STUDY PROTOCOL

UPBEAT

UK Pregnancies Better Eating and Activity Trial

Guy's and St Thomas' Hospital NHS Trust

National Institute for Health Research

Title

Short Title	**UPBEAT**
Aim	The aim of this study is to determine whether an intervention focused on reducing the glycemic load and increasing physical activity in obese pregnant women leads to a reduction in gestational diabetes mellitus and a lower risk of delivering a large for gestational age infant.
Co-Sponsors	Guy's and St Thomas' NHS Foundation Trust & King's College London Research Governance Office 16th Floor, Tower Wing Guy's Hospital London SE1 9RT
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Chief Investigator	Professor Lucilla Poston
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Protocol amendments

Protocol version	Date	Reason for update	Substantial amendment number	Summary of changes
1	March 2009	Submitted to ethics	NA	Initial protocol for phase 1
1	07th September 2009	Intervention development phase commenced	1	Phase 1 participants recruited to complete questionnaires and assess appropriateness of developed intervention
3	24th September 2010	Staff training regarding measurement of neonates and 6 month olds	3	Permission is sought from the mothers of non-study babies for carrying out anthropological assessment using tapes, skin calipers and PeaPod technology as initial training and ongoing inter-observer validation studies throughout the duration of UPBEAT.
3	25th May 2011	Conclusion of pilot trial, Phase 3: Multicentre RCT	4	Lifestyle questionnaires removed. UPBEAT EXTRA – 1:15 recruits randomly selected at visit 1 to give additional dietary information. For all recruits: accelerometry removed Removal of RPAQ to be replaced by shorter IPAQ Food frequency questionnaires to be replaced by shortened version with ethnically diverse foods. Introduction of binge eating screening questionnaire.

Protocol Amendments

5 (*version 4 omitted from sequence)	October 2011	Re-introduction of accelerometry in UPBEAT-EXTRA and all women in Newcastle/Sunderland	5	All women in Newcastle and Sunderland and in all centres 1:15 women randomised to UPBEAT EXTRA will be asked to wear an accelerometer on 2 occasions in pregnancy (baseline and 28 weeks) and at 6/12 postnatal follow up visit.
6	8th May 2012		6	Addition of NVQ screening and interview substudy. Addition of ultrasound scan to assess fetal growth at 28 week appointment Permission to reconsent women who withdraw in pregnancy for 6 month follow up Addition of placental collection. Permission to contact women at 4 months postnatally, send birthday cards to the children aged 1 and set up a facebook page for the women to join postnatally.
7	June 2012	Publication of protocol on website	7	
8	Xth August 2012	Amalgamation of visits 1 and 2.	8	

Protocol Approval

ISRCTN 89971375

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Local PI Acknowledgement

_____ _____
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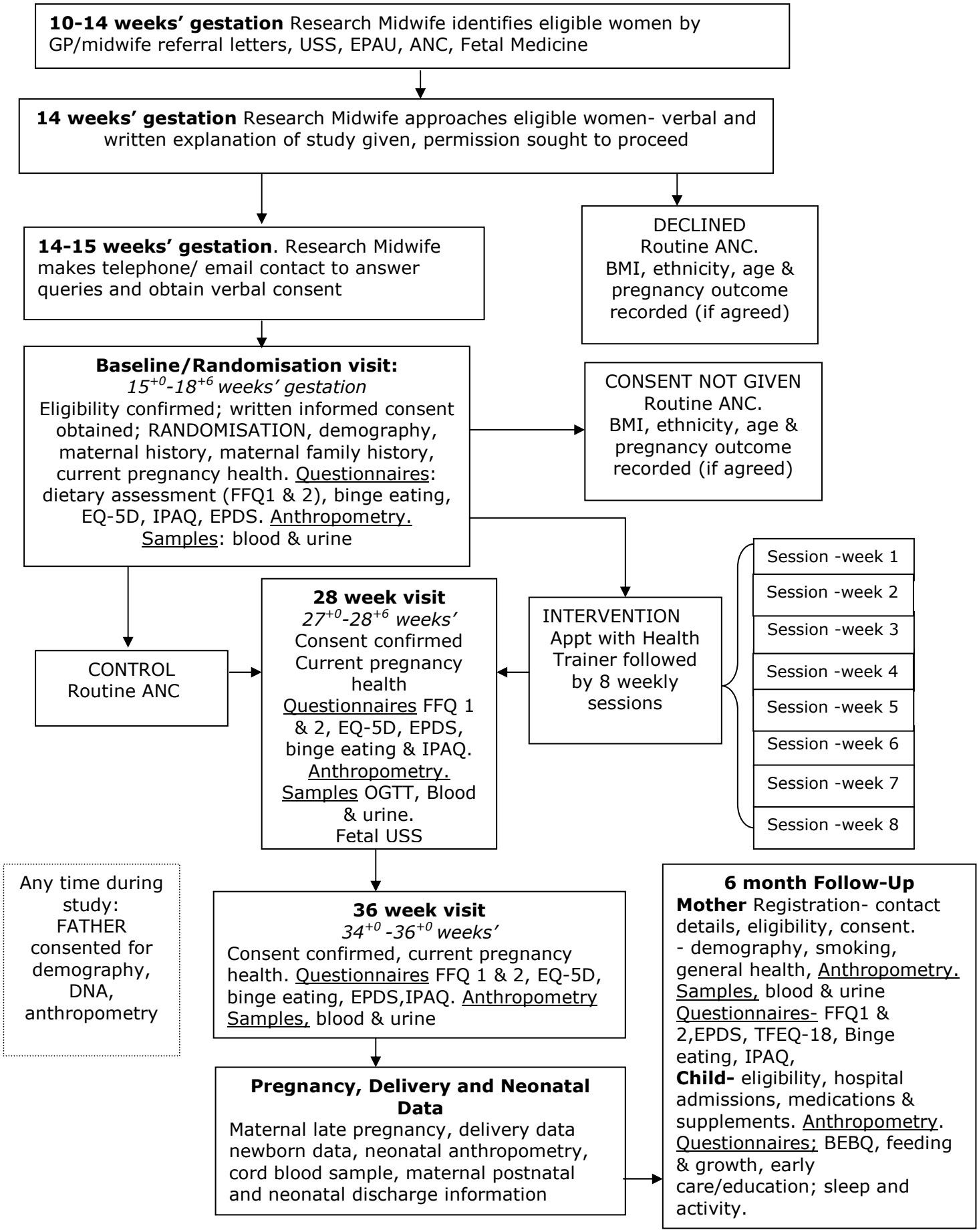
List of Abbreviations

AE	Adverse event
ANC	Antenatal clinic
BMI	Body Mass Index
CS	Caesarean Section
EPAU	Early pregnancy assessment unit
EPDS	Edinburgh postnatal depression scale questionnaire
EQ-5D	EuroQuol 5-D questionnaire
FFQ	Food frequency questionnaire
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
GI	Glycaemic Index
GL	Gylcaemic Load
GWG	Gestational Weight Gain
HDL Cholesterol	High density lipoprotein cholesterol
IPAQ	International physical activity questionnaire
ISF	Investigator Site File
LDL Cholesterol	Low density lipoprotein cholesterol
LGA	Large for gestational age
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OGTT	Oral Glucose Tolerance Test
PET	Pre-eclampsia
SAE	Serious Adverse Event
SGA	Small for Gestational Age
SMART goals	Specific, Measureable, Achievable, Relevant and Time specific goals
SOP	Standard Operating Procedure
USS	Ultrasound scan
VLDL Cholesterol	Very low density lipoprotein cholesterol
VTE	Venous Thrombotic Embolism

Flow diagram of participants through study



Background and Rationale for Study.

Although widely recognised that obesity is associated with greater risk of several adverse outcomes in pregnancy, no intervention has yet been shown to improve outcomes for the mother or infant. Increasing evidence also suggests that the child of an obese mother may be permanently affected by the maternal metabolic 'environment' experienced 'in utero', leading to an increased risk of obesity in later life. Thus interventions in obese pregnant women should address not only the acute influence of maternal obesity on the health of the mother and child but also the longer term health of the child. The UPBEAT study is a randomised controlled trial comparing the influence of a complex lifestyle intervention in obese pregnant women to standard antenatal care. The primary outcome for the mother is gestational diabetes and, for the infant, being born large for gestational age (LGA). Secondary outcomes include infant body composition at birth and 6 months of age.

The rise in the global incidence of obesity has reached pandemic proportions [1]. In 2008, the World Health Organization (WHO) estimated there were 1.5 billion individuals with a body mass index (BMI) $\geq$ 25Kg/m^2 including nearly 300 million obese women (BMI $\geq$ 30Kg/m^2) [2]. In the United Kingdom (UK) in 2002 more than half (54.5%) the women of reproductive years (16-44) were overweight or obese (BMI $\geq$ 25 Kg/m^2) [3]. The adverse effects of obesity on reproductive health and childbearing are manifold. Obesity reduces fertility, and in pregnancy is associated with a heightened risk of gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy including pre-eclampsia and failure to progress in labour. Caesarean section rates are high, and infants of obese mothers are at greater risk of congenital malformation, macrosomia, shoulder dystocia and stillbirth. Following delivery, obese women are more likely to suffer a postpartum haemorrhage, and have longer hospital stays than women with a normal BMI (18.5-24.9 Kg/m^2) [4-5]. The effects of obesity may extend beyond health in pregnancy; increasing evidence suggests that the children of obese women or of those whose gestational weight gain (GWG) was excessive may be at greater risk of obesity because of antenatal exposure to adverse metabolic influences *in utero*, or in the early postnatal period [6-7].

In the UK, in contrast to the United States (US), women are no longer routinely weighed in pregnancy, except at their first antenatal appointment. The US Institute of Medicine (IOM) guidelines for gestational weight gain in pregnancy provide recommendations for women according to their pre-pregnancy BMI, recommending that obese women should gain less weight in pregnancy (11-20lb; 5-9Kg) than those with a lower pre-pregnancy BMI, this advice being based on observational studies suggesting improved outcomes with lower weight gain [8]. The UK National Institute for Health and Clinical Excellence (NICE) guidelines on 'dietary interventions and physical activity interventions for weight management before, during and after pregnancy' concluded that more evidence of improved outcome from interventional studies is required before these or similar guidelines for limitation of GWG are adopted [9]. Whilst review of the literature suggests that intervention studies designed to limit GWG may sometimes be effective in achieving a reduction in GWG, there is at present no evidence for improvement of pregnancy outcome [10-13]. However most studies, including those in overweight and obese pregnant women, have been small, not powered for clinical outcomes and with limitations to the design [14]. Larger randomised controlled trials, such as the ongoing LIMIT trial (limiting weight gain in overweight and obese women during pregnancy to improve health outcomes) adequately powered to address clinical outcomes, will determine whether restriction of weight gain in obese pregnancy is achievable and whether it is associated with improved clinical outcomes [10].

The role of insulin resistance in obese pregnancies.

An alternative approach to restricting GWG is to focus on the adverse clinical outcomes associated with obesity, and to develop interventions which more directly address clinical outcomes. A pre-pregnancy BMI $\geq$30Kg/m^2 is the most important independent determinant of the risk of caesarean section, delivery of a large-for-gestational-age (LGA) infant and postpartum weight retention irrespective of the amount of weight gained during pregnancy [15]. Moreover, the evidence linking GWG with GDM, in contrast to the strong association with pre-pregnancy BMI, is relatively weak [16]. This is, at least in part, likely to be a reflection of the strong association between fat mass and insulin resistance [6]. Importantly, pregnancy *per se* is associated with insulin resistance and the obese pregnant woman is at greater risk of developing GDM. Maternal hyperglycemia and, more recently, maternal hypertriglyceridaemia are strongly implicated in the development of fetal macrosomia [17-20]. Using the method of continuous blood

glucose monitoring, Harmon *et al* have shown, as might be anticipated, that obese pregnant women have an exaggerated *post-prandial* glucose response [19]. As the magnitude of the *post- prandial* response is directly implicated in fetal macrosomia through fetal hyperinsulinemia, a dietary intervention focusing on reducing *post-prandial* hyperglycemia by lowering the dietary glycemic load could improve maternal glucose control, reduce the incidence of GDM and lower the risk of macrosomia. Similarly, pre-eclampsia is associated with maternal insulin resistance, and improved glucose homeostasis might lower the risk of pre-eclampsia in obese women [20].

Improving glycemic control in pregnancy.

Specific dietary advice and increased physical activity could contribute to improved maternal glucose homeostasis [21]. In a study of 50 obese Danish women designed to limit GWG, Wolff *et al* [22] found that an intense dietary regime (10 one-hour sessions with a dietician) focusing on healthy eating, resulted in a reduction of plasma insulin compared to women in the control arm of the study. Another study reported that a diet and exercise regime led to a reduction in GWG and a decrease in the incidence of GDM in 126 overweight and obese Australian women [23], but no difference in birthweight (3.5Kg versus 3.4Kg). In non-obese women with mild GDM, in whom improved glucose homeostasis is achieved through a strict regime of dietary intervention and insulin treatment when required, a reduction in the risk of adverse pregnancy outcome is achievable, as shown in two randomised controlled trials [24-25]. Higher levels of physical activity in normoglycemic pregnant women and those with GDM have also been shown to improve insulin sensitivity [6].

Systematic review of the literature.

Louie *et al* [26] conducted a systematic review of the influence of lowering dietary glycemic index (GI) in pregnancy. Of the eight studies included, two suggested that a low GI diet can reduce the risk of LGA infants in healthy pregnancies, but one reported an increase in small-for-gestational age (SGA) infants. In pregnancies complicated by GDM (n = 3) the evidence supported the overall advantages of a low GI diet. This review recommended that until larger-scale intervention trials are completed, a low GI diet should not replace the current recommended pregnancy diets from government and health agencies and that further research regarding the optimal time to start a low GI diet for maximum protection against adverse pregnancy outcomes is warranted.

In a systematic review of nine randomised trials including 743 overweight and obese pregnant women, Dodd *et al* reported that there was no significant effect of interventions designed to limit GWG on weight gain or on delivery of a LGA infant [14] and another systematic review of four trials addressing dietary interventions to restrict GWG, reported a reduction in GWG among 537 obese pregnant women without any influence on birth weight [11]. Similarly, in a recent systematic review of interventions in overweight and obese pregnant women we have observed that overall interventions were associated with restricted gestational weight gain, but no evidence for any change in birthweight or caesarean section rates. We recommended that a trend towards a reduced prevalence of gestational diabetes be interpreted with caution as the available studies were of poor to medium quality [27]. Similarly, Tanentsapf *et al*, in a meta-analysis of 10 trials contributing data on total GWG in normal, overweight and obese pregnant women, concluded that dietary advice during pregnancy appears effective in decreasing total GWG and long term postpartum weight retention, but with limited evidence for benefits on infant and maternal health [28]. Sui *et al* have also concluded in a systematic review of GWG that physical activity may reduce GWG with little evidence for improved outcomes [12].

We have also reviewed dietary and physical activity interventions for the purpose of limiting GWG; in a systematic review we assessed 12 trials in normal BMI and obese pregnant women (n= 1656 women). Overall, diet and physical activity change was effective in reducing GWG, but there was considerable heterogeneity in outcomes [29]. The analysis highlighted differences in sample characteristics and aspects of intervention design, content, delivery and evaluation which might explain variation in effectiveness. Furthermore, failure to evaluate changes in behaviour or its psychological determinants could have obscured identification of the processes by which weight change is effective, and limited the ability to discern active intervention ingredients. We concluded that interventions should be more systematically designed and build on insights from behavioural science.

We subsequently developed a complex behavioural intervention comprising dietary and physical activity changes to improve glycemic control in obese pregnant women. The intervention is based on established control theory with elements of social cognitive theory [30-31]. All elements of the intervention have been evaluated in a pilot randomised controlled trial

Study Objectives

The primary hypothesis being tested in this randomised controlled trial of obese pregnant women is that an antenatal intervention package of low glycemic dietary advice combined with advice on increased physical activity will reduce the incidence of maternal GDM and LGA infants. A secondary hypothesis is that the intervention will reduce the risk of obesity in the child.

Specific objectives

Primary objectives

The primary objective is to determine whether the intervention delivered over a period of 8 weeks (between 20 and 28 weeks' gestation) leads to fewer women developing GDM in the intervention arm than in the control arm. This is the primary endpoint for the mother. For the infant, the primary objective is to determine whether the intervention leads to fewer LGA babies being born in the intervention arm rather than the control arm.

Secondary objectives.

For the mother we shall determine whether being in the intervention arm compared to the control arm leads to:

- Fewer cases of pre-eclampsia
- A reduction in the number of deliveries by caesarean section
- More vaginal deliveries
- A reduction in the requirement for insulin or oral hypoglycaemic treatment
- An improvement in the plasma lipid profile
- A reduction in plasma fructosamine
- An improved quality of life
- A reduced incidence of depression and/or anxiety
- A lower fat mass as assessed by anthropometric measures
- A lower dietary glycemic load
- A higher level of physical activity
- Reduced saturated fat intake
- Reduced sugar intake

- A lower BMI and fat mass at 6 months postpartum
- A higher level of physical activity postpartum at 6 months
- A lower dietary glycemic load at 6 months
- Less anxiety and depression at 6 months postpartum.

For the infant we shall determine whether, if the infant's mother was in the intervention, compared to the control arm led to:

- More babies born at weights appropriate for gestational age
- Improved Apgar scores at delivery
- Fewer admissions to neonatal intensive or special care
- Less phototherapy for neonatal jaundice
- Higher breast feeding rates.
- Less fat deposition, assessed by circumferences and skinfold thicknesses, at age 6 months.

Study Endpoints

Primary maternal outcome

GDM diagnosed by OGTT at 27^{+0} – 28^{+6} weeks' gestation according to the criteria recommended International Association of Diabetes in Pregnancy Study Group (IADPSG) Diagnosis of GDM; fasting capillary glucose $\geq$ 5.1mmol/L and/or 1 hour glucose $\geq$10mmol/L; 2 hour glucose $\geq$8.5 mmol/L [39].

Primary neonatal outcome

LGA delivery defined as birthweight >90th centile for gestational age adjusting for maternal height, weight, ethnicity, parity, gestation at delivery, birthweight and sex of baby [40].

Secondary outcomes

Maternal - PET, severe PET; mode of delivery, CS (elective, emergency, pre-labour, in labor), vaginal delivery, operative vaginal delivery; induction of labour; blood loss at delivery (>1000ml; >2000ml); inpatient nights (antenatal, postnatal); GWG; fasting plasma glucose, fasting plasma insulin, insulin resistance calculated by homeostatic model assessment 2 (HOMA2-IR) [41] at 28 weeks' gestation; referral to GDM antenatal service following OGTT; requirement for insulin or oral hypoglycaemic treatment during pregnancy, fetal growth at

28weeks' gestation, health related quality of life at 28 and 36 weeks' gestation. At 28 and 36 weeks' gestation and 6 months postpartum; mid-arm, neck, hip, thigh and wrist circumference and skinfold thickness (subscapular, triceps, biceps, supra-iliac); plasma fructosamine, triglycerides, LDL, VLDL and HDL cholesterol, plasma insulin,
C-reactive protein; dietary glycemic load, saturated fat and total sugar intake; physical activity; measures of anxiety, depression; maternal smoking. At 6 months postpartum, postnatal weight retention; existing maternal morbidity (diabetic status, hypertension, thromboembolism, psychiatric disorders including depression),
Neonatal; Gestational age at delivery, delivery at <37 weeks', delivery at <34 weeks'; birthweight, birthweight >4000g, <2,500g; birthweight <10th customised birthweight centile (SGA), neonatal death, days in special care baby unit, total inpatient days, need for mechanical ventilation and duration, discharge home on O_2, suspected and confirmed infection, evidence of intraventricular haemorrhage and other complications, (pulmonary haemorrhage, necrotising enterocolitis), retinopathy of prematurity, hypoglycaemia. Occipito-frontal head circumference, abdominal circumference, mid-arm circumference, chest circumference, crown-rump length and crown-heel length (neonatometer), biceps and triceps subscapular skin fold thicknesses and estimated fat mass.
Infant at 6 months; duration of breast feeding, choice of formula milk, weaning history (introduction of foods and frequency/timing of foods), a single measure of appetite (derived from enjoyment of food, food responsiveness, slowness in eating, and satiety responsiveness); anthropometric measurements (occipito-frontal circumference, abdominal circumference, mid-arm circumference, chest circumference, crown-rump length and crown-heel length by infantometer, biceps and triceps skin fold thicknesses and estimated fat mass; activity (total number of 14 standard milestones reached) and sleeping patterns (time spent sleeping; morning, afternoon and night; health care resource use (hospital admissions and medications); frequency of use of kindergarten/mother's help.

Study Design

The design is a randomised controlled trial. The study is not blinded.

Study Population.

We will invite obese pregnant women to take part in a randomised controlled trial in which they are allocated to a control arm (standard antenatal care) or to the intervention arm. The intervention, delivered by a health trainer includes advice on both diet and physical activity. We will study all women at intervals during pregnancy and test for development of gestational diabetes. We will also collect information on all pregnancy complications which occur for mother and baby and will measure infant weight and fatness at birth and at six months of age.

Women will be recruited from the following centres; St.Thomas' Hospital London, King's College Hospital, London, Newcastle Royal Infirmary, Glasgow Hospitals, St Mary's Hospital Manchester, Bradford Royal Infirmary and Sunderland Royal Hospital.

Number of Participants.

We plan to recruit 1546 obese pregnant women.

Inclusion Criteria:

Women with a singleton pregnancy, 15^{+0}- 18^{+6} weeks' gestation and body mass index $\geq$30 Kg/m^2 at first antenatal appointment.

Exclusion Criteria:

Women unable or unwilling to give informed consent; $<15^{+0}$ or $>18^{+6}$ weeks' gestation; essential hypertension requiring treatment either pre-pregnancy or in index pregnancy; pre-existing renal disease; systemic lupus erythematosus (SLE); antiphospholipid syndrome (APS); sickle cell disease; thalassemia; coeliac disease; thyroid disease; current psychosis; multiple pregnancy; currently prescribed metformin.

Participant Selection and Enrolment.

Identifying and consenting participants

Eligible women are identified in antenatal clinics and from general practitioner and midwives referral letters. Verbal and written information is given. Research midwives contact potential recruits, obtain verbal consent and arrange the first appointment. For those who decline to participate permission is sought to collect minimal pregnancy outcome data.

Screening for eligibility.

Ineligible and non-recruited participants

Information regarding date of birth, ethnicity (broad groups) and parity are collected from all women. Additionally, at first contact, all women are asked to consent to the researchers accessing minimal pregnancy outcome data from NHS electronic patient records, even if they do not participate in the study.

Randomisation

Randomisation is undertaken using a secure internet based data management system (MedSciNet™). The randomisation schedule is minimised according to ethnicity, parity (0 *vs* $\geq$ 1), age and BMI (BMI 30-34.9 Kg/m^2 *vs* 35-39.9 Kg/m^2 and > 40Kg/m^2).

Randomised women are allocated sequential study numbers, regardless of centre, or allocation to the intervention or standard care group.

Treatment Allocations.

Intervention:

Women randomised to the intervention group attend a one-to-one interview with the health trainer, which includes discussion of the potential benefits of attending the weekly group sessions. In the UK, health trainers help people to change their behaviour to achieve personal choices and goals and generally do not have pre-specified health professional qualifications, but relevant experience. All health trainers in this trial receive study-specific training in all aspects of the intervention and ongoing support throughout the trial. Women in the intervention group receive a participant handbook, a DVD of an exercise regime safe for pregnancy, a pedometer and a logbook for recording weekly SMART(Specific, Measurable, Achievable, Relevant and Time specific) goals, and steps as assessed by pedometer. They are invited to attend 8 group sessions with the health trainer on a weekly basis, each lasting 1.5 hours. Women are encouraged to attend as many sessions as possible but if they are unable to participate, the health trainer covers the session material by phone or email. Attendance and coverage of session material are documented in the study database. Following a general review of the dietary and physical activity intervention, each session is designed to deliver a different element. The strategies include behavioural goal setting using SMART goals, self monitoring, provision of feedback regarding goal attainment, identification and problem solving of barriers, enlisting social support and providing opportunities for social comparison. At each session, review of the previous week's goals is undertaken.

The dietary intervention aims to promote a healthier pattern of eating similar to that used in diabetes prevention studies but does not aim to restrict energy intake. In order to decrease the glycemic load, dietary advice includes exchanging starchy foods with medium/high glycemic index (GI) for those with a lower dietary GI and restricting the consumption of sugar-sweetened beverages (including fruit juice) but not fruit. Participants are also given dietary advice to

reduce saturated fatty acid intake (use of low fat in place of high fat dairy products, exchanging lean meat and fish for fatty meats and meat products). Advice regarding physical activity focuses on increasing daily step count incrementally, and being more active in daily life. Pedometers are used for monitoring and motivation. The emphasis is on walking at a moderate intensity with additional options included, especially for those who are already engaging in some physical activity.

Standard Care:

Women randomised to the standard care group attend routine antenatal care according to local health care provision. UK recommendations state that women with a BMI ≥ 30Kg/m^2 should be advised by a health professional at the earliest opportunity of the risks of obesity in pregnancy and be given advice about a healthy diet and safe levels of physical activity. Recommendations for referral to a registered dietician are infrequently implemented. Women are not weighed routinely except at the first antenatal visit [9].

Unblinding

This is not a blinded study and therefore there are no unblinding procedures required.

Premature withdrawal

Participants can withdraw at any point without giving a reason. Permission will be sought to access routinely collected clinical pregnancy outcome data.
Women who withdraw after the 28 week visit may be re-consented at 6mths postpartum.

STUDY PROCEDURES: SUMMARY					
Visit	**Baseline/ Randomisation**	**28 week visit**	**36 week visit**	**Delivery and Neonatal**	**6 month follow-up**
Pregnancy gestation	**15^{+0}-18^{+6}**	**27^{+0}-28^{+6}**	**34^{+0}-36^{+0}**	**Up to 72hours post birth**	**5.5-6.5 months**
eligibility	X				X
consent	X				X
demography	X				X
randomisation	X				
History; maternal and family	X				X
Current pregnancy health	X	X	X		
Questionnaires: FFQ 1 &2, Binge eating EQ-5D, IPAQ, EPDS.	X	X	X		X
Maternal anthropometry	X	X	X		X
Maternal Blood and Urine Sample	X	X	X		X
Maternal OGTT		X			
Fetal USS		X			

Neonatal anthropometry				X	X
Cord blood sample				X	
Infant anthropometry					X
BEBQ					X
Infant Feeding and Growth questionnaire					X
Infant; hospital admissions, medications and supplements					X
Questionnaires: Infant early care and education; sleep and activity					X
Paternal anthropometry, medical history and blood sample*					

- *on one occasion at any point

Study Assessments.

Baseline/randomisation visit

15^{+0}-18^{+6} weeks' gestation

At the first appointment, eligibility is confirmed and written informed consent obtained. Demography, medical and family history and current pregnancy health information is collected. A short validated food frequency questionnaire (FFQ) is completed to evaluate dietary glycemic load, dietary glycemic index, saturated fat, total sugar intake and other dietary variables. Randomisation occurs at this visit. Anthropometric measurements and blood and urine samples are taken. Behavioural and psychological measures assessed by questionnaire include EuroQuol Quality of life (EQ-5D) [32], the International Physical Activity Questionnaire (IPAQ) [33], the Edinburgh Postnatal Depression Scale (EPDS) [34], and 'binge eating'.

28 week visit

All women in both randomisation groups attend for an oral glucose tolerance test (OGTT) at 27^{+0}- 28^{+6} weeks' gestation (fasting for a minimum of 10 hours, 75g glucose load). The diagnosis of GDM is according to the criteria recommended International Association of Diabetes in Pregnancy Study Group (IADPSG); fasting capillary glucose $\geq$ 5.1mmol/L and/or 1 hour glucose $\geq$10mmol/L; 2 hour glucose $\geq$8.5 mmol/L [39].

At this visit consent in confirmed, anthropometric measurements are taken, health in current pregnancy noted, additional blood and urine samples taken, and dietary assessment (FFQ), EQ-5D, EPDS and IPAQ questionnaires completed. Early pregnancy data including blood pressure, blood chemistry and anomaly scan reports are entered from routine clinical records. When possible a fetal growth ultrasound scan is performed.

36 week visit

Women in both arms of the study attend the clinic at 34^{+0}-36^{+0} weeks' gestation. Current health in pregnancy is recorded, anthropometric measurements taken, blood and urine samples collected and dietary FFQ, EQ-5D, EPDS, IPAQ questionnaires completed.

Pregnancy Outcome, Delivery and Neonatal Data

Following delivery, information is collected from maternal medical records regarding health in late pregnancy, labour onset, mode of delivery and antenatal inpatient nights. Where possible a cord blood sample is taken.
Neonatal and postnatal outcome data includes admission to special care baby unit and inpatient nights. To address the influence of the intervention on neonatal growth and adiposity, neonatal anthropometry and length measurements are undertaken within 72 hours.

Six Months Postpartum

To determine whether the intervention has led to sustained change in maternal dietary and physical activity behaviours, diet will be assessed by FFQ and physical activity by IPAQ. Maternal demographic data, health since pregnancy and smoking history will be obtained. Maternal anthropometric measures will be taken. EPDS questionnaires will be completed. To address safety and the influence of the intervention on the long term health of the child, details regarding the child's health from birth are obtained. If cord blood was not taken and the parents consent, a saliva sample will be taken (Oragene™). To address the potential influence of the intervention on infant adiposity at 6 months and obtain information on known determinants of childhood obesity, infant length and other anthropometric measures are taken. The mother provides information for an infant feeding and growth questionnaire [35] and a validated questionnaire addressing appetite (BEBQ) [36] Information on activity using questions from the Infant Behaviour Questionnaire – Revised (IBQ-R) [37] and sleep patterns is obtained [38] and information on infant care (kindergarten, other carers) collected.

Paternal Data

At any point during the pregnancy or at the 6 month postnatal appointment the father of the baby is asked to consent to taking part in the study to provide information which may influence the health of the child. A brief medical history is taken. Anthropometric measurements will include height, weight, triceps, biceps, subscapular and suprailiac skinfold thicknesses, neck, waist, mid-arm, wrist, hip and thigh circumferences. Blood pressure and pulse will be recorded and a blood sample taken for provision of DNA

Sub-Study

In order to obtain detailed dietary information and an objective assessment of physical activity, additional information is collected in one in 15 randomly selected women. A triple pass 24 hour dietary recall is obtained at each appointment and repeated one week later. Similarly women are asked to wear an accelerometer (Actigraph™) for seven consecutive days following the first and third appointment.

Data collection

Data is collected on-line on a study specific password protected database with all patient data analysed (MedSciNet™).

Stats and data analysis.

Sample size calculation

1546 women provide 80% power to detect a 25% reduction in the incidence of GDM and a 30% reduction in large for gestational age infants.

Proposed analyses.

A detailed analysis plan will be drawn up. To determine whether the trial participants are representative of the general population, relevant parameters available from electronic patient records will be compared between eligible women agreeing and declining to take part. Analyses will follow the intention-to-treat principle. Following CONSORT guidelines, risk ratios and risk differences will be estimated by binary regression for Yes/No outcomes. Where measurements are repeated over time, results [mean (SD) or n (%)] will be presented separately at each time point. Randomised comparisons with 95% confidence intervals will be made using linear regression with robust standard errors, adjusting for the baseline value where appropriate.

Multiple regression models will be used to address the influence of maternal and neonatal exposures on childhood obesity and the role of paternal factors.

SAFETY REPORTING (Research other than CTIMPs)

In other research other than CTIMPs, a *serious adverse event* (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

- *Related* – that is, it resulted from administration of any of the research procedures, and
- *Unexpected* – that is, the type of event is not listed in the protocol as an expected occurrence.

	Who	What and when	How	Action by REC
SAE	Chief Investigator (CI) or sponsor	Any SAE that is related and unexpected. Within 15 days of the CI becoming aware of the event.	SAE report form for non-CTIMPs, available from NRES website. To main REC only.	Acknowledge by signing and returning copy of form. Review at REC or sub-committee meeting. Write to sponsor and CI following review if appropriate.
Urgent safety measures	Chief Investigator or sponsor	(i) Immediate notification. (ii) Within 3 days, setting out in full the reasons for the urgent safety measures and the plan for further action.	(i) By telephone. (ii) Notice in writing. To main REC only.	Review at REC or sub-committee meeting. Write to sponsor and CI following review.

PROGRESS REPORTING

Type	Who	When	How	Action by REC
Progress reports	May be submitted by sponsor, sponsor's legal representative or Chief Investigator (CI). Must always be signed by CI.	Annually (starting 12 months after the date of the favourable opinion) *Main REC may exceptionally request more frequent reports.* Co-ordinator of main REC to send reminder using SL38 if not received.	Annual progress report form on NRES website. Separate forms to be used for CTIMPs and non-CTIMPs.	Acknowledge using SL37. Review by Chair and/or any member of the REC. Notify REC in Co-ordinators' report.
Declaration of the conclusion or early termination of the research (CTIMPs)	Sponsor, sponsor's legal representative or CI	Within 90 days (conclusion). Within 15 days (early termination). *The end of the trial should be defined in the protocol.*	"Declaration of the end of a clinical trial" form prescribed by the European Commission (Annex 3 to ENTR/CT1), available from EudraCT website.	Acknowledge using SL39. Review by Chair and/or any member of the REC or Scientific Officer. Notify REC in Co-ordinators' report.
Declaration of the conclusion or early termination of the research (non-CTIMPs)	May be submitted by sponsor or CI. Must always be signed by CI.	As for CTIMPs.	End of study declaration form (non-CTIMPs) on NRES website	As for CTIMPs.
Summary of final report	Sponsor, sponsor's legal representative or CI	Within one year of the conclusion of the research. Co-ordinator of main REC to send reminder using SL41 if not received.	No standard format. The summary should include information on whether the study achieved its objectives, the main findings and arrangements for publication or dissemination including feedback to participants.	Acknowledge using SL40. Review by Chair and/or any member of the REC or Scientific Officer. Notify REC in Co-ordinators' report.

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Detecting SAEs

All SAEs must be recorded from the time a participant is randomised until after the last baby is born and discharged from hospital or the end of the postnatal period (28 days of life), whichever is sooner.
The investigator should ask about SAEs at each visit during the study. Open-ended non-leading verbal questioning of the participant should be used to enquire about SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimes. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.
Information to be collected includes type of type of event, onset date, investigator assessment of severity and causality, date of resolution in addition to treatment required, investigations needed and outcome.

All adverse medical events reported by the participant should be documented in the handheld maternity records.

The clinician will assess **ALL** reported SAEs. Some adverse events are expected and will not therefore be reported as SAEs but will be recorded on the database and presented to the DMC, as part of the ongoing safety review.

For this study the following events will **NOT** be considered SAEs:

- Pregnancy is neither an AE or a SAE, as requirement for inclusion criteria
- Hopsitalisation for treatment planned prior to randomization and hospitalization for elective treatmenat or pre-existing condition will not be considered as an SAE. This includes pregnancy. However , ***complications occurring during such hospitalization will be SAEs.***
- Miscarriage
- Preterm labour
- Preterm delivery in maternal interest
- Preterm delivery in fetal interest
- Hospitalization for pregnancy induced hypertension
- Hospitalization for "maternal discomfort"
- Hospitalization for "rest"
- Hospitalization for "observation" or "monitoring" for which the woman is admitted for less than 24 hours
- Delivery complications such as Caesarean section or postpartum haemorrhage
- Admission of the baby for neonatal care for a period of up to 14 days.

Evaluation of SAEs

Seriousness, causality, severity and expectedness should be evaluated.

Assessment of seriousness

The investigator should make an assessment of seriousness according to the criteria:
A serious adverse event is any adverse event that (at any dose):

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect.

Assessment of causality

The investigator must make an assessment as to whether the SAE is likely to be related to treatment according to the following definitions:

1) As there is no cTIMP in this study, all SAEs will be judged as having a reasonable suspected causal relationship (eg possibly, probably, definitely) to the study intervention, and adverse reactions/serious adverse reactions (AR/SAR) will not apply.
2) Similarly there will be no assessment as to whether the SAE is likely to be caused by an interaction between study drugs and rescue/escape drugs.
3) **Unrelated**: where an event is not considered to be related to the intervention.
4) **Possibly**: although a relationship to the intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant treatment or temporal relationship make other explanations possible.
5) **Probably**: the temporal relationship and absence of a more likely explanation suggest the event could be related to the intervention.
6) **Definitely:** the known effects of the study intervention or it's consequence, suggest that the intervention should be considered and investigated.

Assessment of severity

The investigator should make an assessment of severity for each SAE and record this according to one of the following categories:
Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
Moderate: an event that is sufficiently discomforting interfere with normal every day activities.
Severe: an event that prevents normal every day activities.
Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but not severe.

Assessment of expectedness

This relates to adverse reactions and serious adverse reactions and therefore is not required in this non cTIMP trial.

Reporting SAEs

Once the investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the Trial Co-ordinating Centre within 24 hours.

The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator or designee. If the investigator does not have all the information regarding the SAE, they should not wait for this additional information before completing the SAE form. The form can be updated when subsequent information becomes available.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the Trial Co-ordinating Centre.

The SAE form should be transmitted by fax to the Trial Co-ordinating Centre on 020 7620 1227, or transmitted by hand to the office.

FOLLOW UP PROCEDURES

After initially reporting an AF or recording and reporting an SAE, the investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to The trial Co-ordinating Centre.
AEs/SAEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.

OUT OF HOURS COVER

The Trial Management Team, Trial Steering Committee, Trials managers and Co-sponsors do not provide out of hours advice for study participants. The protocol will be available on the labour ward at each participating centre , and the study team will attempt to ensure that all senior obstetricians within participating units are aware of the study.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by the Trial Management Group (TMG) consisting of the Coordinating Centre Staff, co-applicants and site Principal Invesitgators.

The Trial Manager will oversee the study and be responsible to the Chief Investigator. The checking of the database for completeness, plausibility and consistency will be the responsibility of the trial manager and designated members of the midwifery team. Queries will be resolved at each site by the study centre midwife and/or the Principal Investigator.

A delegation list will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

Division of Responsibilities of the Trial Management Group (TMG)

- Chief Investigator, Poston: overall responsibility for the design, conduct, analyses and reporting of the trial; assisted by the TMG
- Seed for statistical support .
- Site Principle Investigators will have responsibilities for the conduct of the trial in their centre.

Central Trial Office

The trial manager will co-ordinate the study based in the Maternal and Fetal Research Unit, KCL Division of Women's Health, St Thomas' Hospital, London. The trial manager and core staff will provide support for participating sites. MedSciNet ™ will be responsible for randomisation, collection and storage of the data in collaboration with the Trial Manager.

Trial Steering Committee (TSC)

A trial steering committee has been established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee will be developed separately. The names and contact details of the TSC members are detailed on page 45.

Data Monitoring Committee (DMC)

An independent data monitoring committee (DMC) is not required to oversee the safety of subjects in the trial. This is not a CTIMP, therefore the TSC will take overall responsibility for the conduct of the trial.

Inspection of Records

Investigators and institutions involved in the study will permit trial related monitoring, audits, REC review and regulatory inspection(s). In the event of an audit the investigator agrees to allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

Study Monitoring

The trial will be monitored by designated members of the study team and the trial manager on behalf of the Co-Sponsors. A study start-up visit will be completed.

Good Clinical Practice

ETHICAL CONDUCT

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCO). A favourable ethical opinion will be sought form the appropriate REC and local R and D approvals obtained prior to commencement of the study.

Investigator Responsibilities

The investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the investigator.

Responsibilities may be delegated to an appropriate member of the study staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

Informed Consent

The investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to take part in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information- appropriate Patient Information and Informed Consent Forms will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all the elements specified in the Participant Information Sheet/Informed Consent Form.

The participant must be given every opportunity to clarify points they do not understand and it necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant should sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant should receive a copy of this document and a copy filed in the Investigator Site File.

Study Site Staff

The investigator must be familiar with the protocol and the study requirements. It is the investigator's responsibility to ensure that all staff assisting with study are adequately informed about the protocol and their trial related duties.

Data Recording

The investigator is responsible for the quality of data recorded in the database.

Investigator Documentation

Prior to beginning the study, each investigator will be asking to provide particular essential documents to the main trial office, including but not limited to:

- Curriculum vitae (CV) signed and dated by the investigator indicating that it is accurate and current.
- A valid GCP certificate.

The main trial office will ensure all other documents required by GCP are retained in a Trial Master File (TMF) and that appropriate documentation is available in local ISFs.

GCP Training

All study staff must hold evidence of appropriate GCP training or undergo GCP training. The co-sponsors require that GCP is updated every two years throughout the trial.

Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regularity Authorities, or the REC. The Investigator and the study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Data Protection

All investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Study Conduct Responsibilities

Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

Protocol Violations and Deviations

Investigators should not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC, Regulatory Authority and R&D approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the eCRF. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and R&D for review and approval if appropriate.

Study Record Retention

This is a study involving pregnant women and research records should be retained according to NHS Guidelines for the retention of documentation involving pregnant women. All medical records will be retained for at least 25 years after publication of the final study report. Guidelines on retention of other research related documents are continually under review. We plan to retain all documents for 5 years and then will review according to current guidance at the time.

Serious Breach Requirements

A serious breach is a breach which is likely to effect to a significant degree:

a) The safety or physical or mental integrity of the subjects of the trial (this should be relevant to trial subjects in the UK); or
b) The scientific value of the trial.

If a potential serious breach is identified by the Chief Investigator, Principal Investigator(s) or delegates, the Co-sponsors must be notified within 24 hours. It is the responsibility of the Co-sponsor to assess the impact of the breach on the

scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

Not every deviation from the protocol needs to be reported to the regulatory authority as a serious breach, if the Co-sponsors deem the incident to be a minor deviation from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within TMF or ISF.

END OF STUDY

The end of the study declaration will be submitted to the relevant authorities after the last baby is born and discharged from the hospital or the end of the postnatal period (28 days after the birth), whichever is sooner. The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

INSURANCE AND INDEMNITY

The Co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Co-sponsors' responsibilities:

- The protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol designed by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the Sites concerned. The Co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefits of NHS Indemnity.
- Sites out of the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

Reporting, Publications and Notification of Results

AUTHORSHIP POLICY

Ownership of the data arising from this is set out in the collaborators' agreement and an authorship policy will be developed. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with GCP guidelines.

PUBLICATIONS

The clinical study report will be used for publication and presentation at scientific meetings. The results of the study and any protocol deviations will be published in writing by the team headed by the Chief Investigator, which will report to the Trial Management Committee. Individual investigators may be able to produce oral reports with the permission of the Trial Management Committee.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

Peer Review

The study was peer reviewed as part of the process of gaining NIHR grant funding.

Trial Steering Committee

CHAIR: **Professor Catherine Nelson-Piercy** Professor of Maternal Medicine, Academic Department of Women's Health Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London SE1 7EH	**MEMBERS:** **Professor Patrick Catalano** Director, Clinical Research Unit of the CTSC Case Western Reserve University/MetroHealth Case Western Reserve University School of Medicine, Cleveland, Ohio, USA
Professor Stephanie Amiel RD Lawrence Professor of Diabetic Medicine, Head of Diabetes & Nutritional Sciences Division King's College London, 3rd floor Weston Education Centre, Denmark Hill Campus, 10 Cutcombe Road, London SE5 9RJ	**Dr Daghni Rajasingam** Consultant Obstetrician Academic Department of Women's Health, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London SE1 7EH
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Professor Keith Godfrey Professor of Epidemiology & Human Development, MRC Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton SO16 6YD	

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