achieving goal. Then a participant will select which strategies she will use and there will be an option for women to add barriers and strategies.

Step 6: Based on the goal area a participant will select self-monitoring tool(s) and a participant will finalize her action plan by setting the frequency of the goal, timeline for the goal and reviewing the strategies and self-monitoring that have been selected for the goal.

Step 7: A list of potential rewards for achieving goals will be displayed on the website and the participant will select what reward they'd like if/when she achieves her goal.

Step 8: An action plan will be displayed for the participant to print or simply review. She will then be directed to content related to her goal and also to her selected self-monitoring templates.

Blogs*

A community component of the intervention site will include blogs that will be user-generated, but only posted after moderator approval. E-Moms Roc will also allow for moderator-approved comments on blogs. Bloggers may earn community points on the site by posting blogs and by composing blogs that are "liked" by participants.

Resource Directory*

Another community component of the intervention site is a resource directory for pregnant women in Rochester like Digg or iVillage. Below are categories of resources that the e-Moms Roc staff has identified and will post online:

- Pregnancy/Baby Resources
- Breastfeeding Resources*
- Single-Parent Resources/Custody including foster care*
- Holistic Pregnancy and Feeding*
- Diaper Delivery Resources/Services*
    - Maternity and Infant Clothes*
- Childcare/Childcare Referral
- Monroe County Farmer's Markets
- Food Assistance in Monroe County (Include information on WIC)
- Healthy Restaurants – Be a Healthy Hero
- Places to run in Rochester
- City of Rochester Trails & Parks/Monroe County Parks
- Stroller-friendly WalksGyms/Exercise
- NYS Health Insurance Information*
- Smoking Cessation Resources*
- Alcohol/drug cessation resources*
- Preventing domestic violence (housing shelters)*
- Food stores
- Product Recalls*

Participants will be able to rate and comment each resource that is posted in the resource directory. Additional resource categories and resources may be added and posted, if approved by the moderator.

Doctor Appointment Reminder*

Upon logging into the site a participant will be prompted to enter the date(s) and time(s) of upcoming prenatal care visits. Based on a participant's communication preferences, text or e-mail reminders of visits will be sent out in advance of the appointment. During the time, of the appointment an additional prompt will be sent to text or e-mail the weight taken at the prenatal care appointment back to e-Moms Roc. One hour after the scheduled appointment, a reminder will be sent to update the currently scheduled prenatal care appointments using the online form or by texting/e-mailing the date and time of the next appointment back to the intervention site.

Tips*

Two types of tips will be sent to participants: knowledge/educational tips and practical/logistical tips. Participants will be able to select their preference for method of tip delivery and then also to indicate their preference for time of day of text message and preference for frequency of text message upon logging into the intervention website. The time of day would be divided into: overnight, morning, afternoon, evening. For

frequency of receiving messages the range will be from as many as 2 per day to as few as 1 per week. If a woman doesn't set frequency and timing preferences, the default will be 3 per week between 11am-6pm and messages will be sent via e-mail. These tips will be based on the newsletters in Bassett Mothers Health Project Too. Women will be given messages appropriate to either their week or trimester of pregnancy and to the particular goal area that they are focusing on.

Content Articles & FAQs*

At least 100 different topics of content will be available to participants in e-Moms Roc. Sample topics include: Snack ideas during pregnancy; How much food is 300 calories; Dietary strategies to address pregnancy heartburn; Fetal development*; Each content page will be tagged by a keyword and will be pushed to a participant based on her goals, reading of a tip or a frequently asked question. New content pages will be added throughout the study to keep the content new and exciting. A participant will be directed to new content from her dashboard.

There will be a frequently asked questions (FAQs) section of the e-Moms Roc website that includes over 125 questions and answers that were originally submitted by participants in Bassett Mothers Health Project Too and answered by study personnel and updated in 2010. FAQs are added to throughout the study to keep the content new and exciting.

e-Intervention 2: Postpartum Intervention

For each phase of the randomized controlled trial, there are several behavioral targets that the intervention features are designed to facilitate participants reaching. Below are the behavioral targets for the women in Intervention Group 2 during postpartum portion of the study:

- Postpartum women will input their weight into the weight loss tracker at least once a month.
- Postpartum women, if lactating, will consume a similar amount of food as consumed during pregnancy.
- Postpartum women, if not lactating, will decrease food intake to pre-pregnancy levels.
- Postpartum women will maintain or improve nutritional quality of diet (F&V, whole grains, low-fat dairy, decrease fast food consumption, decrease sugar sweetened beverage consumption, improve healthy food choices when eating away from home, decrease portion sizes).
- Postpartum women will engage in 30 minutes of moderate to vigorous physical activity on 5 or more days a week.

Intervention Features

Weight Tracker

Similar to e-intervention 1, there will be a way for women to plot their weight over time. However during postpartum there isn't a particular range that women should lose within a certain period of time based on BMI. Rather the goal is to return to their pre-pregnancy weight, to reach healthy weight or to reach another target weight. Thus the weight loss tracker will use the pre-pregnancy weight collected at recruitment and all other weights will be plotted across time either above, at or below that line. Since during the postpartum phase participants will not be under routine medical care to the degree that they were when pregnant, they will not be weighed regularly unless they have a scale or are seeking additional medical care. The frequency suggested for entering weights in the weight loss tracker is at least once a month and no more than once a week. Weigh-in reminders may be set by the participant and weights may be entered via text or web form.

Diet Goal-Setting (see e-Intervention 1 for the overall goal-setting structure)

The diet goal-setting feature will be the same as it was during the pregnancy time period.

Physical Activity Goal-Setting (see e-Intervention 1 for the overall goal-setting structure)

The physical activity goal-setting feature will be modified to the appropriate recommendation for all US adults rather than the recommendation for pregnant women. Both moderate and vigorous activity will be recommended and the listing of types of activity will be expanded to include sports and exercise that are deemed unsafe during pregnancy. Similarly, the initial sections on safety of exercise during pregnancy will be removed. Additional strategies for meeting physical activity goals with an infant and toddler will be added.

Health Diary

Within the goal setting section of the website an online health diary has been added for subjects to create a physical activity diary, diet diary or a diary that includes entries related to both diet and physical activity. The diary contains a date field, a text field and a dropdown menu to select the type of diary entry. Guidance and prompts for keeping a health diary are included around the diary and in a help section with the diary.

Healthy Behavior Sharing /Campaigns/Goal Groups

Participants will use this website feature to participate in campaigns that will be focused on physical activity and diet at strategic times of the year. they will be able to see the photos of other participants' diet and physical activity entries and be able to connect and encourage other participants that are participating in the campaign. Participants will be anonymous and known to each other through their usernames in the e-Moms Roc site. This feature may be used for self-monitoring and it may also be used for social support for dietary and physical activity change. In January of 2013 and 2014 a New Year's 6 week RU Ready to Lose it Campaign is run, which features new content and tools related to weight loss, physical activity and diet.

Blogs (see e-Intervention 1)*

Resource Directory (see e-Intervention 1)*

Additional resources and resource categories will be added of additional relevance to postpartum women.

Problem Solving Tool*

This tool will be available to all postpartum women and it will provide step-by-step guidance for how to solve any particular problem that a subject is facing. The steps that the tool leads a participant through are summarized below:

1. *Recognizing emotional symptoms*
2. *Clarifying and defining problem*
3. *Setting realistic goal*
4. *Brainstorming/displaying strategies to address the specific problem*
5. *Choosing the best solutions*
6. *Developing/creating an action plan for carrying out the solution*
7. *Reviewing and evaluating outcome*

The participant has the option to make her problem public and by doing so she would be recommended to connect with other women that are facing a similar problem, which would allow women to support each other and share about strategies and solutions.

Social Support Network*

This feature will allow postpartum women in the greater Rochester area to connect and feel supported by other women in the area. It will incorporate features such as a meet-up, and status updates like Facebook and

Babycenter. Participants will be anonymous and known to each other through their usernames in the e-Moms Roc site.

Meal Planning

The meal-planning tool will allow women to plan out their meals for either a week, two weeks, three weeks or a month via adding meals to a calendar. The tool then prompts them to look at their meal planning and evaluate how they did related to: whole grains, vegetables, fruits and low-fat options. The tool will remind women of the servings of each that they should be getting and ask them to indicate how they did for each four categories with a thumbs up or down for all meals planned that period. Participants will be able to store their own recipes on the site and be provided with recipe resources within the meal planning tool.

Your Child's Doctor Appointment Reminder*

Similar to the intervention feature described for e-intervention 1, women will be able to enter and update their child's doctor appointments and set what type of reminders they would like.

Tips (see e-Intervention 1 for details on how the tips feature will be set-up)*

These tips will be based on formative research that was done with postpartum women in Rochester as well as incorporating any previously used tips from the literature. Participants will be given messages appropriate to either the age of their infant and/or to the particular goal area that they are focusing on.

Content Articles & FAQs*

At least 100 different topics of content will be available to participants in e-Moms Roc. Sample topics include: snack ideas; exercise strategies with an infant; and infant development*. Each content page will be tagged by a keyword and will be pushed to a participant based on her goals, reading of a tip or a frequently asked question. New content pages will be added throughout the study to keep the content new and exciting. A participant will be directed to new content from her dashboard.

Standardizing Delivery of the Intervention

These interventions will all be delivered via the e-Moms of Rochester website and associated texting and e-mailing systems. There will be no face-to-face contact between interventionists and participants. There will be no variation by participant in the content available online or in text or e-mail messages. The only variation in content pushed or received at a particular time will be due to the particular goal that a participant is currently focused on.

Facilitating Participants' Retention in the Intervention

In the 2005 article by Coday et al on retention strategies in behavioral intervention trials (73), eight retention strategy themes were identified that apply to both data collection and intervention. In the following section selected themes from that paper are identified and aspects of the e-Moms of Rochester interventions that apply to each theme are described.

1. *Emphasize benefits of participation*-Throughout the study the benefits of participating in a healthy lifestyle research project that benefits both the health of women and their babies will be emphasized via articles, tips, and additional marketing of the project to both the public and participants.
2. *Provide incentives*- Badges are awarded to participants for utilizing intervention features. Participants will be able to increase the level achieved for each badge as they use a feature multiple times. Community features such as, blogs, resource sharing and the social network, allow users to accumulate points for participating.

3. *Give instrumental or tangible support*- The Resource Sharing feature provides instrumental support to participants by providing links and recommendations of resources that are of relevance to our study population.
4. *Be patient yet persistent*- Weekly e-mails go out to participants to encourage them to visit the site. Content will be updated and added and pushed to participants through multiple channels (text/e-mail/dashboard)
5. *Be flexible*- The interventions will be available via multiple modes including web, mobile web, text messages, and e-mail messages.
6. *Provide social support*- The intervention features incorporate social support through online features such as, blogs, blog commenting, healthy behavior social network, and the social support network.
7. *Maintain a good tracking system*- Cohesive tracking by web-based system for both pushing content to participants and for monitoring adherence to the interventions.

Intervention Contact Schedule

Table 4: Intervention Contact Schedule for Pregnancy

Intervention Arm	**Control Group**	**Intervention Group 1**	**Intervention Group 2**
Description and Approach	Non-weight related information and tools	Behavior change through weight monitoring, interactive behavioral goal setting, and self-monitoring of goal achievement with logistical support (pregnancy only)	Behavior change though weight monitoring, interactive behavioral goal setting and self-monitoring of goal achievement with logistical and social support
Frequency and Type of Contacts			
Internet			
Behavioral Goal-Setting	0	1/month	1/month
Content Articles and FAQs	As desired by participant	As desired by participant	As desired by participant
Tips	1-3/week	1-3/week	1-3/week
Weight Monitoring	0	1/month 1st -2nd trimester 2/month 3rd trimester	1/month 1st -2nd trimester 2/month 3rd trimester
Blogs	As desired by participant	As desired by participant	As desired by participant
Resource Directory	As desired by participant	As desired by participant	As desired by participant
E-mail/Text			
Weight Monitoring	0	1/month 1st -2nd trimester 2/month 3rd trimester	1/month 1st -2nd trimester 2/month 3rd trimester
Weekly e-mail reminder	1/week	1/week	1/week
Appointment Reminder	1/month 1st -2nd trimester 2/month 3rd trimester	1/month 1st -2nd trimester 2/month 3rd trimester	1/month 1st -2nd trimester 2/month 3rd trimester
Tips	1-3/week	1-3/week	1-3/week
Self-Monitoring of Goal Achievement	0	Daily-Weekly	Daily-Weekly

Table 5: Intervention Contact Schedule for Postpartum

Intervention Arm	Control Group	Intervention Group 1	Intervention Group 2
Description and Approach	Non-weight related information and tools	Non-weight related information and tools	Behavior change though weight monitoring, interactive behavioral goal setting and self-monitoring of goal achievement with logistical and social support
Frequency and Type of Contacts			
Internet			
Behavioral Goal-Setting	0	0	1/two months
Content Articles and FAQs	As desired by participant	As desired by participant	As desired by participant
Health Diary			As desired by participant
Tips	1-3/week	1-3/week	1-3/week
Weight Monitoring	0	0	1/month after 6 weeks postpartum
Blogs	As desired by participant	As desired by participant	As desired by participant
Resource Directory	As desired by participant	As desired by participant	As desired by participant
Meal Planning Tool	0	0	As desired by participant
Social Support Network	As desired by participant	As desired by participant	As desired by participant
Health Behavior Sharing	0	0	1 campaign/ 2 months
Problem Solving Tool	As desired by participant	As desired by participant	As desired by participant
E-mail/Text			
Weight Monitoring	0	0	1/month after 6 weeks postpartum
Weekly e-mail reminder	1/week	1/week	1/week
Appointment Reminder			
Tips	1-3/week	1-3/week	1-3/week
Self-Monitoring of Goal Achievement	0	0	Daily-Weekly

Overall e-Intervention Tracking

- Website will track length of each session.
- Website will track number of sessions.
- Website will track which website sections were viewed in a session, and how much time was spent in those sections out of total session time.
- Website tracks weights entered, diet and physical activity goals that have been set as well as monitoring of goals.
- Website tracks type of feature viewed, category of content viewed and keywords associated with content viewed.
- Website will track how an individual accesses the site.
- Website will track online incentives that each participant has accumulated.
- Website will track what mood icon is selected and what page/content/tool is viewed subsequent to selecting mood.

Intervention Modification for Safety Concerns

e-Moms of Rochester has two primary end points: excessive weight gain in pregnancy and postpartum weight retention. It includes a different intervention for each time point and each will be discussed in relation to intervention modification related to safety values for weight loss.

During pregnancy and until 6 weeks postpartum, every research participant is in the care of a health care provider and women's weights for research purposes will be obtained from an audit of their medical records completed between 6 weeks and 6 months postpartum. In our intervention features, we provide content and tools aimed at increasing weight gain for those who are gaining inadequately and slowing the rate of weight gain for those who are gaining excessively. For women who have level 1 and level 2 alerts for inadequate weight gain, the interventionist will encourage women to utilize intervention features that support getting weight gain back into the recommended range. (See page 32-33 for further description of intervention modification with under gain during pregnancy).

Major weight loss occurring in a short amount of time may interfere with exclusive breastfeeding, especially in the first 6 months postpartum, therefore our intervention features will promote adequate, but not excessive rapid weight loss. After six weeks postpartum, for women in the intervention arm whose weight loss exceeds 6% of their previous weight based on weights reported within one month our non-blinded interventionist will contact the research participant and inquire about the recent substantial, quick weight loss to determine if it is due to illness, if it is related to the study, or if it is purposeful. She will also be encouraged to take advantage of the available content on slowing the rate of excessive weight loss and given related advice about an appropriate increase in calorie intake and decreasing excessive exercise if these appear to be the reasons for the major weight loss.

Section 11: Safety Monitoring

Potential Risks

The potential risks to the participants are psychological distress due to interviews/questionnaire and the handling of DNA material; privacy issues, and risks due to increase physical activity:

- Psychological distress in completing the interviews/questionnaires. It is assessed that these risks are small; data being collected via online surveys is not anticipated to elicit distress, measurement of weight will occur throughout pregnancy so it is not likely to elicit a distress response. Measurement of weight after pregnancy will occur at pediatric visits and might be stressful for the mom.
- A potential risk is psychological distress/concern regarding the handling of DNA materials and concerns/fears of unauthorized use of DNA. Education regarding DNA collection and handling will be used to minimize concerns—risk of unauthorized use will be minimized through use of coding DNA samples for storage to protect identity. One list of the subjects and the identifying numbers will be kept in the PI's office in a locked file cabinet. Only the PI and study team members who contact participants will have access to this list. The list will be destroyed at the end of the study. Other members of the research team will not be able to connect the participant with DNA samples.
- The website and database will be maintained by a qualified vendor and be fully compliant with HIPAA guidelines for patient privacy and data security involving storage and remote access to electronic personal health information so there will be minimal risk of individuals other than the research team accessing the data. The vendor will comply with current standards for security as they evolve.
- Minor musculoskeletal injuries may occur when participants in the intervention arms increase the amount of physical activity.
- Falling may also occur when participants in the intervention arms increase the amount of physical activity.

Surveillance and Reporting Procedures and Safety Monitoring Plan

- Adverse events will be self-reported by the participants online at every data collection point (prenatal II, 6 weeks, and 6-12-18 months postpartum). To reduce participant burden, we will collect data for the online questionnaires and adverse events at the same time.

Determination of serious adverse events (SAE): When a participant answers affirmatively to any of the first two questions in the medical events form (hospitalization or medical complication), a list of events reported by ID number will appear on the SRI adverse events review webpage.

- The study staff will complete an on-line Staff Review Form with a summary of the adverse events.

- The study staff will only contact the participant or the practice/clinic for more information if the answers to questions 3.a., b., and c. from the prenatal II, questions 4.a., b., and c. from the 6-weeks postpartum or questions 2.a., b., and d. from the 6-12- and 18 months postpartum medical events form need further clarification.
    - For all time points when potential SAEs are reported with incomplete information provided by the subject, study staff will contact the participant or the practice within two business days. The additional information will be entered in the on-line Staff Review Form.
    - Study staff will determine whether there is enough information to determine a SAE.
    - If study staff determines the presence of a SAE, or participant cannot be contacted, or the additional information is not sufficient to determine a SAE, the study staff will refer participant's information to the study clinicians.
- The final determination of SAE will be done first by Dr. Susan Groth, a women's health nurse practitioner and a co-investigator in the project. Dr. Groth will consult with the study clinician, Dr. Loralei Thornburg, an ObGyn, in case of doubts in the ascertainment of an SAE. The clinician will then review an on-line Clinicians Review Form. This form will include a summary of the adverse events and a summary of the staff review responses. Study clinicians will also determine if:
    - For the prenatal II and 6-weeks postpartum forms, whether the event is a Serious Adverse Event (SAE). No referral of non-SAE is necessary since participants will be under the care of health care provider.
    - For the 6-12-18 months postpartum, whether the event is a SAE or a non-serious adverse event requiring referral (procedure for referral below).
- If a SAE is confirmed, a SAE form will be filled by the study clinician (Drs. Groth or Thornburg) and reported to NHLBI, OHRP, and our local IRB. The SAE form is part of the Clinician Review form. All events that are fatal or life threatening or otherwise serious and unexpected and definitely, probably or possibly related to the study must be reported to NHLBI within 7 days if life threatening or within 15 day if otherwise serious and to OHRP within 30 days. Otherwise, a SAE will be reported to the DSMB at regular meetings.
- Study clinicians and principal investigator will determine if a SAE is unexpected or definitely, probably or possibly related to the study (see below for definitions and a list of expected SAE).
- University of Rochester (U of R) Institutional Review Board: A 'local event' is an incident, experience, or outcome that occurs to a subject participating in a RSRB-approved research study. A local event is only reportable to the RSRB as an individual event report when the event <u>is serious, unexpected and related to participation in the study (SAE)</u>. These individual events must be reported within 10 calendar days and will typically be reported as a Type 1 "adverse event" or a Type 4 "unanticipated problem involving risks to subjects or others " (e.g.' laptop with unencrypted data stolen, a recruitment letter sent to the wrong person breeching privacy, incarceration of a subject in a protocol). The University of Rochester (UR) has established an electronic reporting system for events that need to be reported to the Research Subjects Review Board (RSRB). A local event that **does not** meet the above definition does not require immediate reporting and will be submitted at the time of continuum review as a summary of events with an assessment of risk (e.g., no change, greater/less than expected, etc.) in the progress report "Adverse events/overall risk" section.
- In the event of a miscarriage or a stillbirth before 28 weeks gestation, participants will be terminated from the study. Once a participant is terminated, the study staff will stop sending study messages and reminders. If stillbirth occurs after 28 weeks gestation or a neonatal or infant death occurs, the participant will <u>not</u> be automatically terminated but will have the choice to continue in the study.

Reporting of Interim Adverse Events

- An interim adverse event will be only recorded or reported to the DSMB or NIH outside of biannual reporting if it is a SAE.
- Once an interim adverse event comes to the study attention:
    - During a participant's pregnancy, study staff will contact participant or practice if insufficient information is provided.
    - During the postpartum period, study staff will contact participant if insufficient information is provided.
- Study staff will fill an on-line medical events form and will assess whether:
    - participant has had a life-threatening event or experienced a significant or persistent disability
        - Participant has been hospitalized for a non-pregnancy related event overnight.
    - participant has been hospitalized for a pregnancy related event for >12 hours
    - baby has a congenital anomaly or birth defect

To clarify, preterm labor (i.e. <37 weeks gestation) that results in hospitalization for >12 hours will be considered an SAE, whereas hospitalization for >12 hours for a term birth (i.e. >=37 weeks gestation) will not be considered an SAE as this is expected. Similarly, miscarriages that result in a hospital stay >12 hours (e.g. for a D &C and observation) will be considered an SAE prior to subject termination.

In the event that multiple SAE and AE events occur together due to the fact that they are related, these events will be sent together to the medical officer for review. The medical officer will use her clinical judgment to determine if more than one distinct SAE has occurred and which event(s) qualify as SAEs or AEs. In general, the medical officer will follow the precedent that the precipitating event will be coded as the SAE-related event.

- Study staff or study clinician can contact the participant for more information.

- If the interim adverse event might be a SAE, study staff will follow the same procedures as above.
- If the interim adverse event might be a non-SAE:
    - For pregnant and 6-weeks postpartum women, referral will <u>not</u> be initiated since these women are already under a health care provider's supervision.
    - For 6-12-18 months postpartum women, study clinicians will evaluate whether the event is a non-SAE requiring follow up depending on whether the event appears to be of a concerning and timely nature.
- If study clinicians find a SAE, they will complete a SAE form and will indicate that the information was obtained between data collection points.
- All study staff will be trained in identifying potential SAEs during non-data collection contacts and in and reporting SAEs following study procedures.

Participant Termination

At the end of the on-line Staff Review form, staff will indicate whether any reason for termination occurred. In case of termination an on-line Study Termination form will be completed by study staff, including the reason for the termination. If a participant withdraws from the study, the reason for withdrawal is recorded by the staff member.

<u>Procedures for Participant Referrals to Health Providers</u>

<u>Referrals will be done when participants report an adverse event at 6, 12, and 18 months postpartum that is not serious and for which they report not having sought medical attention.</u>

<u>If study staff or clinicians determine that the medical adverse appears to be of a concerning and timely nature for 6, 12, 18 months postpartum, a referral letter (see appendix) will be generated directing the participant to seek medical attention.</u>

<u>The referral letter will include the addresses of internal medicine and family practices clinics in case the participant does not have a primary care provider. Referrals may also be done when a participant has rapid weight loss (see page 32) and/or decreases to a low BMI (defined as less than 18.5 kg/m2). The alert values for rapid weight loss will come from the weight loss tracker and the alert values for BMI will come from the weight collection visit. An alert e-mail will be immediately generated to study staff and then the interventionist will contact the subject to discuss the weight loss/change in BMI and a referral will be initiated, if the criteria for referral has been met. The criteria for referral is</u>

three months in a row of a weight loss larger than 6% or who now have a BMI <18.5 and a starting BMI of at least 20.5. The interventionist will contact the participant within two weeks of the weight or BMI alert.

Safety alerts regarding weight loss or BMI that drops below 18.5

e-Moms of Rochester has two primary end points: appropriate weight gain in pregnancy and postpartum weight retention. It includes a different intervention for each time point and each will be discussed. During pregnancy and until 6 weeks postpartum, every research participant is in the care of a health care provider and women's weights for research purposes will be obtained from an audit of their medical records completed within 6 months postpartum. Weight gain is expected during pregnancy in order for a woman to have a healthy baby. Thus in our intervention features, we provide content and tools aimed at increasing weight gain for those who are gaining inadequately and slowing the rate of weight gain for those who are gaining excessively. Using data from the online weight gain grids, we will monitor the BMI-specific goal ranges for each trimester and shorter time intervals. Women are encouraged to enter their weights at each prenatal care visit, which is monthly up until 28 weeks, then every 2 weeks from weeks 28 to 36 and then weekly thereafter. We will use these time intervals for monitoring. When a woman enters a weight that indicates a weight gain outside the recommended range, the study website tells her she is "off track," to stay within the shaded area of the graph (i.e. the IOM recommended range), and why the adequate weight gain is important. Anytime a research participant logs into the e-Moms site, on her dashboard, she will see her progress on the Weight Gain Tracker and be informed of her status (i.e. "off " or "on track"). In addition, women are encouraged to view content (e.g. tips, articles, goal-setting) on the website that is appropriate for her weight gain status. Thus, the initial warning for weight gain that is outside the recommended range is built into the intervention.

We have defined two different safety alert levels for inadequate pregnancy weight gain for each of the 3 BMI groups using the 2009 IOM guidelines in determining minimal weight gain alerts for participants. For women in the first 28 weeks of pregnancy who have weight gains below the recommended range for two consecutive 4-week (month) intervals, the non-blinded interventionist will send a personalized e-mail encouraging them to gain weight within the range, refer to specific content on the project web site, and suggest the women talk over weight gain with their prenatal care provider at their upcoming regular visit. For the last 12 weeks of pregnancy, we will use any two consecutive entries for the alert level (two-week intervals and then one-week intervals). These will be reported to the DSMB as Level I Inadequate Weight Gain Alerts.

In addition, we will maintain and expand the original plan for safety alerts for women who have serious under-gain that reaches the small-for-gestational-age (SGA)-risk threshold. (The weight gain values for increased risk of SGA are show in Table 6 below.) For these women, the interventionist will go beyond the personalized e-mail alert and follow-up with a phone call and a referral letter to each woman indicating the need to discuss inadequate weight gain with her prenatal care provider. These will be reported to the DSMB as Level II Seriously Inadequate Weight Gain Alerts.

Table 6. Risk of SGA and associated weight gain values for level II safety alerts

BMI Group	Risk of SGA with Wt Gain in IOM Recommended Range (A)	Weight Gain Safety Alert Value (40 wk)	Risk at Alert Value (B)	Risk Ratio (B/A)
Normal	10%	15 pounds	15%	1.5
Overweight	2%	6 pounds	3%	1.5
Obese, class 1	10%	0 pounds	14%	1.4

Major weight loss occurring in a short amount of time may interfere with exclusive breastfeeding, especially in the first 6 months postpartum, therefore our intervention features will promote adequate, but not excessive rapid weight loss. After six weeks postpartum, for women in the intervention arm whose weight loss exceeds 6% of their previous weight based on weights reported within one month, our non-blinded interventionist will contact the research participant and inquire about the recent substantial, quick weight loss to determine if it is due to illness, if it is related to the study, or if it is purposeful. For subjects for whom there have been three months in a row of a weight loss larger than 6% or who now have a BMI <18.5 and a starting BMI of at least 20.5 then the subject will be directed to see a

health care provider. She will also be encouraged to take advantage of the available content on slowing the rate of excessive weight loss and given related advice about an appropriate increase in calorie intake and decreasing excessive exercise if these appear to be the reasons for the major weight loss.

Safety alerts regarding the depression scales

CES-D: A questionnaire for depression screening.

e-Moms participants will complete the CES-D online during pregnancy (baseline and 32-36 weeks gestation) and at 12 and 18 months postpartum. A program will be set up to generate an email alert to the study coordinator when responses to the CES-D have a score of 13 or greater suggesting symptoms compatible with depression. A letter from the study will go out to the respondent within 2 weeks of their data collection telling them that their answers to our survey suggests they may have symptoms compatible with depression, encouraging them to consult with their provider.

The Edinburgh Postpartum Depression Scale (EPDS):

This screening tool is a questionnaire validated for screening of major and minor depression. e-Moms participants will fill the EPDS on line during pregnancy (at 6 weeks and 6 months postpartum). A program will be set up to generate an email alert to the study coordinator when responses to the EPDS have a score of 10 or greater and/or the participant answers "yes" to question 10 indicating symptoms compatible with depression. A letter from the study will go out to the respondent within 2 weeks of their data collection asking them to consult with their obstetrician and primary care provider. If a participant answers 'yes, quite often' or 'sometimes' to question 10 of the EPDS (**the thought of harming myself has occurred to me: 'Yes, quite often'; 'Sometimes'; 'Hardly ever'; 'Never')** regardless of the total score (it could be less than 10), then the participant will receive a referral letter within a week.

Expected SAE

Expected SAE is one that is known to be associated with the intervention or condition under study.

Related to intervention

During pregnancy:

-Hospitalization for a musculoskeletal injury due to physical activity.

-Weight loss: A weight loss of more than 20% of a participant's pre-pregnancy body weight will be considered serious.

-Less than recommended weight gain during pregnancy: 1) for Obese, class I participants **0 pounds** of weight gain is associated with an increase in risk of SGA of 14% (10% risk within the recommended range) (74); 2) for Overweight participants **6 pounds** of weight gain is associated with an increase risk of LBW of 3% (2% risk with the recommended weight gain) (79, 80); and 2) for Normal BMI participants **15 pounds** of weight gain is associated with a risk of SGA of about 15% (10% risk for women gaining in the midpoint of the recommended weight gain) (77).

-Motor vehicle accident because of increased use of cell phones.

Postpartum:

-Hospitalization for a musculoskeletal injury due to physical activity.

-Weight loss: after six weeks postpartum, women in the intervention who exceed the 6% weight loss criterion in a single month or whose BMI drops below 18.5 (not including the 6-week time period in which the infant is delivered and body fluids lost. This is necessary to avoid defining all our women in our study who give birth as having an SAE.)

-Motor vehicle accident because of increased use of cell phones.

Related to condition

During pregnancy:

-Preeclampsia/Eclampsia: Obesity is a strong risk factor for this condition and may result in hospitalization
-Vaginal bleeding
-Preterm labor
-Rupture of membranes
-Gestational Diabetes
-Intrauterine growth restriction
- Congenital anomaly (e.g., heart defect, spina bifida)
-Placenta Previa
-Abruptio Placentae
-Miscarriage
-Stillbirth
-Preterm premature rupture of membranes
-Preterm delivery

Postpartum: the conditions below are associated with overweight obesity and could be an expected SAE if it meets the conditions for one (above)
Type II Diabetes
Hypertension
Gall bladder disease

Section 12: Power and Sample Size

A summary of sample retention overtime is presented in figure 6. There has been no substantial change in the number of births in Monroe County (the country in which Rochester is located) in recent years. In Rochester NY, there are approximately 10,851 births expected in 15 months of accrual according to 2007 Finger Lakes Perinatal Data System Data System (FLPDS). The accrual estimates provided by the FLPDS accounted for most of our eligibility criteria (ie, age 18-35, BMI 18.5-<35, without weight affecting conditions, delivering a full -term singleton birth at the 4 main Rochester hospitals). However, these estimates needed to be further adjusted downward (conservatively by 40%) to account for non-consent to participate, no access to the internet, and entering prenatal care after 20 weeks resulting in 5,765 women who are eligible for final screening and entry in to the study. **We plan to randomize a total of** 1,641 **eligible and consenting subjects in 15 months**. We also assume we will lose 15% of subjects post randomization but prior to delivery for women moving from the area, and very early miscarriage. This will yield 1395 women available at delivery for analysis of gestational weight gain. Subsequently, we estimate that we will have 40% attrition between delivery and 18 months postpartum yielding 837 women at the end of the study.

The study has **three primary hypotheses**:

H1: The proportion of women in the combined Intervention Groups 1 and 2 (receive same intervention during pregnancy) who gain more weight in pregnancy than is recommended by the IOM will be 10 percentage points lower than the proportion of women in the Control Group who gain excessively (45% vs. 55%).

H2a: The Control Group will have an at least 5 pound greater weight retention at 18 months postpartum than Intervention Group 1 (intervention curing pregnancy only).

H2b: The Control Group will have an at least 5 pound greater weight retention at 18 months postpartum than Intervention Group 2 (intervention during pregnancy and postpartum).

In the secondary hypotheses we hypothesize that Intervention Group 1 will have a greater mean postpartum weight retention at 18 months than Intervention Group 2. We hypothesize that the interventions will have a larger effect on each of the major study endpoints listed above in higher income compared to lower income and in normal weight compared to overweight/obese women.

Sample Size

While there are three primary hypotheses, the overall sample size is driven by the number of women who must be recruited and retained for the testing of the 18 month postpartum weight retention hypotheses above, H2a and H2b. Thus we begin the justification for the revised sample size and then present the sample size justification for the gestational weight gain hypothesis, H1, above. The significance level (2-sided) will be 1.66% (Bonferroni correction due to 3 primary comparisons in study).

Statistical Power **for Hypotheses H2a and H2b**

The mean difference in weight retention at 18 months postpartum which is important to detect between either of the two intervention arms and the control arm is 5 pounds (9 pounds in the control group vs. 4 pounds in an intervention group at 18 months postpartum). The standard deviation in postpartum weight retention is 16 pounds. The statistical power to detect this difference is set at 90%. These are justified in the following paragraphs.

Justification of Postpartum Weight Retention in the Control Arm. We arrived at 9 pounds of weight retention based on the following: The original, large cohort studies of postpartum weight retention found a mean weight retention of 1.5 kg or 3 pounds at 6 to 12 months postpartum (1, 10,11,13). More recent studies with more diverse samples of women have found much higher levels of weight retention (ranging from 6 to 17 pounds) at similar time points (22, 78-81). Very few studies have followed women with frequent weight measurements past 12 months after delivery. From the data in the newer studies, we estimate that the control group in e-Moms will have a mean weight retention of 9 pounds at 18 months postpartum. This value is the mean of the newer studies.

Justification of the Mean Difference between Control and Intervention Arms. A recent Cochrane review of rather intensive intervention studies aimed at postpartum weight loss show a mean difference between control and intervention groups of 2.89 kg or 6.36 pounds (26) at 6 to 12 months postpartum. While postpartum weight loss and weight retention are not measured in exactly the same way, Leermakers, Anglin and Wing (28) show that these are fairly similar so for the purpose of sample size calculation, the values for these terms can be used somewhat interchangeably. Based on this information, we define a **5 pound difference between control and intervention group** in weight retention at 18 months postpartum as meaningful and important to detect (9 pounds in the control group vs 4 pounds in an intervention group of weight retention at 18 months postpartum). This value is more conservative than the Cochrane review based on the nature of our less intensive interventions.

Justification for the Standard Deviation. Power for hypotheses H2a and H2b is calculated for a simple un-stratified t-test with equal sample sizes per group and a common standard deviation (SD). The recent literature shows the variation postpartum weight retention is large. It differs by gestational weight gain, BMI, income, and race/ethnicity of the sample, as well as, the postpartum time of measurement. In the more recent studies, the SD for weight retention at 6 to 12 months postpartum is a mean of about 11 pounds (22, 78-81). We expect that with our sample and the 18 month postpartum measurement time point (later than studies cited), our SD will be higher than 11. Thus in Table 7 below, we show SDs that range from 12 to 16. This is done in the spirit of being conservative in our sample size calculations. Table 7 shows the required number of subjects per arm given each of the three SDs and for three levels of statistical power.

Table 7. Required sample per arm for postpartum weight retention at 18 months with three SD and three levels of statistical power, total (Per arm)

	Total Subjects (Subjects/Arm) Required for Range of Statistical Power		
Estimated SD (lbs) / ES*	80%	85%	90%
12.0 / 0.42	369 (123)	414 (138)	474 (158)
14.0 / 0.36	498 (166)	561 (187)	642 (214)
16.0 / 0.31	651 (217)	729 (243)	837 (279)

* ES = Effect size, defined as difference in means / SD.

In the spirit of being conservative, we have selected the largest SD (16 lbs) and the highest level of statistical power (90%). Thus, we need 279 subjects in each of the 3 arms for a total of **837 subjects with measured weights at 18 months postpartum.**

We also estimate that 60% of the delivery sample will be retained at 18 months postpartum. The reasons for the 40% loss of sample include drop outs, loss-to-follow-up, and very importantly a second pregnancy within 18 months of the e-Moms delivery. We anticipate that in the Rochester study sample, this factor alone could account for one-fourth to one-third of women who are not retained.

Based on these assumptions and the sample size goal of 837 at 18 months postpartum for the second primary endpoint of weight retention, 1395 women will be needed in the delivery sample (1395 = 837 / 0.60 or, 465 in the control arm and 930 in the intervention arm). **This will require randomization of 1641 subjects** (1641 = 1395 / 0.85). Figure 6 shows the sample sizes and expected attrition across the study at the major data collection time points.

Statistical Power for Hypothesis 1

Because the absolute weight gain during pregnancy has a very different impact on the outcome of the pregnancy (both mother and child) depending on the initial BMI of the mother and given that IOM has established specific weight gain criteria based on initial BMI, the proportion of women who exceed the IOM criteria (Excessive gestational weight gain) is the best measure of the gestational weight gain outcome, rather than gestational weight gain measure in pounds as a continuous outcome. the Finger Lakes Perinatal Data system estimated the rate of excessive gestational weight gain for women age 18-35 without weight-affecting medical conditions (hypertension, diabetes) delivering full-term, singleton births in 4 main Rochester hospitals to be 55% in 2007. This is our expected control group rate.

Based on the sample requirements for the weight retention at 18 months postpartum endpoint and based on study attrition described in detail below, we expect to have in the delivery sample, 465 control subjects and 930 intervention subjects available for the analysis of excessive gestational weight gain in pregnancy. We will have 90% power to detect an improvement from 55% in the control group to 45% in the intervention group using a simple test of proportions at the 1.66% significance level (2-sided).We assume that 85% of the randomized sample will be retained at delivery. The 15% loss of sample is due to several reasons including miscarriages, fetal deaths, drop outs, medical charts unavailable for audit for gestational weight gain (GWG). Using study data on women who have delivered or are in the third trimester (thus at reduced risk of miscarriage), sample retention is 89%. With a potential additional loss of 2% in the third trimester, we expect an overall retention of 87% which is in line with the 85% estimate. The first primary endpoint, GWG, will be assessed in the delivery sample.

Sensitivity Analysis Accounting for Sample Attrition

The sample size calculations shown in Table 7 above assume that the estimated 40% of the delivery sample that is not available for the 18 month postpartum endpoint will have ignorable missing weight data. With this assumption, the estimates expected at 18 months among those observed are assumed to represent all those who started the postpartum intervention, not just those who finished. To explore the impact of this assumption on the power analysis, we have re-calculated the minimum detectable average weight retention and effect sizes assuming that the 40% of the delivery sample on the intervention arm follows the same distribution as the control arm (the sensitivity scenario in

Table 8). This is a very conservative scenario and coupled with a large proportion of subjects not retained, the power suffers. Thus, a modified scenario is also shown below where we assume that of the 40% who do not reach the 18 month weight assessment, half (20% of delivery sample) experience no effect of the intervention and are equal to the controls and half (20% of delivery sample) experience a partial effect with mean weight retention of 6.5 pounds. This would yield an average weight retention of 7.75 pounds among the drop outs on the intervention arm. With this small adjustment, there is now sufficient statistical power to detect an intervention effect with 82.5% power.

Table 8: Impact of sample attrition on statistical power with three different scenarios

		Original Scenario	Sensitivity Scenario	Modified Scenario
Control Arm	Observed	9 +/- 16 (n=279)	9 +/- 16 (n=279)	9 +/- 16 (n=279)
	Drop-out	(NA)	9 +/- 16 (n=186)	9 +/- 16 (n=186)
	Combined	9 +/- 16 (n=279)	9 +/- 16 (n=465)	9 +/- 16 (n=465)
Intervention Arm	Observed	4 +/- 16 (n=279)	4 +/- 16 (n=279)	4 +/- 16 (n=279)
	Drop-out	(NA)	9 +/- 16 (n=186)	7.75 +/- 16 (n=186)
	Combined	4 +/- 16 (n=279)	6 +/- 16 (n=465)	5.5 +/- 16 (n=465)
	Power	90% (delta=5)	67.7% (delta=3)	82.5% (delta=3.5)
	MDD* at 90%	5	3.86	3.86
	MDD/sd**	5 / 16 = .31	3.86 / 16 = .24	3.86 / 16 = .24

*Mean Detectable Difference (MDD)

**Mean Detectable Difference/Standard Deviation (MDD/sd)

Section 12 Addendum: Power and Sample Size for Hypothesis 2

Introduction and Hypotheses

Due to financial constraints, the original scope of the eMoms project needs to be revised. The primary endpoint for weight retention (WTR) will now be the 12 month postpartum time point, rather than the 18 onth postpartum time point. As the study is well into the data collection for the 12 months time point, the re-design of the project begins with a blinded summary of the new primary endpoint to inform the statistical power calculations which follow.

The study continues to have **three primary hypotheses**. The change in the primary endpoint related to the postpartum intervention does not effect in any way the statistical power and analysis plans for H1 related to the pregnancy intervention. At 12 months from delivery, it will be important to have sufficient power to detect an average difference in 4 pounds between the intervention and control arms.

H1: The proportion of women in the combined Intervention Groups 1 and 2 (receive same intervention during pregnancy) who gain more weight in pregnancy than is recommended by the IOM will be 10 percentage points lower than the proportion of women in the Control Group who gain excessively (45% vs. 55%).

H2a: The Control Group will have an at least 4 pound greater weight retention at 12 months postpartum than Intervention Group 1 (intervention during pregnancy only).

H2b: The Control Group will have an at least 4 pound greater weight retention at 12 months postpartum than Intervention Group 2 (intervention during pregnancy and postpartum).

Table 9. Summary of data as of January 3, 2014 (data available at the time report was prepared for the DSMB to make a decision about change of endpoint)

Subjects randomized (completed July 2012)	1689
Has not yet reached timepoint	4
Pending 12 mo weight	92
Missed 12 mo weight	536
Terminated from study prior to 12 mo	432
No weight obtained and past window	104
Obtained 12 mo weight	1057
Weight was obtained outside window	14

No measured anchor weigh (will be imputed in final analysis)	45
Currently evaluable for WTR at 12 mo	998
Mean WTR (STD) in pounds	3.74 (12.98)

The collection of 12 month weights continued until May 2014 and weights were ultimately collected from 1,167 women. As of January 3rd 2014, there were 1057 completed weights and 96 pending. Table 10 demonstrates that the study design is well powered to detect a clinically meaningful result should it exist.

Based on available data from the current study, the standard deviation for the power calculations in Table 10 below is estimated to be in the range of 13.0 to 15.0 pounds.

Justification for Expected Sample Size

A recent Cochrane review of rather intensive intervention studies aimed at postpartum weight loss show a mean difference between control and intervention groups of 2.89 kg or 6.36 pounds (26) at 6 to 12 months postpartum. While postpartum weight loss and weight retention are not measured in exactly the same way, Leermakers, Anglin and Wing (82) show that these are fairly similar so for the purpose of sample size calculation, the values for these terms can be used somewhat interchangeably. Based on this information, we define a **4 pound difference between control and intervention group** in weight retention at 12 months postpartum as meaningful. Our target difference is more modest than those proposed in Cochrane review to reflect the nature of our less intensive interventions.

The significance level (2-sided) will be 1.67% (Bonferroni correction due to 3 primary comparisons in study). The mean difference in weight retention at 12 months postpartum which is important to detect between either of the two intervention arms and the control arm is 4 pounds (for example, 6 pounds in the control group vs. 2 pounds in an intervention group at 12 months postpartum). The standard deviation for postpartum weight retention is estimated from current data to be in the range of 13 to 15 pounds. Table 10 illustrates the sample size required to detect a meaningful difference in weight retention, assuming a range of likely standard deviation estimates with a range of statistical power.

Table 10. Required sample per arm for postpartum weight retention at 12 months with three SD and three levels of statistical power, total N (per arm)

	Total Subjects (Subjects/Arm) Required for Range of Statistical Power		
Estimated SD (lbs) / ES*	80%	85%	90%
13.0 / 0.31	669 (223)	750 (250)	861 (287)
14.0 / 0.29	774 (258)	870 (290)	999 (333)
15.0 / 0.27	888 (296)	996 (332)	1146 (382)

* ES = Effect size, defined as difference in means (4 lbs) / SD.

Therefore, if the final standard deviation is less than 15 pounds then there will be sufficient power to detect a 4 pound difference between randomized groups with 90% power and the Bonferroni correction. If the final standard deviation estimate is 15 pounds, which does not seem likely given the current estimate, then the power will be between 85 and 90%, depending on the final number of weights measured.

Retention of Sample

eMoms randomized 1,689 subjects across 3 arms. Of these, 1,519 (90%) were not terminated during pregnancy and delivered a singleton. Currently, we have obtained valid 12 mo weights for 1,043 subjects (including those who will need an imputed baseline), which is 62% of the randomized sample and 69% of the delivery sample. This matches almost exactly the original estimate of retention at 12 months, which was 70% of the delivery sample. This rate is expected to be an accurate estimate for the remaining 96 pending subjects. Therefore, we would expect to obtain a total of 1109 valid 12 mo weights.

Sensitivity Analysis Accounting for Sample Attrition

The sample size calculations shown in Table 1 above assume that the estimated 30% of the delivery sample that is not available for the 12 month postpartum endpoint will have ignorable missing weight data. With this assumption, the

estimates expected at 12 months among those observed are assumed to represent all those who started the postpartum intervention, not just those who finished. To explore the impact of this assumption on the power analysis, we have re-calculated the minimum detectable average weight retention and effect sizes for the case where the standard deviation is 14 pounds and we have 333 subjects per arm under two hypothetical scenarios. First, we will assume a very conservative scenario where the 30% of the delivery sample on the intervention arm follows the same distribution as the control arm (the sensitivity scenario in Table 11). We also explore a modified scenario where we assume that of the 30% who do not reach the 12 month weight assessment, half (15% of delivery sample) experience no effect of the intervention and are equal to the controls and half (15% of delivery sample) experience a partial effect with mean weight retention of 4 pounds. This would produce an average weight retention of 5 pounds among the drop outs on the intervention arm. With this small adjustment, there is now sufficient statistical power to detect an intervention effect with 85% power.

Table 11. Impact of sample attrition on statistical power with three different scenarios

		Original Scenario	Sensitivity Scenario	Modified Scenario
Control Arm	Observed	6 +/- 14 (n=333)	6 +/- 14 (n=333)	6 +/- 14 (n=333)
	Drop-out	(NA)	6 +/- 14 (n=143)	6 +/- 14 (n=143)
	Combined	6 +/- 14 (n=333)	6 +/- 14 (n=476)	6 +/- 14 (n=476)
Intervention Arm	Observed	2 +/- 14 (n=333)	2 +/- 14 (n=333)	2 +/- 14 (n=333)
	Drop-out	(NA)	6 +/- 14 (n=143)	5 +/- 14 (n=143)
	Combined	2 +/- 14 (n=333)	3.2 +/- 14 (n=476)	2.9 +/- 14 (n=476)

**Mean Detectable Difference (MDD)*
***Mean Detectable Difference/Standard Deviation (MDD/sd)*

Section 13A: Analysis Plan for Hypothesis 1

Introduction

Treatment groups will be expressed according to randomization (intent-to-treat, ITT), regardless of the treatment received. Randomization is stratified by income (Medicaid eligible vs. not) and initial BMI (normal BMI vs. overweight or obese class I). All models discussed below will include the stratification factors as covariates.

Our study determines the primary outcome, excessive gestational weight gain, through a review of the medical charts. In the course or reviewing the charts, subjects were discovered to be ineligible for the protocol, with data contrary to the information available at randomization. Subjects who were discovered to be under age 18, or without a signed consent form, or a fraudulent (fictitious) subject, will not be included in any analyses. However, all other ineligible subjects who were randomized will be analyzed in the primary ITT analysis. A "modified-ITT" analysis will be conducted where only subjects who fit the target population will be included as a secondary analysis in the primary outcome paper.
As a preliminary step, the treatment groups will be compared on important demographic and biologic characteristics to verify that the randomization process was successful. These factors will specifically include age at delivery, smoking and parity. Although not anticipated, any imbalances in these important subject characteristics between randomized groups will be addressed in the models discussed below by also including these factors as covariates.

All primary analyses will be conducted using the SAS statistical software package. Assumptions for all statistical models, including the presence and impact of outliers, will be checked graphically using residual plots and other appropriate diagnostic methods available within SAS.

Hypothesis 1: Excessive **Gestational weight gain** [Primary Pregnancy Outcome Paper]
The primary outcome for the pregnancy intervention is gaining more weight than is recommended during pregnancy as established for each BMI group by the IOM. Gestational weight gain (GWG) is the difference in kilograms between the last measured weight taken prior to delivery and the first measured or imputed (baseline) weight taken in early

pregnancy (<=14 weeks gestation). Excessive GWG is defined as >35 pounds for normal weight women (BMI 18.5-24.9), >25 pounds for overweight women (BMI 25.0 – 29.9), and >20 pounds for obese women (class I: BMI 30.0-34.9).

A multiple logistic regression model that adjusts for possible correlation of subjects within clinic will be used to assess the effect of the pregnancy intervention on the odds of excessive gestational weight gain. The covariates included in the primary analysis besides randomized treatment assignment and the stratification factors will be baseline BMI (continuous) and (ultrasound adjusted) gestational age of the baby to account for differing pregnancy durations. Two additional covariates will be included to account for measurement time: (1) the weeks between the first pregnancy weight and the last pregnancy weight and (2) the weeks between the last pregnancy weight and delivery.

This project has 3 primary hypotheses. To protect the overall type I error rate to 5% for all 3 primary hypotheses, the significance level used for the arm comparison will be 1.67% (2-sided) using a Bonferroni correction.

Secondary analyses for the excessive GWG endpoint will build on the model described above by adding covariates including important demographic factors (smoking history, smoking in pregnancy, age at delivery, gender of baby, and parity), changes in physical activity during pregnancy, diet factors, and intervention intensity measures. Covariates which are determined to be distributed differently between randomized groups and possibly associated with gestational weight gain will be included. to further describe intervention effects and important subgroup effects, interaction terms will be included, particularly the interaction between the intervention main effect with BMI and income groups. This will be the formal assessment of whether the intervention effect varies by BMI and income. As is the standard in the literature for gestational weight gain analyses, a multiple regression model for continuous total GWG will be fit with the same covariates as the final model for excessive GWG to further understand the magnitude of effects of the pregnancy intervention. **In addition, we will examine whether the rate of GWG in the second and third trimesters was excessive when compared to the IOM guidelines for rate of weight gain by trimester using multiple logistic regression models similar to the method for excessive total gestational weight gain. All secondary models will use a two-sided significance level of 5%.**

Clinic Effects

Although the intervention is not delivered through the 38 OB clinics and practices where research participants received care, clinics may vary in the provided standard of care relating to weight gain in pregnancy or other unmeasured factors. Since randomization is being done at the level of the woman, not clinic, such factors will be balanced across the treatment groups with successful randomization. Nevertheless, correlation between subjects within and across treatment groups may exist due to the fact that patients are clustered within clinics. If this correlation is not taken into account, the variance for treatment comparisons may be underestimated, resulting in overestimation of the intervention effect. There are two main ways of handling correlated data in our analyses: explicitly modeling the random effects in a generalized linear mixed model (GLMM) or taking a generalized estimating equation (GEE) approach. Both methods permit one to account for correlation between weight outcomes within clinics, but through different methods. With GLMM, the correlation between outcomes is modeled explicitly and its level is directly quantified through introduction of model variance and possible correlation parameters. With GEE, one merely needs to adjust the standard errors of the estimated fixed effects (e.g. treatment) to account for the presence of correlation. GEE also requires one to specify a working correlation structure, the primary role of this specification being to reduce the variance of the estimated fixed effects (i.e., it is not used to quantify heterogeneity in the same way as GLMM). In this regard, the main advantage of GEE over a GLMM is that the treatment group comparison remains consistent when the working correlation structure is not specified correctly; whereas, inferences may be biased in a GLMM if the correlation structure is mis-specified in any way. In GEE, the resulting “population averaged” interpretation of the intervention effect also corresponds to the overall difference between intervention arms (83-86). Since the primary goal of this trial is to evaluate the overall impact of the intervention and not within-clinic differences, and because it relies on many fewer modeling assumptions, we intend to use GEE for the primary analysis. For comparative purposes, we also plan to conduct a secondary analysis of the data using an analogous GLMM that treats clinic as a random effect. The presence of substantial heterogeneity across clinics on excessive GWG will likely manifest itself through strong evidence of a

clinic-level variance component. In addition, we may also observe a larger estimated (within clinic) treatment effect. As indicated above, one possible interpretation of these results is that clinic-specific standards of care influence GWG levels in their respective untreated populations.

Secondary Outcomes in Pregnancy [Secondary Pregnancy Outcome Paper]

Continuous gestational weight gain will be analyzed in a repeated measures analysis to more precisely examine the trajectories of weight gain across pregnancy between treatment groups, but without incorporating the IOM guidelines. This model will also include initial BMI as a continuous covariate. As standard medical practice, women are routinely weighed approximately 2 times in the first trimester, 3 times in the second trimester and 7 times in the last trimester. We assume that weights measured across time on the same subject will be correlated. The correlation structure in the data will be handled with a linear mixed model approach with linear time and quadratic time (if necessary) expressed as continuous factors. Treating time as a continuous factor is natural given the large number of measurements over a short, 40 week, time period and given the expected pattern in weight gain over the majority of pregnancy. Between subject factors will include smoking, parity and randomized assignment. Net GWG, defined as GWG minus the weight of the baby, will also be analyzed as a secondary outcome, but is not assessed over time. Therefore, This analysis will be assessed analogous to the continuous total GWG analysis plan outlined above using multiple regression analysis.

Genetic Data

Statistical models for excessive gestational weight gain will focus on interaction of the SNP data with physical activity, while simultaneously adjusting for energy intake. We will also include the presence of this polymorphism in our intervention assessments to see if this genetic characteristic alters the effect of the intervention for some subgroups. Because the difficulty of replicating promising genetic associations is well-known and occurs for many possible reasons (82), we view these analyses as both hypothesis-generating and exploratory. Only subjects with genetic data and measured outcome will be included in these exploratory models.

Process Evaluation

We will tabulate the data collected on website usage for each treatment group. We will look at specific tools (notably the weight gain tracker, diet goal setting and self monitoring, and physical activity goal setting and self-monitoring) on the website to see if use is related to success. We will also measure overall intervention intensity initially by calculating the sum of times any feature or tool was viewed or used. This measure may be further categorized depending on the distribution. This index will help examine whether those subjects who appeared to be more engaged in the pregnancy intervention overall had less excessive gestational weight gain using simple logistic models with only these predictors (unadjusted assessment). The data describing the intensity of the intervention actually received will be added to our secondary analysis models for the primary outcome described above to assess the extent to which treatment arm effects are partially explained by including these specific or overall intervention usage variables.

Missing Data Imputation Plan

General EARLY Imputation Strategy

Preparing data for imputation. An inclusive strategy for considering candidate variables in the imputation model is generally considered favorable (87) as it can reduce estimation bias due to NMAR missingness and partially restore lost power. A list of candidate variables is presented for each imputation below. First we will examine the candidate variables for the imputation model by displaying the univariate distributions, degree of missing data, and inter-correlations between candidate variables. Variables that are redundant (ie, correlation >.8) with other candidate variables or binary variables that are highly imbalanced will be removed from consideration as these are anticipated to cause computational problems. Many estimation and imputation procedures for missing data assume multivariate normality, including the default methods in SAS Proc MI for data with arbitrary missingness patterns. Empirical evidence suggests that the results are often robust to this assumption provided the percentage of missing data is not too high.

Candidate variables will be transformed to aid this assumption. Continuous variables which are highly skewed will be transformed with a mathematical function. Each categorical variable will be made into (k-1) binary dummy variables, after first collapsing any very sparse categories to k levels. Binary variables will be handled as described in Graham (88). All dummy and binary variables will be coded 0 or 1 and no rounding will be used in this stage of the imputation.

Performing multiple imputation. Proc MI in the SAS statistical package will be used to generate the imputed data sets. The eMoms study expects, based on past studies, an important interaction between BMI, income, and intervention and accordingly stratified the randomization by BMI and income. Unless imputations are carried out with important interactions in the imputation model (or within strata), these interaction effects will be attenuated towards zero. eMoms will impute data within randomization strata. Next, we will check the pattern of missingness. We do not expect to observe a monotone or nearly monotone missing data pattern. In Proc MI, the default method for handling arbitrary missing data patterns (ie, non-monotone) is a Markov Chain Monte Carlo (MCMC) procedure. Specifically, we will be estimating the conditional distribution of the missing data given the observed data under an assumption of multivariate normality. We will begin by imputing 10 data sets, specifying 250 burn-in iterations and 250 iterations between imputed data sets. To determine if 10 imputed data sets are sufficient, we will examine the DF for the posterior parameter estimates. Allison (89) suggests all variables have a DF>100. Otherwise, there may be excessive variability among the imputations for that variable and the number of imputed data sets will be increased by 10 and the process repeated. The optimum number of imputations from a statistical power fall-off perspective is estimated to be higher than based on relative efficiency of parameter estimation (88).

Assessing the imputation process. After the imputation process, the following diagnostics will be examined. Trace plots and autocorrelation function plots of the "worst linear function of parameters" (90) will be examined. The WLFP has the highest asymptotic rate of missing information and converges most slowly among parameters. The absence of long term trends will indicate that the imputation has converged.

If all indicators are acceptable, the candidate variables which were initially transformed will be back transformed. For binary variables and dummy variables resulting from a categorical variable, the imputed value is rounded to the nearest value of zero or one. For categorical variables, Allison (91) suggests a fix when two or more dummy variables are rounded to one. In particular, he suggests assigning a 1 to the dummy value with the highest imputed value and reset all other dummy variables to zero.

Performing analyses using imputed data. Once the data sets are imputed, SAS Proc MIANALYZE will be used to combine the results within each data set in the standard way using Rubin's Rules. The primary analysis models are specified in the analysis plan.

<u>Specific eMoms Imputation Strategy for Pregnancy Intervention</u>

Excessive GWG is a binary outcome determined by comparing the full term gestational weight gain to the IOM guidelines, which vary by BMI category. Excessive GWG will be determined after missing gestational weights are imputed.

Gestational weights are obtained from an audit of the medical record. To calculate this measure, we need a measured anchor weight in the first trimester (<14 weeks gestation). The average weight gain during the first trimester is 2kg. We will take the first measured weight <14 weeks gestation as our anchor weight. Currently, 6% of 752 chart audits completed are missing a measured anchor weight. Currently, the measured anchor weight is taken on average at 8 weeks gestational age. We also need a late pregnancy (>=37 weeks) weight measurement to assess the full-term gestational weight gain. Full-term gestational weight gain is the difference in the last pregnancy weight taken at least 37 weeks gestation minus the anchor weight. Currently, 17% of chart audits are missing this weight, including subjects who miscarry, have fetal loss, premature deliveries, or withdraw from the study. On average, there are 12 (25%ile=11,75%ile=14, max=28) weights collected per subject from the medical chart.

The table below lists the candidate variables which will be used in the imputation model. Candidate variables include all variables that may be used in the analyses, including outcome, covariates, design variables, and variables

which predict missingness. Some of the candidate variables may themselves have missing data. These will all be imputed simultaneously. At least ten imputed data sets will be created, but likely more will be required.

Table 12. Pregnancy Intervention: Candidate variables for imputation model

Within 4 Imputation Strata Defined by BMI & Income Level at Randomization:

Factor	***coding***
Intervention assignment	0/1 = intervention
Anchor weight	continuous
Gestational age of anchor WT	2-14
Last WT in pregnancy	continuous
Gestational age of last WT	37-42
Avg WT (GA <14)	continuous
Avg WT (GA 14-18)	continuous
Avg WT (GA 18-22)	continuous
Avg WT (GA 22-26)	continuous
Avg WT (GA 26-30)	continuous
Avg WT (GA 30-34)	continuous
Avg WT (GA 34-37)	continuous
Avg WT (GA 37-44)	continuous
Measured BMI in first trimester	continuous
Maternal age at randomization	continuous
Marital Status	0/1 = cohab or married
Parity	0/1 = 1 child
(Baseline = nullipar)	0/1 = 2 or more children
Race	0/1 = only black race
(Baseline= white only)	0/1 = multi or other, I, P, A
Hispanic ethnicity	0/1
Education highest level	0/1 = not a HS graduate
(Baseline= HS grad)	0/1 = more training after HS
	0/1 = college grad or more
Employed at T1	0/1 = yes
Smoking status in pregnancy	0/1 = smoked in pregnancy
Depression CESDS	continuous
Termination reason in pregnancy	Refused, moved, multiples
(Baseline =not terminated)	Preg <28 weeks
Total Mets from PPAQ at T1	Continuous, log-transformed
Sugar sweetened beverage consumption at T1/T2	Continuous, log-transformed
Fast food frequency at T1/T2	0/1 = 1 / month
(Baseline=never)	0/1 = 2-3 / month
	0/1 = 1-2 / week
	0/1 = 3+ / week
Baby's BWT	continuous
Gestational diabetes	0/1 = yes

Censored Data. As part of the EARLY Network, this study will censor all weights after the following events: bariatric surgery occurring while a study participant and limb amputation. Weights following these events will not be imputed using the methods described above according to the EARLY guidelines approved by the DSMBs. Missing weights in pregnancy due to termination from the study for any reason including miscarriage, pre-term delivery, and withdrawal will be imputed as described above.

NMAR sensitivity analysis The primary reasons for missing gestational weights relate to miscarriage, premature delivery and withdrawal and occur on both arms. A benchmark analysis will be conducted where we assess in a very simple way the impact on treatment comparisons by making the assumption that all subjects on either arm who are missing an estimate of gestation weight gain are assigned the average mean GWG observed on the control arm. This is equivalent to a single mean imputation with the assumption that those on the intervention arm who are missing the outcome experienced no benefit from the intervention. The treatment mean estimates and standard errors will be compared descriptively to those estimated from the primary analysis described above. We predict that the difference in mean GWG by intervention will be smaller, and that the variance estimates will also be smaller. Our approach is consistent with what the EARLY Design and Analysis Subgroup is preparing to suggest to the EARLY Steering Committee and the EARLY DSMBs as a common approach across EARLY Trials.

Section 13B: Analysis Plan for Hypotheses 2A and 2B

Primary Analysis for Weight retention at each time point postpartum is defined as the difference in the measured weight at these times minus the anchor weight in early pregnancy. Weight retention will be measured at 6 weeks, 6, 12 and 18 months postpartum with the 12 month measure as the primary endpoint. We assume that weights measured across time on the same subject will be correlated. The correlation structure in the data will be handled with a generalized estimating equations approach, unless significant clinic effects indicate the mixed model approach, as discussed above.

The primary analysis model will contain the factors time, randomized treatment, income strata at randomization and baseline (early pregnancy) BMI as a continuous covariate (rather than BMI strata). Given only 4 time points across 18 months postpartum follow-up, time will be treated as a categorical factor rather than making assumptions about the functional form of weight retention over time. Weights measured within 3 weeks of the 6 weeks time point and within 6 weeks of any subsequent time point will be considered to be representative of that time. Otherwise, the weights will be considered missing and imputed (see below). Randomized treatment assignment will be included in the model as two dummy variables representing the effect of the two intervention arms versus control. The test of Hypothesis 2A and 2B will be treatment contrast of weight retention at 12 months.

A secondary model will include main effects for randomized treatment (2 dummy variables for interventions), time (4 categorical times), income (low vs high), BMI group (normal vs. overweight or obese) plus all interaction terms. The three-way interaction between each intervention main effect with BMI group and income main effects will indicate if the effect of the interventions was different for the four BMI / income combinations on average over time. The four-way interaction terms of BMI group x Low income x Treatment dummy x Time will indicate whether the intervention groups had a significantly different pattern of weight retention across time depending on the BMI / income group. If a four-way interaction is significant, we will use contrasts to compare changes in mean weight retention at each time point between treatment groups within analysis subgroups to further characterize the differences detected by the overall test.

Secondary Aims <u>for Weight Retention</u>

Two secondary binary outcomes in the postpartum period will include returning to early pregnancy weight and retaining >5 pounds or more (excessive weight retention) after 12 months. The effect of the intervention on weight

retention at 18 months will also be examined. We will examine these outcomes following the general outline above for continuous weight retention, using logistic regression models.

The proposed study will produce a rich data resource to *explore many important ideas related to additional treatment group contrasts, other weight endpoints, and the behavioral and biological moderators and mediators through which the online interventions may exert an effect on the weight outcomes.* The main foci for the latter will be physical activity, diet quality, breastfeeding (initiation and intensity), smoking (change in status at each time point), and intervention usage. First, we will assess whether these domains significantly differ by randomized arm; that is, using them as the outcomes. Then, change in physical activity and change in diet domains will be calculated over time points corresponding to the weight measurements. Adding these factors to the models described above as main effects (possible mediator for intervention effect) or interaction terms with treatment arm (effect moderators), and with BMI and income will assess whether the effect of the intervention may operate through these changes in behavior or modify the effect of the intervention.

Genetic Data Statistical models for these outcomes will focus on interaction of the SNP data with physical activity, while simultaneously adjusting for energy intake. We will also include the presence of this polymorphism in our intervention assessments to see if this genetic characteristic alters the effect of the intervention for some subgroups. Because the difficulty of replicating promising genetic associations is well-known and occurs for many possible reasons (82), we view these analyses as both hypothesis-generating and exploratory.

Process Evaluation We will tabulate the data collected on website usage within BMI and income sub-groups, as well as for each of the treatment groups. At the end of the study, we will examine whether those subjects who appeared to be more engaged in the intervention according to these measures had better weight outcomes. Finally, the data describing the intensity of the intervention actually received will be added to our primary analyses to assess the extent to which treatment arm effects were partially explained by including these specific intervention usage variables. These data will also be used to conduct a Social Network Analysis, which may be informative in analyzing weight gain in groups of women, particularly in the context of Christakis & Fowler's (92) work suggesting that obesity tends to occur in clusters of socially linked individuals.

Missing and Incomplete Data

Missing data will be addressed using multiple imputation in a manner consistent with the plan outlined for the gestational weight gain outcome.

Censored Data

As part of the EARLY Network, this study will censor all weights after the following events: bariatric surgery, limb amputation, and subsequent (second) pregnancy. These weights will not be imputed using the methods above. We expect the incidence of these events to be small and not impact our analysis plans in any significant way.

Section 14: Data Management

Data Confidentiality

Cornell University and the two organizations whose services have been secured for (1) online data collection and management and (2) website development and data storage are responsible for all aspects of data processing and storage. The University of Rochester is responsible for management and storage of the DNA samples that will be collected for this project. All the organizations are fully qualified for their roles and are compliant with HIPAA guidelines for patient privacy and data security involving storage and remote access to electronic personal health information. The vendors whose services have been secured for this project will comply with data security standards as they evolve across the time of this project.

In addition, the following steps will be taken to protect the anonymity of research participants and confidentiality of data:

a) Staff members will not be allowed to abstract data, interview a subject, or process data from a subject that they know personally.
b) Identification codes rather than names will be used on the data collection forms.
c) The Cornell PI will assure that online survey practices adhere to the provisions of the US Privacy Act of 1974 with regard to surveys of individuals for the Federal government.
d) The information that is made public will be limited to the numerical values and statistical summaries.
e) Information linking identification codes with individual names will be only available to the PIs and study staff who contact participants.
f) Although the vast majority of the data will be collected online, in some rare instances, data may need to be collected through paper forms. In that case, data collection forms will be stored in a locked drawer in the Study Coordinator's office space.
g) Data collection forms and other project forms will be shredded when they are no longer relevant.
h) Sensitive data will not be sent via email.
i) DNA will be identified by code only and stored in a secured laboratory.

The following measures will be taken related to the project website to ensure data security:

1. The site and its data will be **hosted** on Amazon's Web Services and either Amazon S3 or Amazon EC2 will be used and both provide very high security and guarantee over 99.95% service uptime and are fully HIPAA compliant.

2. Any or all **web communication** can be transmitted using Transport Layer Security/Secure Socket Layer (TLS/SSL). Sensitive procedures on the site such as sign up, sign in, and any data collection will use secured communications.

3. **Passwords** are stored using industry-standard best-practice hashing techniques; currently, that means using SHA-512. This makes the password values irreversible so there is no way to acquire the password from the stored value. Passwords are also never sent via email. In the case of a forgotten password, we use a password-reset process that utilizes the email address used by the account holder during signup. Our vendor also ensures that password values are not entered in any server or application log in plain-text.

4. Any **sensitive information** that is stored on the server will be encrypted using appropriate techniques for the needs of accessing that information. This information can be divided into two distinct groupings: information that the needs to be accessed by the site, and information that does not. Information that needs to be accessed by the site might be private information that the user or study staff can change, such as any current medical conditions. Information that does not need to be accessed by the site might be the user answering a survey question. For the most part, this applies to user-specific, identifiable information, but the decision of how to treat any particular piece of information can be handled on a case-by-case basis.

-If the site does need to have direct access to some sensitive user-submitted information, we will use symmetric encryption.

-User-submitted information that the site does not need to have direct access to will be encrypted using an asymmetric key system. This means that the web application will encrypt the information using a public key, and a complementary private key will be needed to decrypt the information. Access to the private key can be restricted to as few people as necessary.

5. Each data entry through an online survey is directly stored in a secure database where transactions are backed up several times daily to minimize the possibility of data loss. All data sent between a subject's computer and the study web server uses Transport Layer Security encryption of the same grade used in online

banking. All servers are hosted in a Cornell Information Technologies datacenter employing uninterruptible power supplies, environmental controls for heat, cooling, and humidity, and 24/7 monitoring by the campus network operations center.

Data Analysis

A plan for the manuscripts to be written will be developed; authorship and order of authors will be discussed and agreed upon prior to the analysis of data and writing of manuscripts at regular project staff meetings. Authorship will follow a well-understood standard of authorship and that is substantial intellectual contributions to the work presented.

Data Release

The data management/analysis team will prepare and distribute a dataset to NHLBI via the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). The data release documentation provides detailed, organized documentation of the study and study variables.

Section 15: Trial Organization

This project is directed by multiple principal investigators (PIs). For Phase 1 of the project (formative research for intervention development), Dr. Olson serves as the Principal Investigator, while Dr. Fernandez serves as the Principal Investigator for Phase 2 (randomized clinical trial-RCT). Dr. Olson serves as the point of contact for the funding agency.

Governance and Organizational Structure: The governance of the overall project is shared among the multiple Principal Investigators. On July 18, 2013, Drs. Eva Pressman of the University of Rochester and Dr. Patrick Stover joined the team as additional PIs. The specific leadership roles are divided primarily between the four PIs based on the phases and functions of the project.

For the RCT, Dr. Olson and the Cornell-based staff are responsible for the development and implementation of the interventions and the online survey data collection. The intervention development group at Cornell includes faculty and students from the Department of Communication and the Division of Nutritional Sciences. Bi-weekly study meetings are led by Dr. Olson. Meredith Graham serves as the Cornell-based Study Coordinator for the formative research leading to intervention development. She is the primary contact for the incentive processing entity, the website developer and for the ASA-24. Myla Strawderman is the primary contact for the Survey Research Institute at Cornell that is programming and hosting the online surveys.

For the RCT, Dr. Fernandez and the Rochester-based staff are responsible for recruiting participants and implementing the RCT, designing and implementing the medical chart audit data collection, and monitoring and reporting participant safety. Dr. Groth is responsible for the genetic sub-study and Dr. Fernandez is responsible for the physical activity calibration study. Jennifer Reschke is the Study Coordinator for the RCT. She will supervise the study recruiters and medical chart auditors.

The data analysis for the RCT will be done by the biostatistician based at Cornell University, Myla Strawderman. Dr. Olson is this individual's supervisor but the data analysis plan was developed by the research team and Drs. Fernandez, Olson and R. Strawderman will provide leadership and supervision for this aspect of the project.

Communication and Scientific Decision Making: Monthly face-to-face and conference call meetings with co-investigators, the biostatistician, research staff, and graduate students are held. These meetings are used to discuss recruitment, data collection, data analysis, budgetary issues, future projects and overall progress on the project. The agenda is set with input from co-investigators and staff and distributed to the team prior to each meeting. Decisions are reached by consensus. We expect that as the project progresses, the agenda for meetings will expand to include presentation of findings and scientific issues that have arisen in the course of the research.

Conflict Resolution: In the event of unforeseen circumstances that alter the course of the project or its deliverables, Pressman and Stover will work together and with the other PI at their respective institutions to modify the course of the project to maximize the scientific impact and value of the project. Regarding disputes, as noted above, the new PIs will work out all arrangements, collaborations, representations, and decisions for the project in consultation with their respective institution's PI. Disagreements, if any and including manuscript authorship, will be resolved between the new PIs and their respective institution's PI, and then resolved between the newly appointed PIs. In the event that the new PIs cannot reach consensus, the Rochester Dean for Research and Associate Vice President for Research and the Cornell Senior Vice Provost for Research and Associate Vice President for Research Administration will intercede and make the final decision.

Budgetary Administration: The award comes to Cornell University and allocated according to the budget for each group. Overall budget and financial management is done by the appropriate administrators at Cornell University, including the Grants and Contract Administrator in the Division of Nutritional Sciences. A subcontract was awarded to the University of Rochester for its portion of the budget. Dr. Olson working with her Grants and Contract Administrator oversees the Cornell component of the budget and Dr. Fernandez working with the Department of Community and Preventive Medicine grant administrator oversees the University of Rochester component of the budget.

Section 16: Timeline of Trial

Figure 7: Timeline of Trial*

					Year 2				Year 3				Year 4				Year 5				Year 6			
Activity (by quarter)	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Phase 1																								
Pregnancy Intervention																								
Postpartum Intervention																								
Recruitment																								
Deliveries																								
Pregnancy Intervention																								
Postpartum Intervention																								

*Start date August 2009

Section 17: References

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APPENDIX

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Consent Form

Study Title: **eMoms Rochester**

Principal Investigators:

Christine Olson, PhD; Cornell University Division of Nutritional Sciences

Diana Fernandez, MD, MPH, PhD; University of Rochester Department of Community and Preventive Medicine

Introduction

We would like to invite you to participate in a research study. This consent form describes the eMoms of Rochester research study and what to expect if you decide to participate. You are encouraged to read this consent form carefully. You should ask the person who presents it any questions you have before deciding whether or not to participate.

Dr. Diana Fernandez from the University of Rochester and Dr. Christine Olson from Cornell University are conducting this study. We are asking you to participate in this study because you are pregnant and plan to deliver your baby at Strong Hospital, Rochester General Hospital, Highland Hospital, or Unity Hospital.

Purpose of Study

The purpose of the study is to evaluate the use of electronic communication tools including an interactive website and cell phones to promote healthy lifestyles during and after pregnancy. The goal is to help women have healthy pregnancies by developing and maintaining healthy habits during and after pregnancy. Areas of focus include nutrition, physical activity, sleep/rest, hydration, harmful substances, stress management, and infant care and feeding.

Description of Study Procedures

This study is a randomized controlled trial, which means that you will be chosen by chance to be in one of three groups. What you receive for the intervention and when you receive it will differ depending on the group you are in.

If you decide to participate in this study, you will be asked to complete study activities from now until 18 months after you deliver your baby. These activities are: (1) Logging into the password-protected website with your assigned password and participating in the activities that you find there, and (2) Completing 2 online questionnaires while you are pregnant and 4 online questionnaires after you deliver your baby.

Allow the research team to access your medical record information through your 6 weeks postpartum visit and your child's delivery medical record information.

- You may be asked to participate in social networking with other women involved in the study. An example of social networking is a blog, where participants can share opinions and discuss various topics on the study website once approved by study moderator.
- Meet a member of the eMoms study team at your pediatrician's office 6 months, 12 months, and 18 months after delivery to measure and record your height and weight.
- Communicate with study staff through the website, emails, text-messages, and/or phone.
- You will be asked to give a sample of your saliva (spit) in a plastic container at the beginning of the study. The DNA in your saliva will be used to look at a gene(s) that might be related to pregnancy weight gain. Pregnancy weight gain

might be different depending on the form of the gene(s) a person has. We do not expect to discover any information that will affect your care or treatment while you are pregnant and are not testing for genetic diseases like the BRCA gene for breast cancer. There may be leftover DNA samples after all of the testing is complete. You can indicate at the end of this form if you want your leftover specimens to be available for future research. We do not have specific research plans at this time, but would use the samples for studies related to pregnancy or health and disease in women. We will store your sample in a secure place and your name and other information will be kept separate from the sample. We will keep the files that link your name to the code number in a locked cabinet. Future research using these samples will not involve testing for specific genetic diseases. If there is a future study that may involve any form of genetic testing for a specific disease it will require you to sign a separate consent form.

- You can only take part in the study one time.

Number of Subjects

There will be nearly 1600 pregnant women taking part in this study.

Risks of Participation

There are minimal risks to taking part in this study.

- There is a small risk of psychological distress if it disturbs you to complete on-line questionnaires about yourself and your pregnancy or you have fears of what might be done with your DNA. These risks are minimal because the questions are not anticipated to cause any distress and can be left blank if you are uncomfortable answering them. All possible precautions are in place to protect the DNA samples we collect from you. In addition, all data will be reported in group format, and no individuals will be identified.
- Your participation in the online surveys and website activities presents no greater risk than everyday use of the internet. If you participate in social networking and wish to remain anonymous, you should not include any personal, identifying information on the study website.
- Please note that e-mail communication is neither private nor secure. Though the study is taking precautions to protect your privacy, you should be aware that a third party could read information sent through e-mail.
- There is a small risk of gallstones from rapid weight loss. Since this study seeks to help women have a healthy pregnancy and be healthy after delivery, rapid weight loss is not anticipated.

Benefits of Participation

You may or may not benefit from being in this research study.

Sponsor Support

The University of Rochester and Cornell University are receiving funds from the National Heart, Lung, and Blood Institute, part of the National Institutes of Health, to conduct this study.

Costs

There is no cost to you to participate in this research study.

Payments

In return for your time and effort, you will receive up to $140 dollars for participating in this study and completing the 6 surveys during the 2-year period. Your name will be entered into drawings for additional prizes if you complete all questionnaires and weight collections; these drawings will be held at the end of the study and will consist of 100 winners of $150 in gift cards. Your payment will be withheld if it is determined that you have completed the on-line screening information more than one time.

Circumstances for Withdrawal

You will be withdrawn from the study if any of the following occur:

- a second pregnancy during the time you are enrolled,
- the ending of your current pregnancy at less than 28weeks gestation,
- you find out that you are expecting multiple babies (twins or more), you have bariatric surgery or limb amputation,

- if the study team determines that for any reason your safety or the scientific integrity of the study will be compromised by your continued participation in the study.

By signing this consent form, you agree to submit and post truthful and accurate answers and information about yourself and anyone else on the eMoms of Rochester Study website, surveys, or over the telephone.

Confidentiality of Records and HIPAA Authorization

While we will make every effort to keep information we learn about you private, this cannot be guaranteed. In some cases, your information could be reviewed by representatives of the University, the Data Safety Monitoring Board, the Research Coordinating Unit, NHLBI, or Cornell University for purposes such as quality control or safety. Results of the research may be presented at meetings or in publications, but your name will not be used.

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires us to get your permission to use your health information that we either create or use as part of the research. This permission is called an Authorization. We will use research record, related information from your medical records, results of genotyping, and both clinical and research observations made while you take part in the research, survey forms, questionnaires, and interview information.

We will use your health information to determine research results and possibly to develop new interventions. Health information is used to report research results to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies and study plans. Strong Health policies let you see and copy health information after the study ends, but not until the study is completed. If you have never received a copy of the Strong Health HIPAA Notice, please ask the investigator for one.

To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: The University of Rochester; the Department of Health and Human Services; National Heart Lung and Blood Institute, Cornell University, and the Research Coordinating Unit.

If you decide to take part, your Authorization for this study will not expire unless you cancel (revoke) it. The information collected during your participation will be kept indefinitely. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, you will also be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information as stated above.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing without your consent, information that would identify you as a participant in order to prevent serious harm to you or others. However, no voluntary disclosures will be made.

Your authorization for the use and disclosures described in this Data Privacy Statement (DPS) does not have an expiration date. You have the right to see and copy your personal health information related to the research study for as long as this information is held by the study doctor/investigator or the University of Rochester. However, to ensure the scientific integrity of the study, you will not be able to review some of the study information until after the study has been completed.

Contact Persons

For more information concerning this research, or if you feel that your participation has resulted in any emotional or physical discomfort, please contact:

I. Diana Fernandez, MD, MPH, PhD at 585-275-9554, Diana_fernandez@urmc.rochester.edu or Jennifer Reschke at 585-273-5554, Jennifer_Reschke@urmc.rochester.edu at the University of Rochester.

Christine Olson PhD, at 607-225-2534, cmo3@cornell.edu or Meredith Graham at 1-866-361-4600, mlg22@cornell.edu, at Cornell University.

If you have any questions about your rights as a research subject, or have any concerns or complaints you may contact the Human Subjects Protection Specialist at the University of Rochester Office for Human Subject Protection, Saunders Research Building, 265 Crittenden Blvd., Box CU420628, Suite 1-250, 14642, (585) 273-4127, for long-distance you may call toll-free, (877) 449-4441. You may also call this number if you cannot reach the research staff or wish to talk to someone else.

Voluntary Participation

Participation in this study is voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner. You may choose to withdraw your saliva samples at a future date and your samples will be destroyed at that time.

Please check the appropriate box beside each statement you agree with:

1. ( ) **yes** ( ) **no** **I agree to provide a saliva sample from which DNA can be extracted**.

2. ( ) yes ( ) no I agree to allowing my DNA to be stored and used for future research that does not involve testing for genetic diseases.

3. ( ) yes ( ) no I agree to allowing other researchers to have access to the de-identified data from my DNA.

4. ( ) yes ( ) no I agree to be re-contacted by the research team for future study activities with this research study.

Signature/Dates

Subject Consent
I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

Study Subject: _____ Print Name

Study Subject: _____ Signature

_____ Date

Person Obtaining Consent
I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. The subject was given an explanation of the research and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

_____ Print Name and Title

_____ Signature

_____ Date

Dear (subject name),

I am the study interventionist for e-Moms of Rochester and noticed that you have (lost some weight since entering the study OR not gained the recommended amount of weight during the last month). [Customized advice related to type of inadequate Gestational Weight Gain] Weight loss during the first trimester due to nausea and vomiting is not uncommon, but we just want to make sure that you are aware of this OR Gaining just a little bit below the range is not a need for major concern, but we just want to make sure that you are aware of this.

Remember for your body size, you will want to gain between (25-35 pounds OR 15-25 pounds OR 11-20 pounds) during this pregnancy and since you are now in your (second OR third) trimester you will want to increase how much you eat. Please let me know if you have any questions about weight gain during pregnancy.

You should eat about (300-350 extra calories per day OR 350-400 extra calories per day OR 350-450 extra calories per day) during this trimester. Below is a long list of (300-350 calorie OR 350-400 calorie OR 350-450 calorie) food combinations that you could consider adding to your diet:

(Insert list of appropriate food combinations)

We realize that your prenatal care provider is likely tracking your weight, but we just want to make sure you have a healthy pregnancy.

Please let me know if you have any questions or concerns.

Thanks,

Meredith

Meredith Graham
Study Coordinator
e-Moms of Rochester Healthy Pregnancy Study
www.emomsroc.org
admin@emomsroc.org
1-866-361-4600

Department of Community and Preventive Medicine

Dear [subject name],

We would like to thank you again for your participation in the e-Moms of Rochester study. Your participation in our study will directly contribute to a better understanding of how we can make pregnancy and postpartum healthier.

We are writing to you because in the latest questionnaire you filled in, your answers to the questions about depression suggest you have symptoms compatible with depression. It is not uncommon to become depressed during or after pregnancy. Being depressed not only affects you but it can also affect your baby. You do not have to suffer because there are treatments for it. We strongly encourage you to follow-up with your obstetrician and/or your primary care physician. In the event that you do not currently have a primary care physician, the following clinics can be contacted for primary care appointments:

Contact information for: 1) the participant Ob; and 2) the primary care clinic according to the hospital they are affiliated to.

Additional resources:

- St Joseph's Neighborhood Center
  417 South Ave, Rochester, NY 14620
- Lifeline number 275-5151
- Catholic Family Center 546-7220

You could find helpful information in the website of the National Women's Health Information Center http://www.womenshealth.gov/mental-health/ and for Postpartum Support International http://www.postpartum.net/Get-the-Facts.aspx

If you have any questions or concerns, please feel to contact the study coordinator, Jennifer Reschke(273-5554, jennifer_reschke@urmc.rochester.edu), or the lead investigator of the study, Dr. I. Diana Fernandez (275-9554, Diana_fernandez@urmc.rochester.edu).
This research would not be possible without participants like you. Again, we appreciate your commitment to our study.

Sincerely,

I. Diana Fernandez, MD, MPH, PhD and the eMoms Study