Study Protocol

A pragmatic approach to preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings **(PAPAGENO)**

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PROTOCOL APPROVAL SIGNATURE PAGE

PAPAGENO Study

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Name		08/04/2019
Chief Investigator	**Signature**	**Date**
Name		08/04/2019
Trial Statistician	**Signature**	**Date**
Name		08/04/2019
Sponsor Representative	**Signature**	**Date**

The Principal Investigator must sign below to document that the protocol has been read and understood and he/she will abide by the requirements of the protocol.

Name		Malawi	08/04/2019
Principal Investigator	**Signature**	**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

This is not an exhaustive list.
Any additional abbreviations used within the protocol must also be added here.

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
ECRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
iDSMC	Independent Data Safety and Monitoring Committee
DSUR	Development Safety Update Report
eECRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
EDD	Estimated Date of Delivery
GCP	Good Clinical Practice
GDM	Gestational diabetes mellitus
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LMIC	Low and middle income countries
NICE	National Institute for Health and Care Excellence
pECRF	Paper Case Report Form
PI	Principal Investigator
PIL (PIS)	Patient Information Leaflet (Sheet)

PMG	Project Management Group
PMPB	Pharmacy Medicines and Poisons Board (Malawi)
QA	Quality Assurance
QMRI	Queen's Medical Research Institute (Edinburgh)
QP	Qualified Person
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee
ROM	Rupture of Membranes
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
WHO	World Health Organisation

TRIAL SUMMARY

Trial Title	A pragmatic approach to preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings
Study Acronym	PAPAGENO
Clinical Phase	Phase III, Feasibility study
Trial Design	Randomised Control Trial
Trial Participants	Pregnant Women
Planned Number of Participants	100
Planned Number of Sites	2
Countries Anticipated to be Involved in Trial	Malawi
Treatment Duration	From consent to delivery (approximately 12-42 weeks gestation) approximately 30 weeks
Follow up Duration	28 days postnatal
Total Planned Trial Duration	18 months
Overall Objective	The overall objective of this study is to determine the feasibility of a pragmatic placebo controlled-randomised trial of metformin to prevent gestational diabetes and pregnancy hypertensive disorders in obese pregnant women.
Specific Objectives	A. To assess the number of eligible women recruited into the study. B. To ascertain the proportion of pregnant women presenting at or before 28 weeks gestation [when the intervention will be started]. C. To assess adherence to therapy (ascertained by review of diary and returned study medication) D. To determine the proportion of women in the placebo group and proportion of those in the active group (if tested prior to starting metformin) who have gestational diabetes at 24-30 weeks E. To assess the ability to measure key clinical variables F. To verify the proportion of women who are recruited but then lost to follow up for the primary and secondary outcomes. G. To identify an appropriate method by which we can identify women and avoid double randomisation to address co-enrolment (i.e. GPS home identifiers, thumb or finger print).
Primary Endpoint	The ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period
Secondary Endpoints	• Number of eligible women who are recruited into the study. • Proportion of pregnant women presenting at or before 28 weeks gestation [when the intervention will be started]. • Adherence to therapy (ascertained by review of diary and returned study medication) • Proportion of women in the placebo group and proportion of those in the active group (if tested prior to starting metformin) who have gestational diabetes at 24-30 weeks • Ability to measure key clinical variables: • Proportion of women who are recruited but then lost to follow up for the primary and secondary outcomes. • Identify an appropriate method by which we can identify women and avoid double randomisation to address co-enrolment (i.e. GPS home identifiers, thumb or finger print). • Adverse events in each group

IMP(s)	Metformin or placebo
IMP Route of Administration	Oral
NIMP(s)	N/A
Lay Summary of Trial	This is a feasibility study of a randomised clinical trial of metformin (compared with matched placebo) for the prevention of gestational diabetes and pregnancy hypertensive disorders in obese pregnant women. This study will help to determine whether we can recruit enough women to conduct a larger trial in the future, to measure if the routine administration of metformin could prevent gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings (in Malawi and Zambia). Gestational diabetes (too much sugar in the blood in pregnancy) and pregnancy hypertensive disorders (high blood pressure that occurs in pregnancy) both cause maternal and neonatal deaths and long term problems. Gestational diabetes with an estimated global prevalence of 16% (with higher rates in in South Asia and Africa) increases the incidence of the adverse pregnancy outcomes. If left untreated it also increases the risk of future obesity and diabetes. Pregnancy hypertensive disorders account for 17.3% of maternal deaths in low income countries, and are the second commonest cause of maternal death after haemorrhage (severe loss of blood). In resource rich countries, testing for gestational diabetes is routinely undertaken in women considered high risk, together with treatment of those affected and regular monitoring. Such an approach is difficult and inappropriate in resource poor settings due to the high cost of testing of blood sugar monitoring and the lack of availability of suitable and cost effective equipment. However, measurements of maternal body mass index (weight and height) cheaply and effectively identifies obese women who are a high-risk group for both gestational diabetes and pregnancy hypertensive disorders. Additionally, one of the current treatments (metformin) for gestational diabetes is relatively cheap, widely available, and is safe, regardless of blood sugar levels. Recent evidence suggests that metformin might also reduce the incidence and severity of pregnancy hypertensive disorders. In this feasibility study we will measure if women are willing to be recruited and take a medication. We will then use this information to determine, if a larger study to prevent gestational diabetes could be conducted in the future.

1. INTRODUCTION

1.1 BACKGROUND

The estimated global prevalence of gestational diabetes (GDM) is 16%, with higher rates in South Asia and Africa (Federation 2015). GDM increases the incidence of the adverse outcomes of caesarean section, pregnancy hypertensive disorders, birth injury, future obesity and future diabetes: untreated, it contributes to a cycle which promotes obesity and diabetes in future generations (NICE 2015). Pregnancy hypertensive disorders account for 17.3% of maternal deaths in low income countries, and are the second commonest cause of maternal death after haemorrhage (Collaborators 2016). Overweight and obesity rates are increasing rapidly in women of reproductive age throughout the world. Obesity increases the incidence of both gestational diabetes and pregnancy hypertensive disorders (Poston, Caleyachetty et al. 2016): hence obese women will be the focus of our study.

This project aims to ascertain if women are willing to be recruited, and take a medication to prevent (and/or reduce the adverse consequences of) gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in Malawi. For the purpose of this study, we will use an ethnic-specific body mass index (BMI) threshold of ≥ 26 kg/m^2 in African women to define obesity, given evidence that African ethnicity lowers the BMI risk threshold for diabetes in non-pregnant people (Chiu, Austin et al. 2011). Hence reference to "obesity" from sections 2 onwards of this study means a BMI of ≥ 26 kg/m$^{2.}$

1.2 RATIONALE FOR STUDY

Gestational diabetes and pregnancy hypertensive disorders are an increasing threat to maternal and fetal health in both resource rich and resource poor settings. The prevalence of gestational diabetes is rising, driven by obesity and high glycaemic diet (Berntorp 2016). A systematic review of previously published literature showed the reported prevalence of gestational diabetes in Africa is between 0 % and 13.9% (Macaulay, Dunger et al. 2014). Using the newer World Health Organisation criteria for hyperglycaemia, a subsequent comprehensive global analysis has suggested that the true incidence of diabetes in pregnancy in Africa is higher at around 17%, with 80% of such women having gestational diabetes (Guariguata, Linnenkamp et al. 2014). There are few good estimates of the prevalence of pregnancy hypertensive disorders in Africa: but a WHO estimate of the prevalence of the more severe forms of the condition (pre-eclampsia and eclampsia) in women with BMI ≥ 26 is 4.9% (Bilano, Ota et al. 2014).

This trial will address the increasing importance of non-communicable disease in the global burden of ill health, the rising prevalence of obesity and diabetes throughout sub Saharan Africa (including in Malawi) and strategic development goal 3. There is no coherent approach to screening and treatment for gestational diabetes in Malawi and therefore no mitigation of the risks associated with gestational diabetes. In resource rich settings, treatment of gestational diabetes with drugs to lower blood glucose is proven to significantly reduce the risk of short term adverse outcomes and likely reduces the risk of long term adverse outcomes (Farrar, Simmonds et al. 2017). In resource rich settings, this also involves formal glucose tolerance testing, and four times daily monitoring of blood glucose for women found to have gestational diabetes. Such an approach is impractical in resource poor settings because of the high cost of

testing and monitoring per patient (estimated to be £28.58 and £112.07 per pregnancy respectively, 2015 NHS costs) and the irregular availability of glucose monitoring strips. However, metformin endorsed as first line treatment for gestational diabetes in the UK (metformin) is relatively cheap (£11.68 per pregnancy (Excellence 2008)), safe to give without blood glucose monitoring (even for women who are normoglycaemic) (Chiswick, Reynolds et al. 2015, Syngelaki, Nicolaides et al. 2016), and widely available. We propose that, in high risk groups (obese women) routine treatment with metformin, without formal testing for gestational diabetes and without blood glucose monitoring, is a pragmatic approach to preventing and treating gestational diabetes in resource poor settings (which we will test in a trial called PAPAGENO), and will result in improved health care outcomes.

This trial is timely because it makes use of new information on the effect of metformin in obese women without gestational diabetes, where metformin reduces gestational weight gain and pre-eclampsia, is well tolerated and has no major adverse effects (Chiswick, Reynolds et al. 2015, Syngelaki, Nicolaides et al. 2016, Romero, Erez et al. 2017). Notably, *in vitro* studies support a beneficial effect of metformin in reducing pregnancy hypertensive disorders (Brownfoot, Hastie et al. 2016). Together with information on the efficacy of metformin in pregnant women with GDM (Rowan, Hague et al. 2008), these studies pave the way for the strategy we propose here, using metformin without formal testing or monitoring in an unselected group obese women. We anticipate a reduction in GDM and pregnancy hypertensive disorders and we can be confident that women with normoglycaemia will not be harmed.

We hope that this study will show that a larger trial conducted in the future to test metformin as a pragmatic approach to preventing and treating gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings is feasible. Additionally, we anticipate that we will identify the high prevalence of GDM and pregnancy hypertensive disorders in obese pregnant women. It is hoped that the results of this feasibility study will facilitate a funding application for a definitive randomised trial of metformin in this scenario following which we hope to show that universal treatment of overweight/obese pregnant women with metformin is effective in reducing GDM and pregnancy hypertensive disorders, safe, easy to implement and affordable. If so, since metformin is cheap and widely available (on the WHO essential medicines list), such a strategy could be rolled out in other Low and Middle Income Countries (LMIC). Inclusion of policy makers in our collaborative group will facilitate wide implementation.

2. STUDY OBJECTIVES

2.1 SMART OBJECTIVES

2.1.1 Overall Objective

The overall objective of this study is to determine the feasibility of a pragmatic placebo controlled randomised trial of metformin to prevent gestational diabetes and pregnancy hypertensive disorders in obese pregnant women.

2.1.2 Specific Objectives

A. To assess the number of eligible women recruited into the study.
B. To ascertain the proportion of pregnant women presenting at or before 28 weeks gestation [when the intervention will be started].
C. To assess adherence to therapy (ascertained by review of diary and returned study medication)

D. To determine the proportion of women in the placebo group and proportion of those in the active group (if tested prior to starting metformin) who have gestational diabetes at 24-30 weeks
E. To assess the ability to measure key clinical variables like incidence of gestational diabetes and pregnancy hypertensive disorders in women with BMI $\geq$ 26 kg/m2 in this setting, the proportion of women who present early in pregnancy (<20 weeks gestation) and are eligible for recruitment
F. To verify the proportion of women who are recruited but then lost to follow up for the primary and secondary outcomes.
G. To identify an appropriate method by which we can identify women and avoid double randomisation to address co-enrolment (i.e. GPS home identifiers, thumb or finger print).

2.2 ENDPOINTS

2.2.1 Primary Endpoint

For this trial, the primary endpoint is the ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period

2.2.2 Secondary Endpoints

A. Number of eligible women who are recruited into the study.
B. Proportion of pregnant women presenting at or before 28^{+0} weeks gestation [when the intervention will be started].
C. Adherence to therapy (ascertained by review of diary and returned study medication)
D. Proportion of women in each of the placebo group and the active group (if tested prior to starting metformin) who have gestational diabetes between 24^{+0}-30^{+6} weeks
E. Ability to measure key clinical variables:
    - The incidence of gestational diabetes and pregnancy hypertensive disorders in women with BMI $\geq$ 26 kg/m^2in this setting
    - Feasibility of recruitment and randomisation
    - The proportion of women who present early in pregnancy (<20 weeks gestation) and are eligible for recruitment
    - The proportion of eligible women (and clinicians) are willing to participate in the study and be randomised (or randomise) to metformin or placebo?
    - In what proportion of women can we record other secondary outcomes planned for the substantive trial
    - The proportion of women who have an ultrasound scan before 20 weeks gestation so that gestational age can be determined.
    - The resources are required for outcome data ascertainment and collection
F. Proportion of women lost to follow up for the primary and secondary outcomes.
G. Determination of an appropriate method by which we can identify eligible women and avoid double randomisation to address co-enrolment (i.e. GPS home identifiers, thumb or finger print).

3. STUDY DESIGN SUMMARY (PICO)

This is a feasibility study of a double masked randomised clinical trial of metformin (compared with matched placebo) for the prevention of gestational diabetes and pregnancy hypertensive disorders in women at high risk of both conditions.

Population: 100 pregnant women (BMI ≥ 26 kg/m^2) in Malawi.

Intervention: Metformin oral tablets (500mg slow release), up to 2000mg daily from consent (first visit) until delivery.

Comparator: Matched placebo taken with same frequency over the same duration of pregnancy again taken in addition to the current standard of care

Duration of trial: First participant's first visit to the last baby delivered plus 28 days.

Treatment Phase: The treatment phase will be from first visit (expected to between 12^{+0} to 28^{+0} weeks gestation) until delivery. Follow up will continue for 28 days after delivery.

Outcomes:
Primary: The ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period
Secondary outcomes: Proportion of pregnant women presenting at or before 20 weeks gestation, adherence to therapy (ascertained by review of diary and returned study medication) and clinical staff ability to measure key clinical variables.

Stopping Rules: Stopping rules are detailed in section 11.3.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit 100 eligible women in total.

4.2 INCLUSION CRITERIA

To be eligible to take part in the PAPAGENO study, the below inclusion criteria must be met:

(i) Pregnant women with a BMI ≥ 26 kg/m^2
(ii) Pregnant Women between ≥ 12^{+0} and ≤ 28^{+0} weeks gestation
(iii) Women estimated age ≥ 18 years
(iv) Women with a signed (and witnessed, if applicable) informed consent
(v) Willing to be contacted, if necessary.

4.3 EXCLUSION CRITERIA

A. Conditions identified in the current pregnancy, which exclude study participation:

- Women with a BMI < 26 kg/m^2
- Pregnancy gestation > than 28^{+0} weeks
- Women who are known to have a multiple pregnancy at the time of trial entry

- Women who are currently lactating
- Women known to have diabetes
- Women who have been taking HIV antiretroviral medication for less than 6 months
- Women currently taking dolutegravir
- Acute conditions at the time of trial entry with the potential to alter renal function such as:
    - Dehydration sufficient to require intravenous infusion
    - severe infection
    - shock
    - intravascular administration of iodinated contrast agents
    - acute or chronic diseases which may cause tissue hypoxia such as:
        - cardiac or respiratory failure,
        - Pancreatitis
        - recent myocardial infarction,
        - hepatic insufficiency, acute alcohol intoxication, alcoholism

B. History of the following pre-existing conditions, at the time of trial entry:

- Had a previous delivery of a baby <3rd centile for gestational age (e.g. a baby born ≥ 37 weeks gestation and the birthweight was ≤2.25KG)
- A known history in a previous pregnancy of gestational diabetes (needing drug treatment)
- A known history of conditions affecting either the heart, lungs, liver, kidney or brain, which require regular medication at the time of recruitment
- A known history of allergy to metformin or to any of the ingredients as listed in the current Summary Products Characteristics (SPC))
- Known liver failure or dysfunction at the time of trial entry
- Known severe renal failure or dysfunction at the time of trial entry
- Known (any type of) acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- A previous known diabetic pre-coma
- Previous known severe renal failure (GFR < 30 mL/min).

Note, the exclusion conditions listed in B above do not require additional testing to identify them. It is not currently clinical practice to perform formal testing for these conditions prior to giving metformin. Additionally testing to exclude all conditions will add an additional burden to Low Middle Income Country involved. However, the investigator(s) will review the woman's medical history by asking the woman questions and using available information to determine, if the woman has had any of these conditions.
Note, although metformin is not licensed for use during pregnancy its use in this scenario is endorsed by the National Institute for Health and Care Excellence.

5. CO-ENROLMENT

Women involved in other non-CTIMP trials will be permitted to co-enrol. Women in other CTIMPs will be eligible for co-enrolment at the discretion of the Chief Investigator for both studies. The local PI should contact the CI to seek advice and confirmation for co-enrolment. A record of all co-enrolled trials will be maintained and the woman's participation recorded in the eCRF.

6. PARTICIPANT SELECTION AND ENROLMENT

6.1 IDENTIFYING PARTICIPANTS

Current clinical practice is that on arrival at the antenatal clinic all women are weighed and their height measured. Height is recorded as <than 150cm or >than 150cm on the health passport carried by each woman. Women then attend a health education class (which lasts 15- 30 minutes). For the purpose of the study, all women in attendance will be provided with verbal information about the study and asked to present themselves to a member of staff, if they are interested in participating. Each woman is also reviewed by the local clinician (usually an obstetrician or midwife) and if considered potentially eligible she will be given further verbal and written information.

6.2 SCREENING FOR ELIGIBILITY

Women with a pregnancy between ≥12^{+0} and ≤ 28^{+0} week gestation and with a height recorded as less than 150cm and a weight ≥ than 55kg (BMI equivalent 26) or a height > than 150cm and a weight greater than 60kg (BMI equivalent 26) will be reviewed by an appropriately trained, individual/delegated clinicians who will calculate their actual BMI, with repeat measurements of height and weight as required. Since measurement of height and weight is carried out routinely, we will not seek formal written consent for this. Further eligibility criteria will be ascertained from the patient notes / history. Again, given these questions are routine, we will not seek formal consent to determine initial eligibility. Women who appear to fulfil the inclusion criteria will be asked if they wish to participate in the study. An anonymised screening log will be maintained on the eCRF for all patients considered eligible for the trial, including those who decline to participate. The log will include estimated maternal age, gestation and BMI at presentation, as well as any exclusion reason or reasons (if provided) for declining. Eligibility will be confirmed by an obstetrician before randomisation.

If a participant declines to participate, withdraws prior to randomisation, or is excluded following consent but prior to randomisation for any reason, the minimal anonymised information will remain on the screening log. If participants are willing to offer a reason for declining to participate, this will also be held on the screening log.

6.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Details will be maintained as above for ineligible participants including reason for ineligibility, and these patients will be treated as per local guidelines.

For participants who consent to participation but who are not randomised, reason for this will be recorded in the screening log e.g. Participant withdrew consent or delivered prior to administration of first dose of intervention. This is a feasibility study and the barriers to recruitment and participation are collected in order to assess the impact of a potentially larger trial.

6.4 CONSENTING PARTICIPANT

Women who appear eligible for the study after the screening assessment will be provided with further information about the study in the form of a copy of the written information sheet in English and Chichewa. All written information will be read to the woman in full by either the investigator or delegate who may be a Community educator/nurse. An independent witness will be requested for women with low literacy skills. Women will then be given a suitable period of time (usually a minimum of 24 hours) to consider if they would like to participate in the study and to talk to their husbands and other family members if they wish. Interested women will usually be asked to attend the clinic the following week. However, many women travel long distances to attend antenatal care and if she prefers, the woman may waive the time

to consider the study, and consent at the first study visit. This will be recorded on the eCRF.

Women who are willing to participate will be asked to provide written informed consent prior to undertaking any study procedures. Women with low literacy skills may need to sign the consent form using a thumb print (preferred). In this scenario an independent witness will be sought to countersign the consent form to confirm that the woman appears to have given consent and that she appears to understand the nature of the study and what she is being asked to do. Women who undergo the informed consent process and provide a written consent will then undergo screening for eligibility determination.

7. RANDOMISATION

7.1 Randomisation Procedures

Participants will be randomised to treatment (active or placebo) in a 1:1 ratio. Recruiting centre will be the only stratification variable, using simple randomisation under a randomly permuted block design. Randomisation codes will be provided by ECTU to ISG and packs dispensed in a sequential fashion. Details of the study pack number allocated will be recorded in the participant's medication record as well as in the drug accountability logs.

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7.2 EMERGENCY UNBLINDING PROCEDURES

In a clinical emergency, where continued treatment with metformin is considered potentially harmful by the woman's attending clinician, participating women should be treated as if they were taking the active treatment (metformin) and should stop the study treatment. It is anticipated that breaking of the study blind should be performed only where knowledge of the treatment is absolutely necessary for further management of the participant. It is not anticipated that the development of gestational diabetes will be an indication for unblinding as the study treatment must stop, as described in paragraph 5.9.

The on-site pharmacy will hold the unblinding information. Thus unblinding (emergency or otherwise) can be carried out locally by a pharmacist, if requested by a senior clinician (normally a consultant). This unblinding process will be available during normal working hours. A 24/7 telephone unblinding will also be available. In the case of any unblinding, the name of the clinician requesting the unblinding and the reason for it will be sent to the sponsor's representative via e-mail, who will inform the CI. In case of a SUSAR, the sponsor will contact ECTU for the unblinding code for that participant.

The reasons for unblinding will be documented and added to the eCRF. Unless there is a clinical requirement, the blind will not be broken to any member of the trial team until after data entry is complete and the database locked. Details of the unblinding will be kept in pharmacy.

7.3 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point if they wish. Additionally, a participant can be withdrawn by the Investigator.

If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's medical records and eCRF, if possible. The participant will have the option of withdrawal from:

(i) Taking the study medication, with continued study procedures and collection of clinical and safety data.

(ii) All aspects of the trial. In this scenario, study teams can continue to use data collected up to that point

If a participant wishes to withdraw from the trial (or if the investigator advises withdrawal). The trial team will be informed and withdrawal will be recorded in the medical notes and eCRF, along with the aspects from which they wish to withdraw.

7.4 CESSATION OF STUDY MEDICATION

Medication (but not study participation) will be stopped in any of the following circumstances:

- Fetal demise in utero
- Diagnosis of diabetes (gestational or otherwise)
- If the participant develops severe pre-eclampsia or HELLP syndrome
- Delivery of the baby (end of pregnancy)
- If the clinical team judge that immediate delivery is advised in the next 48 hours, for example in the case of development of severe sepsis or evidence of fetal compromise.

Metformin should be stopped temporarily if any of the following occur:

- Elective surgery (metformin should be stopped 48 hours prior)
- Severe diarrhoea or vomiting or fever
- Reduced fluid intake
- Non steroidal anti-inflammatory drug therapy for more than two days

Metformin can be restarted once the event/ episode above has ceased:

Participants who stop treatment following administration of the first dose of intervention or any doses thereafter will not be replaced by additional recruited participants. Where possible, data will continue to be collected from all participants after initial enrolment to allow intention to treat analysis.

8. STUDY DRUG

Active drug: Metformin (Glucophage) 500mg slow release film-coated tablet up to 2000 mg per day

Placebo: Placebo tablets will be identical to the active tablets except for the active ingredient.

Both placebo and active drugs will be supplied by Merck KGaA.

8.1 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

8.1.1 Study Drug Manufacturer

Active and placebo drug:
Merck Santé

2 Rue de Pressoir Vert,

45400 Semoy,

France

8.1.2 Marketing Authorisation Holder

Active drug: Glucophage XR 500 mg: A39/21.2/0027 **Placebo:** Not Applicable

8.1.3 Labelling and Packaging

Both the active and placebo treatments will be labelled and packaged in high density polyethylene (HDPE) bottles by Investigational Supplies Group (ISG), 2nd floor, 1 George Square, Edinburgh, EH8 9JZ in accordance with the Pharmacy, Medicines and Poisons Board (PMPB). Drugs will be supplied in bottles each containing Glucophage 500 mg slow release tablets or placebo sufficient bottles for one month supply will normally be dispensed to a participant at any one time.

8.1.4 Storage

This IMP requires storage store at or below 30 °C.

8.1.5 Regulatory Release to Site

This will be performed by the QP from ISG. A working practice document will be generated to clarify how the drug will be distributed.

8.1.6 Destruction of Trial Drug

Destruction of trial drug will be conducted in Malawi in accordance with the local PMPB procedures.

8.1.7 Summary of Product Characteristics (SPC) or Investigators Brochure

A Summary of Product Characteristics (SPC) is available in a separate SPC booklet.

Licensed indications are for the treatment of type 2 diabetes mellitus in adults (including pregnant women for pre-existing diabetes and Gestational diabetes) particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin will not be used within its licensed indications for this study. In the UK, Glucophage® SR is also licensed for a reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired Glucose Tolerance and /or Impaired Fasting Glucose, and/or increased HbA1C (glycated haemoglobin).

Contraindications are noted in the exclusion criteria for this study.

8.1.8 Information on the label.

Medication labels will be (English and Chichewa) and comply with the legal requirements of Pharmacy Medicines and Poisons Board (PMPB) and ICH GCP. They will include storage conditions for the drug, but no information about the participant. Pictures will also be included in the labels to show participants how many tablets to take and when to take them i.e. sunrise and sunset etc.

8.2 DRUG DISPENSING

Drug stocks will be held by the local pharmacy departments and transported to the clinical areas or given directly to the participant after randomisation, as appropriate. Following randomisation, the next sequential pack as allocated will be detailed in the

accountability log and removed from the supply shelf. All treatments will be dispensed by authorised staff and prescribed a physician. Following dispensing, the first dose will be administered to the participant in a timely fashion, ideally on the same day or within 48 hours. There will be space in the participants' daily diary to record the dose administration.

8.3 DOSING REGIME

Women will be prescribed metformin tablets in an incremental dose starting at 500mg (1 tablet per day) increasing over four weeks up to 2000mg (4 tablets per day).

First dose will be administered following consent (first visit between 12 and 28 weeks gestation). Women will be asked to start (week 1) with 500mg metformin (1 tablet, once daily) taken with food in the evening, increasing in week 2 to total daily dose of 1000mg per day (2 tablet, one in the morning and one in the evening daily). In week 3: there will be a further increment to a total daily dose of 1500mg per day (3 tablets, one in the morning and two in the evening daily). In week 4 there will be a final increment to a total daily dose of 2000mg (4 tablets, two in the morning and two in the evening daily). Thereafter treatment is planned to continue at 2000 mg (4 tablets) until women have delivered their baby or met one of the criteria described paragraph 5.9.

Week	Morning Tablets (500mg each)	Evening Tablets (500mg each)
Week 1	0	1
Week 2	1	1
Week 3	1	2
Week 4	2	2
Week 5	2	2

If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman or the woman's physician can adjust the dose to the previous week's dose or to 500mg metformin (whichever is the greater) and wait for a week before increasing the dosage again. They may also recommend to minimize adverse effects that the women take the treatment in the evening as the maximum recommended dose is 2000mg daily, taken as one dose in the evening.

8.4 DOSE CHANGES

The local investigator may alter the above treatment regimen at his/her discretion. Women may also be advised to take the medication as a single dose in the evening, if they prefer, provided the maximum daily dose does not exceed 2000mg. Changes to treatment dose will be recorded on the eCRF as soon as practicable. Where AE are considered by the participant or the local investigator to be excessive, the investigator (or participant) can adjust the IMP dose accordingly.

8.5 PARTICIPANT COMPLIANCE

Participants will be asked to keep a daily diary to record drug intake and to bring all medication including empty packaging to each study visit, so that the health care staff can record how much study drug has been taken.

Unused medication will be requested to be returned to the trial centre and individual tablets will be counted by pharmacy staff to ascertain the number taken.

8.6 PRECAUTIONS

Overdose: Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose

of metformin hydrochloride or concomitant risks may, very rarely, lead to lactic acidosis. Lactic acidosis is a very rare complication of metformin, occurring in less than 4 per 100,000 patients. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

Dehydration: In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily halted and contact with a health care professional is recommended. Treatment may re-commence on advice of the local Principal investigator

8.7 Non-Investigational Medicinal Products

There are no NIMPs used in this CTIMP

8.8 PERMITTED MEDICATIONS

All medications other than those detailed in the current SPC and 6.7.3 (prohibited medications) are permitted.

Medications that participants have been prescribed pre-pregnancy and which have been continued during the pregnancy as per the supervising physician responsible for participant care may be taken during the trial.

Women currently prescribed treatments for HIV will be permitted to join the study provided they have been taking HIV medication for greater than 6 months. Metformin is not currently known to interact with protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs). However, lactic acidosis a side-effect of some nucleoside reverse transcriptase inhibitors (NRTIs). Patients taking these drugs with metformin may be at an increased risk of lactic acidosis (HIV In site 2018 and HIV and Aids information 2018).

Lactic acidosis is a rare event estimated to be 3.3 to 4.3 per 100,000 patient years in patients treated with metformin (Lalau, JD. Drug-Safety 2010). However, in the event any woman experiences a major reduction in urinary output (e.g. output is less than 200ml per day) they should be advised **to stop the study treatments** immediately and seek Medical advice.

8.9 PROHIBITED MEDICATIONS

Should any of the below prohibited medications be inadvertently co-administered with the IMP, the participant should contact their obstetric team and attend for assessment as required.

- **Alcohol** and alcohol containing medicinal products since there is increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of fasting, malnutrition, or hepatic insufficiency. Pregnant women should avoid alcohol in any case, so this is not likely to be a significant issue in practice.
- **Iodinated contrast agents** should also be avoided since intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin hydrochloride accumulation and an increased risk of lactic acidosis. Thus any woman in the study who needs such an agent will be advised to discontinue metformin hydrochloride must be discontinued prior to, or at the time of the test and not restart metformin until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.
- **Glucocorticoids** (systemic and local routes), beta-2-agonists, and diuretics may attenuate metformin's potential hypoglycaemic effect and ACE inhibitors may amplify it. Use of these agents is not prohibited but they should be used with care in women participating in this study and after discussion with the local principal investigator.

9. STUDY ASSESSMENTS

9.1 SAFETY ASSESSMENTS

Safety will be assessed at each routine clinic visit and documented in the medical notes and eCRF. Serious Adverse Events (SAE) will be reported as described in section 12. However, the most common adverse reactions known to be caused by metformin are: nausea, vomiting, diarrhoea, abdominal pain and loss of appetite: most resolve spontaneously. We will record on the eCRF and reported as AE's any of these symptoms that have been experienced during the seven day period, preceding the study visit. Interim un-blinded outcome data will be made available to the Data Safety and Monitoring Committee (DSMC).

9.2 STUDY ASSESSMENTS

INFORMATION VISIT (screening visit)

Conducted between Week 12^{-0} and 28^{+0} weeks gestation

Women attending as described in paragraphs 5.1 to 5.3 and who meet the initial eligibility criteria will be provided with a copy of the Patient Information Leaflet, given the opportunity to discuss the study and to ask any questions. The inclusion / exclusion checklist will be used as a guide to eligibility at this stage, and may be completed in part, if wished. After the woman has had the opportunity to consider whether she would like to participate, if she declines minimal details will be collected and added to the study screening log and the reason for declining collected.
If she verbally agrees she will be invited to give written consent to the study (witnessed if required as described above) and be randomised.

CONSENT

Women who are eligible and wish to participate (as described in paragraph 5.4 above) will be asked to sign a consent form. Eligibility will be formally confirmed by a suitably trained and delegated clinician. The original consent form(s) will be stored in the Investigator Site File (ISF) file, a copy is given to the woman, a copy added to the medical notes.

The consent log will be updated via the eCRF and following completion of the consenting procedures the following baseline assessments will be performed on participating women:

- Demographics
- Medical History including current pregnancy details, previous pregnancies, Height, Weight and Vital signs
- Preferred contact information

RANDOMISATION

Randomisation will occur after eligibility has been confirmed and consent has been given. Women will then be randomised and assigned to one of the study treatments either metformin or placebo.

A prescription will be issued for dispensing of the IMP. Medication will be dispensed in HDPE plastic bottles with sufficient supply for 4 weeks of treatment. A date for starting treatment should be agreed with the participant, and this should be no later than 48 hours after randomisation.

Women should be informed that after they take the medication that they may see a complete tablet in their stool (the placebo is designed to have the same effect). This is normal this is an empty shell of the tablet which is harmless and it indicates that the tablet has passed through her intestine correctly.

MONTHLY STUDY VISITS (+/- 7 days)

Approximately 1 month (plus or minus seven days) after the commencement of study treatment (and every 4 weeks thereafter until delivery) a study visit will be conducted. During the visit the study team will collect information on any side effects, adverse events and pregnancy complications.

Adverse events (AE) will be recorded in the eCRF, and serious adverse events (SAEs) will be recorded on the SAE form as per section 10. Patients will also be asked to return their empty medication packages and unused medication to each visit. They will be asked if they are complying with their study medication and the diary reviewed, if available.

A further drug supply (sufficient for up to 5 weeks of treatment) will be prescribed and dispensed at each study visit, as required.

The number of monthly antenatal study visits completed for each woman will depend on the gestation at which the woman was recruited i.e. if consented and randomised at 12 weeks we would anticipate 8 antenatal visits (consent at 12 weeks plus a monthly visit at each gestational time point: 16/20/24/28/32/36 and 40 weeks maximum) to be conducted and recorded.

WEEK 24^{+0} – 30^{+6} GESTATION VISIT

At one of the monthly visits, which occurs at or between 24^{+0} and 30^{+6} weeks gestation. A 75g OGTT (baseline and 2 hour sample) will be performed (as per the working practice document) and stored locally for future investigations.

Prior to the visit, the woman will be given written information and have this read to her (if applicable) which ask her to fast (take no food, only water) for a period of 8-12 hours before the appointment. With the exception of the 75g glucose load, the woman will remain fasted until after the 2 hour blood sample is taken.

The results of the glucose tolerance test is not a routine test, and the results will be concealed from the woman and from her caregivers until the end of the study. An additional OGTT (outwith the trial) can be performed for clinical reasons at any time if required by the local physician. If a participant develops gestational diabetes during the study, she will be asked to stop the study treatment (IMP) and will be referred to her obstetrician for further advice and treatment, which may include diet metformin and/or insulin. The details of any treatments and reasons for stopping the IMP will be recorded in the eCRF. Following local procedures the clinical care team may also conduct tests to identify other pregnancy related diseases such as a blood pressure monitoring, urine test strip and blood samples to screen for e.g. pregnancy induced hypertension, pre-eclampsia or anaemia. Any diseases identified in a participant/ fetus/ baby will be recorded following the adverse events reporting.

LABOUR and DELIVERY

Admission for delivery will not be a formal study visit and as it is anticipated it will not be recorded as an SAE. Information will be obtained usually from the woman's medical notes on the maternal outcomes of delivery, including method of delivery, indication for delivery method, date and gestation of delivery and blood loss.

Information on the previous 4 weeks' pregnancy and labour and delivery complications will be collected. Adverse events (AE) will be recorded in the patient notes and on the

eCRF. Serious adverse events (SAEs) will be recorded on the SAE form and in the eCRF. All unused study medication returned and sent to pharmacy for recording compliance. The participant diary will be collected and data entered on the eCRF.

The baby outcomes of delivery including baby weight, gender, and birth outcome (e.g. live birth, stillbirth or death in the delivery room) will be collected and recorded by local investigators mainly from hospital notes, and the data will be entered on to the eCRF.

NEONATAL and 28($^{+7}$) DAY POSTNATAL VISIT

Either participants visit the hospital to meet face to face with staff, or staff may visit the woman at her home or local clinic. The woman will be thanked for her involvement and further data collected about both her and her babies' well-being since delivery, this will be in the form of a short questionnaire (in English and Chichewa). The questionnaire will be read to her and her answers translated and recorded on the eCRF.

SAE's will be recorded up to 28days after birth. Events which have not resolved at study completion will be reviewed prior to database lock and a resolution sought where possible. We will also ask women for permission to invite them and their babies for some future studies.

End of trial participation will be recorded in the eCRF and (if available locally) the medical notes.

TRAVEL REIMBURSMENT

Women will be recompensed travel cost as per Government recommendations for each study visit, which is additional to normal antenatal care. It is anticipated women would usually attend three antenatal visits routinely between booking for care and delivery.

Women are expected and encouraged to deliver in hospital and this will not be a considered a study visit. The postnatal (28 day visit) visit would be study specific visit.

END OF STUDY PROCEDURES

At the end of the study, the results of the oral glucose tolerance test taken in pregnancy will be fed back to the participant's health care provider.

TABLE OF STUDY VISITS

Pregnancy gestation	**12^{+0} to 28^{+0} weeks**			**16, 20, 32, 36,40 weeks**	**24-30Weeks**	**Labour Delivery/**	**Neonatal/ 28 day postnatal**
	Screening	**Consent**	**Randomisation**	**Monthly**	**Study visit**	**Study visit**	
Inc/Exc Criteria	X						
Patient Information Leaflet	X						
Consent Form		X					
Demographics		X					
Medical History		X					
Height and Weight		X					
Vital Signs		X		X	X	X	
Confirm eligibility		X					
Randomisation			X				
Study Drug dispensed			X	X	X		
Review Patient Diary (collect at Delivery)				X	X	X	
Complete side effects questionnaire on eCRF				X	X	X	
Review and record pregnancy complications				X	X	X	
Review SAE's				X	X	X	X
Fasted glucose tolerance test (sampling at baseline and 2 hrs)					X		
Stored sample for inflammatory markers etc					X		
Unused Study Drug /packaging returned				X	X	X	
Labour/Delivery Information						X	
Neonatal/28 day postnatal complications and questionnaire							X

10. COMPLIANCE ASSESSMENTS

Treatment Compliance will be recorded in diary as described in paragraph 8.5.

10.1 STORAGE AND ANALYSIS OF SAMPLES

Samples will be collected and stored as per local SOP in local Laboratories. Blood samples for the glucose tolerance test will be processed and then stored in the laboratories of the recruiting sample. Analysis for glucose will be performed after the last patient last visit is complete and any remaining blood discarded.

An additional aliquot of blood will be sent to the laboratories at MEIRU for storage and future analysis of inflammatory markers (and other analytes to be determined). These samples will be stored for 5 years. It is not anticipated that any blood samples will be shipped out of Malawi.

10.2 DATA COLLECTION

Data will be collected by the trial team from the participant verbally and confirmed where possible in the medical records including demographics, details of current and previous pregnancies, contact details, information about blood test collections, labour and delivery outcomes, and neonatal / postnatal outcomes. Participants will be asked about their well-being at each post-randomisation visit to identify side effects and any adverse events for reporting. We will also review diaries for compliance, acceptability and side effects. Results of study blood tests for glucose tolerance testing locally will remain concealed from the participant and her clinician until the trial is completed.

10.3 SOURCE DATA DOCUMENTATION

Source documents are original documents, data and records where source data are recorded for the first time. This is all information entered directly in to original records (mother and baby) and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Data will be derived from the participant's own and their baby's medical records, history from the patient, medication charts, study diary, postnatal questionnaire and laboratory results. All study data will be transcribed on to the eCRF by the recruiting team or by a data clerk based in Malawi. All study data will be entered by authorised and delegated individuals. All electronic data collected will be held securely locally. A copy of an anonymised database will be transferred to the Edinburgh Clinical Trials unit at intervals to be described. Patient identifiers will not be transferred outside Malawi. A separate data management plan will be generated to describe management of the data in more detail.

For the purpose of study archiving the eCRF will be considered source data and archived according to ECTU policies.

10.4 CASE REPORT FORMS

All case report forms (electronic) for this study will be approved by the study sponsors prior to use (as per SOP CR013 eCRF Design and Implementation) and by the ethics committee.

10.5 TRIAL DATABASE

The trial database will be developed and managed by the Edinburgh Clinical Trials Unit. The database will be hosted on servers based at the Malawi Epidemiology and Research Unit (MEIRU). The full trial database will contain patient identifiers to facilitate future follow up. Participants will be asked to consent to this at recruitment. Patient identifiers will only be visible to clinicians entering the data and to nominated data clerks in Malawi.
A copy of an anonymised subsection of the database will be transferred to the Edinburgh Clinical Trials Unit at intervals for analysis. On completion of the study, Edinburgh will store the final version of the anonymised subsection of the database for an indefinite period. The Malawi Epidemiology Research Unit will store the original version of the database (with identifiers) indefinitely. On completion of the study and publication of study results, anonymised data may be shared with other researchers upon request, in line with MRC guidelines.

11. STATISTICS AND DATA ANALYSIS

11.1 SAMPLE SIZE CALCULATION

Sample size. It is not possible generate a formal sample size calculations for feasibility studies, Our proposed sample size is based on the 30-50 per arm recommended for feasibility studies by some funders (National Institute for Health Research) (Chief Scientist Office). The feasibility study described here will be used to determine whether a large randomised trial is warranted and feasible. The remaining outcomes will be used either as safety markers, and will allow an estimate of the prevalence of gestational diabetes and pregnancy hypertensive disorders – all of which will inform the design of a large randomised trial.

PAPAGENO is the first cTIMP by the Chief Investigator in Malawi, and we anticipate that recruitment strategies may require refinement during the pilot before they are fully effective. Hence we plan to recruit at the upper end of the sample size recommended for feasibility studies - 50 per arm (i.e. 100 women in total), to allow us to properly test the feasibility of the study in this novel setting. We anticipate that the first 50 recruits will be used to implement and refine recruitment strategies, and the final 50 recruits will be used to properly determine recruitment rate.

Dropout rates, assumptions and justification. The drop out rate in our previous (UK) trial of metformin in pregnant women was less than 5 % (Chiswick, Reynolds et al. 2015). This is significantly lower than the average drop out rates in clinical trials which approach 30% (Centrewatch news online 27th June 2016). We anticipate that the drop out rate in this trial might be as high as the average, leaving 70 women with usable data at the end of the study.

Recruitment period assumptions and justification. We will recruit over a 12 month period, with follow up (to the end of pregnancy and the neonatal period) over a further 6 months. Recruiting over 12 months requires a recruitment rate of 8-9 women per month. Most of the recruitment will occur in one site. Over 100 new pregnant women are seen each week in this recruiting sites. Hence we are confident that sufficient women are available for recruitment. Failure to recruit 100 women in 12 months will imply that the study is not possible as currently configured. We will also attempt to recruit in a second site. Recruitment in this second site will be considered exploratory only, and will not inform the recruitment rate described below.

11.2 PROPOSED ANALYSES

The primary outcome is the ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period. We will report this separately for the first 50 women, and the final 50 women in the primary recruiting site. The ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period for the final 50 women in the primary recruiting site will be used to inform the timelines for a substantive trial.

Within the placebo group, we will determine the prevalence (with 95% confidence limits) of each of gestational diabetes and pregnancy induced hypertension.

We will generate mean (SD) or incidence of secondary outcomes overall, and in each of the two treatment groups. No formal statistical comparisons will be made between the two treatment groups, given the limitations of study power. A formal statistical analysis plan will be generated prior to study unblinding.

11.3 STOPPING RULES

We have set the following safety rules for PAPAGENO based on maternal and neonatal deaths that are possibly or definitely related to IMP. We have based these rules on the expected frequency of maternal and neonatal deaths in the population.

Maternal death rate in Malawi is 634 per 100,000 (UNICEF 2015). The combined stillbirth and neonatal death rate in Malawi is 44 per 1000 births (UNICEF 2015). With these expected death rates, we consider that a trebling of this rate would be grounds for serious concern. If such deaths were thought to be related or possibly related to study IMP, that will prompt a halt in recruitment pending review by the independent Data Monitoring and Safety Committee (iDMSC).

Our stopping rules will be based on the number of deaths expected within the first 25, 50 and 100 women recruited. The table below shows the number of expected deaths, and the number within each recruitment band that will trigger a rapid review by the iDMSC. The iDMSC will convene to review data within 14 working days. All the deaths are considered to be related, recruitment will be halted pending the iDMSC. If one or more of the deaths is considered unrelated, recruitment will continue pending review by the iDMSC. Whether or not the deaths are considered related, already recruited to the trial will continue on allocated IMP, pending the iDMSC review. The iDMSC will review unblinded data and advise whether the trial should be stopped, or the circumstances under which the trial should continue.

Number of women recruited	Expected number of maternal deaths	Number of maternal deaths that will trigger a halt to further recruitment.	Expected number of combined stillbirths and neonatal deaths	Number of combined stillbirths and neonatal deaths that will trigger a halt to further recruitment.
Up to 25	Less than 1 (0.158)	1	1.1	3
Up to 50	Less than 1 (0.317)	1	2.2	6
Up to 100	Less than 1 (0.634)	2	4.4	13

The most serious adverse effect of metformin is lactic acidosis, with an estimated frequency of 4 per 100,000. In a sample size of 100, we would expect 0.0004 cases of lactic acidosis. Any events of lactic acidosis will prompt a review by the iDMSC within 14 working days. If lactic acidosis is considered related to the study medication, recruitment will halt temporarily, pending review by the iDMSC. If lactic acidosis is not considered related, recruitment will continue, pending review by the iDMSC. Those already recruited to the trial will continue on allocated IMP pending iDMSC review. The iDMSC will review unblinded data and advise whether the trial should be stopped, or the circumstances under which the trial should continue.

12. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC). A specific version (by date) of the SPC will be identified as the source of the RSI, and will be submitted to the PMPB for that purpose.

Participants will be advised to contact their Investigator at any time after consenting to join the trial if any symptoms develop; alternatively participants will be able to report symptoms at their monthly clinic visit. All Serious Adverse Events (SAE) that occur after informed consent until 28 days after delivery of the baby must be recorded and submitted to the regulatory authorities (PMPB) and trial sponsors as soon as possible (within 24-48 hours) after the site becomes aware of the event. In the case of a common AE (known to be caused by Metformin and documented in the SPC) a record of women's experience of these will be collected at each monthly visit.

12.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).
An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant – including neonatal deaths**

- is life threatening*;
- adverse medicine experience
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity**
- congenital anomaly/birth defect or spontaneous abortion (miscarriage)
- cancer new onset or recurrent **
- Immune Dysfunction: new diagnosis either of HIV or life-threatening immunodeficiency diseases.
- An important medical event, based on appropriate medical judgment that jeopardises the participant and may require intervention to prevent one of the outcomes listed above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

** Reportable events regardless of the relationship to the IMP.

^Any hospitalisation that was planned prior to enrolment (such as hospitalisation for delivery of the baby) will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP contained in the Reference Safety Information (RSI) for that IMP. The RSI is contained in the Summary of Product Characteristics (SPC) for the IMP, which was submitted to the PMPB as part of the approvals process. The RSI is usually comprised of the 'undesirable effects' detailed in section 4.8 of the SPC; this section is used to assess the expectedness of an SAR.

12.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs and SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

For this study the following events are **NOT** considered SAEs as they are expected and are collected as described below in the eCRF. However if the PI or delegate believes any of the events listed below are possibly related to the study treatment then an SAE should be submitted.

- Pregnancy is not considered an AE or SAE, as it is an inclusion criteria.
- Hospitalisations for treatment planned prior to randomisation documented in medical notes and the eCRF prior to randomisation i.e. hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. However, ***complications occurring during such hospitalisation will be AE/SAEs.***
- Pregnancy outcomes for which data are collected in the eCRF at a study visit or as Labour/Delivery outcomes will also not be reported as SAE are:

- Preterm labour
- Preterm pre-labour spontaneous rupture of membranes
- Preterm delivery in maternal interest
- Preterm delivery in fetal interest
- Hospitalisation for “maternal discomfort”
- Hospitalisation for “rest”
- Hospitalisation for “observation” or “monitoring” for which the women is admitted for a period of less than 12 hours
- Delivery complications such as caesarean section or postpartum haemorrhage
- Admission of the baby to the neonatal unit for any duration

12.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Principal Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Principal Investigator will then record all relevant information in the eCRF/AE log, including in the eCRF SAE section (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome. Personal identifying information should be limited to that required by the PMPB, and that required by the Sponsor (which may differ from the PMPB requirements).

12.3.1 Pre-existing Medical Conditions

Relevant pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

12.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant’s underlying medical condition should be recorded in the Participant’s medical notes and only be recorded as an AE or SAE, if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs or SAEs..

12.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs/SARs must be assessed for expectedness by the Principal Investigator, or another suitably qualified physician in the research team who has been delegated this role, using the Reference Safety Information (RSI; see section 12.1).

For this randomised double blind study, all events and reactions will be assessed as though the participant is taking active IMP (metformin). Potential SUSARs will be unblinded by the Sponsors and both the PMPB and RECs will be informed by the Sponsor if a SUSAR is confirmed. In order to preserve the study blinding, the investigators will not be made aware of SUSAR confirmations.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE, SAR or potential SUSAR, but can upgrade events, if appropriate.

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12.5 ASSESSMENT OF SERIOUSNESS

The Investigator will make an assessment of seriousness as defined in Section 10.1.

12.5.1 Adverse Event Grading

Toxicity grades should be used by the site clinicians and assigned to all SAE:

1= Mild

2= Moderate

3= Severe

4 = Life threatening

5= death

12.5.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- **Definitely related**
- **Probably related**

- **Possibly Related:** The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the reference safety information of the SPC (refer to the appropriate section).

- **Not related:**

Any AE/SAE that is considered to be 'Definitely Related', 'Probably Related', or 'Possibly Related' to the IMP will be deemed an AR or SAR (and, if unexpected, a potential SUSAR) for onward reporting purposes. Only events that are considered to be 'Not Related' to the IMP will be deemed AEs or SAEs

Where non Investigational Medicinal Products (NIMPs) and the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

12.5.3 Assessment of Expectedness

If the event is an AE the evaluation of expectedness will be made based on knowledge of the reaction and the relevant Reference Safety Information (RSI) information documented in the SPC.

The event may be classed as either:

- **Expected**: the AE is consistent with the undesirable effects of the IMP listed in the RSI (section 4.8 of the SPC).
- **Unexpected**: the AE is not consistent with the known undesirable effects detailed in the RSI

12.5.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the ECRF/AE log or SAE form 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 to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday 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 may not be severe.

12.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the PMPB and Sponsor's office **within 24-48 hours of site awareness**. The information will be input, via a tablet device, into the safety reporting page of the same electronic interface used for the eCRF. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying the authorities and Sponsors. The SAE report can be updated later when the additional information is received.

The SAE form will be printed and transmitted to the PMPB board by fax or hand delivered to:

The Registrar

Pharmacy, Medicines and Poisons Board

P.O. Box 30241

Lilongwe 3

Malawi

Fax 265 1755204

And a scanned copy sent via email to safety@accord.scot

Only forms in a pdf format will be accepted by Sponsors via email. Forms may also be sent by fax on **+44 131 242 9447** Where missing information has not been sent to the Sponsors will contact the Investigator and request that the missing information is provided via the tablet device interface. The Investigator must respond to these requests in a timely manner.
All reports submitted faxed to the PMPB and Sponsors including any follow up information will be retained by the Investigator in the Investigator Site File (ISF) including all acknowledgements of receipt.

12.7 REGULATORY REPORTING REQUIREMENTS

The Sponsor is responsible for pharmacovigilance reporting and has a legal responsibility to notify the regulatory competent authority (PMPB), the relevant ethics committees RECs that approved the trial and Merck KGaA as the provider of the IMP. Fatal or life threatening SUSARs will be reported to the RECs no later than 7 calendar days, and all other SUSARs will be reported no later than 15 calendar days, after the Sponsor is first aware of the reaction.

The Sponsor (or delegate) will inform Investigators at participating sites of all potential SUSARs and any other arising safety information.

The Sponsor will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Chief Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with the sponsor.

12.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the PMPB and the Sponsors office, via the tablet device interface.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the eCRF or SAE log or additional information section of SAE form.

13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), Trial collaborators and Trial Manager.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for reviewing the eCRF for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

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

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in the DSMC & TSC Charters.

13.3 INDEPENDENT DATA SAFETY AND MONITORING COMMITTEE

An independent Data Safety and Monitoring Committee (iDSMC) will be established to oversee the safety of participants in the trial. The iDSMC is established to protect and serve the study participants, in particular with regard to safety and to assist and advise Investigators and the Trial Steering Committee, so as to protect the validity and credibility of the trial. To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in the iDSMC Charter.

The iDSMC will consist of both local and international members with a broad range of clinical, experience. The iDSMC members are independent of the trial (that is, they are not involved with the Study trial in any other way or have some competing interest that could impact on the PAPAGENO trial). Any competing interests, both real and potential, must be declared.

The iDSMC Charter will be signed by the appropriate individuals preferably prior to the trial commencing.

13.4 INSPECTION OF RECORDS

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

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the sponsor monitors and the QA group, in accordance with the sponsor's governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

The sponsor, clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve remote monitoring activities as far as is practical and some onsite monitoring as necessary. The Sponsor's QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 in the UK and the Pharmacy, Medicines and Poisons Act (PMPA) (January 15, 1991) Ministry of Health, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator (PI) 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 ICH GCP. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Informed Consent

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

Potential Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the woman will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if 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 will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form.

If a woman is unable to read an impartial witness should be present during the entire informed consent discussion. If capable of doing so, the woman should sign and date the form; then the independent witness should sign and personally date the consent form.

NB An impartial witness may be:

1. A relative/friend of choice accompanying the woman to the appointment
2. A Member of staff at the site, not involved in the trial (for example support staff)
3. Another participant/ patient in hospital who is literate, and is willing to stand in as witness and is accepted by the prospective participant.

The witness should be made aware that they are confirming that the trial has been accurately explained, appeared to be understood and consent was freely given.

14.3.2 Study Site Staff

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

14.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the eCRF at each Investigator Site.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the Sponsor's Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- The Sponsor will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

14.3.5 ICH GCP Training

All delegated study staff must hold evidence of appropriate ICH GCP training and updated as per the local requirements.

14.3.6 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. The Investigator and 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.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation) in both the UK and Malawi with regard to the collection, storage, processing and disclosure of personal information. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

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.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

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

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority for approval prior to implementation.

15.2 PROTOCOL NON COMPLIANCE

15.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or ICH GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsor within 5 working days and submitted by the sponsor to the regulatory authorities for review. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot only forms in a pdf format will be accepted by the sponsor via email. Where missing information has not been sent to sponsor after an initial report, the sponsor will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the PMPB. This is defined as an urgent safety measure and the investigator must contact the PMPB and discuss the issue with a medical assessor immediately 265-1755166 /165.

The Investigator will then notify the PMPB the REC and Sponsors, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 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 participants of the trial; or
b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

16. STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

All Study documentation will be archived as per the Sponsors Standard Operating Procedure(s) (CR009 Study Closure and Archiving; GS005 Archiving essential Study Documentation) and will be retained in a way which preserves the integrity and readability of the information.

The Trial Master File (TMF) will be retained in Edinburgh and archived by the study Sponsors. The local Investigator site files (ISF) will be retained and archived by the Principal investigator (PI) and stored locally. During the close out process the local Principal Investigator(s) will inform the Sponsors with the details of a named custodian responsible for the secure archiving of electronic and paper research study data. Any transfer of ownership of the archived data must be documented and agreed with the sponsor(s).

17. END OF STUDY

The end of study is defined as the date of last baby delivered plus 28 days of the last participant recruited. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority and Sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Sponsors via email to resgov@ed.ac.uk.

In accordance with SPONSORS SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

18. CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

When the participant delivers her infant or completes the treatment (whichever occurs soonest), administration of the drug will stop.

19. INSURANCE AND INDEMNITY

The Sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff delegated on the project.

The following arrangements are in place to fulfil the Sponsors' responsibilities:

- The Protocol has been authored 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 design by the Chief Investigator and researchers employed by the University.

- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

20. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

20.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. An authorship policy will be agreed by the Co-applicants, CI and TSC prior to analysing the study data. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

20.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to Sponsors, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

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

The results will be communicated via open access primary publications, accessible review articles, conferences and invited presentations to clinicians, researchers, policy makers, funders and those working in pharma/industry. UK collaborators routinely post summaries of our research and links to publications on our website www.crh.ed.ac.uk. Local dissemination in UK, Zambia and Malawi is aided by seminar programs and interest groups

Communication to the general public will be facilitated by our close links with charities such as Tommy's www.tommys.org, who have a strong web presence and media engagement, and who also run a pregnancy information line

21. DATA SHARING

A clinical study final report will be written and provided to the funders, the Ethics' committees, Merck and the Sponsors within 12 months from the end of the trial (Last patient last visit).

The study data will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

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

22. PEER REVIEW

Peer review has been completed as part of the MRC funding application

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24. APPENDICES

24.1 APPENDIX 1: Trial Steering Committee and Data Monitoring Committee

** TO BE CONFIRMED **

Name of Member	Role in TSC	Responsibility	Independent
	Chair of TSC	*Oversight of TSC*	*Y*
	Chief Investigator	*[Insert basic responsibility]*	*N*
	Trial Manager	*[Insert basic responsibility]*	*N*
	[Other members of TSC]	*[Insert basic responsibility]*	*Y*
	[Other members of TSC]	*[Insert basic responsibility]*	*Y*
	[Other members of TSC]	*[Insert basic responsibility]*	*Y*
	Trial Statistician	*Trial Statistician*	*N*

Name of Member	Role in DSMC	Responsibility	Independent
	Chair of DSMC	*Oversight of DSMC*	*Y*
	Chief Investigator	*[Insert basic responsibility]*	*N*
	Trial Manager	*[Insert basic responsibility]*	*N*
	[Other members of DSMC	*[Insert basic responsibility]*	*Y*
	[Other members of DSMC	*[Insert basic responsibility]*	*Y*
	[Other members of DSMC	*[Insert basic responsibility]*	*Y*
	[Other members of DSMC	*[Insert basic responsibility]*	*Y*
	Trial Statistician	*Trial Statistician*	*N*

24.2 APPENDIX 2: Glossary of Terms

Proven Maternal Infection	Proven infection in the mother, defined as Either two of: Temperature> 38ºC on two or more occasions, raised CRP > 10, WCC > 12 or < 4 OR confirmed microbiological growth of an organism known to be pathogenic in blood cultures, MSU / CSU or LVS.
Threatened preterm labour	Patients between 24 and 37 weeks gestation, with painful uterine activity which may or may not progress to Preterm Labour and Delivery.
Gestational age at delivery	As calculated from a dating scan ≤ 16 weeks gestation
Neonatal Morbidity	Composite outcome calculated from multiple neonatal outcomes: • Requirement for admission to NNU or transfer between units, level and duration of care required • Respiratory morbidity: Surfactant requirement, ventilation / CPAP / supplementary O2 use, early respiratory morbidity bronchopulmonary dysplasia • Feeding type, supplementary feeding requirement • Neurological: USS and MRI results, presence of bilateral periventricular leukomalacia or interventricular haemorrhage, additional neurological events e.g. seizures. • Gastrointestinal morbidity: necrotising enterocolitis and treatment, hyperbilirubinaemia • Cardiovascular morbidity: cardiac anomalies, patent ductus arteriosus • Sepsis (confirmed by culture) • Retinopathy of prematurity • Suspect long-term neurodevelopmental outcome at discharge

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