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**TRIAL PROTOCOL**

**Study Title: Metformin Impact on Maternal and Infant Cardiometabolic Health**

**Short Title: MIMICH**

This protocol has regard for the HRA guidance

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**SIGNATURE PAGE**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in theUK Policy Framework for Health and Social Care Research, GCP guidelines, the Sponsor’s SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

|  |
| --- |
| **Study Sponsor:** |
| **\\nask.man.ac.uk\home$\My Pictures\MZsig.PNG**Signature: ..................................................................................................... |  | Date: 07/Sep/2021ddmmmyyyy |
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| Position: Trial Statistician……………………………………….................................  |  |  |

**SIGNATURE PAGE**

**Principal Investigator**

I, Professor Jenny Myers, as Principal Investigator for the MIMICH trial confirm that I will be responsible to ensure that all members of the local clinical trial team are appropriately trained on the trial protocol and have the relevant qualifications and experience to carry out their role in accordance with the trial protocol.

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| Committees |  |

|  |  |
| --- | --- |
| Randomisation details |  |

**ABBREVIATIONS**

|  |  |
| --- | --- |
| **Abbreviation** | **Term** |
| **AE** | Adverse Event |
| **APR** | Annual Progress Report |
| **CI** | Chief Investigator |
| **CTA** | Clinical Trial Authorisation |
| **CTIMP** | Clinical Trial of Investigational Medicinal Product |
| **CTM** | Clinical Trials Manager |
| **DIBD** | Development International Birth Date |
| **DMC** | Data Monitoring Committee |
| **eCRF** | Electronic Case Report Forms  |
| **EFW** | Estimated fetal weight |
| **GDM** | Gestational Diabetes |
| **GCP** | Good Clinical Practice |
| **GPRI** | Growth Potential Realisation Index |
| **HBGM** | Home Blood Glucose Monitoring |
| **HOMA-IR** | Homeostatic Model Assessment of Insulin Resistance |
| **HRA** | Health Research Authority |
| **ICF** | Informed Consent Form |
| **ISF** | Investigator Site File  |
| **ITT** | Intention To Treat  |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **NICE** | The National Institute for Health and Care Excellence |
| **PI** | Principal Investigator  |
| **PIS** | Participant Information Sheet |
| **PPIE** | Public and patient involvement and engagement |
| **R&D** | Research and Development |
| **RCT** | Randomised Control Trial |
| **REC** | Research Ethics Committee |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SGA** | Small for Gestational Age |
| **SmPC** | Summary of Product Characteristics |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **QALYs** | Quality-Adjusted Life Years |
| **UoM** | University of Manchester |
| **USM** | Urgent Safety Measure |

**TRIAL SUMMARY**

|  |  |
| --- | --- |
| Trial Title | Metformin Impact on Maternal and Infant Cardiometabolic Health |
| Internal ref. no. (or short title) | MIMICH |
| Clinical Phase  | Phase 3 |
| Trial Design | Open label RCT comparing fetal growth trajectory and placental function in women treated with or without metformin |
| Trial Participants | Women with type 2 diabetes and GDM, who have concomitant with risk factors for the development of placental disease, for whom metformin would be routinely recommended  |
| Planned Sample Size | A target sample size of 225 women will be recruited from antenatal clinics within Manchester Foundation Trust. Participants will be allocated 1:1 to the intervention (diet & lifestyle ± insulin) or standard care (diet & lifestyle, metformin ± insulin). All research visits will be conducted within the Maternal & Fetal Health Research Centre. |
| Treatment duration | No metformin versus metformin (usual care). Both groups will be offered insulin if fasting hyperglycaemia (≥5.3mmol/L) and/or postprandial hyperglycaemia (≥7.8mmol/L) persists. All other aspects of antenatal and delivery care will follow usual clinical care pathways underpinned by NICE 2015 guidelines for diabetes in pregnancy. Treatment duration from randomisation (6-30 weeks) until the end of the pregnancy. |
| Follow up duration | Outcome data will be collected during the antenatal period and birth up to primary hospital discharge or 28 days post-birth, whichever occurs sooner |
| Planned Trial Period | 36 months recruitment and follow-up |
| Planned recruitment rate | 8 per month |
| Eligibility criteria | 1. Singleton pregnancy between 6+0 and 30+0 weeks’ gestation inclusive
2. Aged 18 years or over and willing and able to give informed consent
3. Diagnosis of diabetes in pregnancy
	1. Type 2 diabetes diagnosed before pregnancy and requiring pharmacological treatment

OR* 1. Type 2/GDM diagnosed <24 weeks’ gestation: abnormal glucose tolerance testa, abnormal HBGMb and/or HbA1C ≥42mmol/L

OR* 1. GDM (diagnosed 24-30 weeks): HbA1C ≥39mmol/L and/or abnormal glucose tolerance testa
1. Abnormal HBGMa (≤30 weeks)
2. Presence of at least one risk factor for placental disease
	1. BP ≥130 and/or ≥80mmHg
	2. pulse wave velocity ≥ 9m/s
	3. age ≥35 years
	4. nulliparous
	5. pre-eclampsia and/or small for gestational age (<10th centile) in a prior pregnancy
	6. mean uterine artery PI ≥95th centilec
	7. placental growth factor <10th centilec
3. EFW ≤50th centile (if ≥22 weeks)c

a. Abnormal glucose tolerance test: fasting glucose ≥5.3mmol/L and/or 2 hour ≥8.5mmol/L b. Abnormal Home Blood Glucose Monitoring (HBGM): 3 abnormal readings (fasting blood glucose ≥5.3mmol/L, 1 hour post meal ≥7.8mmol) in one weekc. To be confirmed/measured at the baseline visit**Exclusion Criteria**1. Medical contraindication to metformin
2. Known diagnosis of Type 1 diabetes
3. Multifetal pregnancy
4. Prior pregnancy complicated by shoulder dystocia
 |
|  | **Objectives** | **Outcome Measures** |
| Primary | To evaluate if withholding treatment with metformin in women, with type 2 diabetes or gestational diabetes (GDM) pregnancy AND risk factors for placental disease, affects fetal growth | Primary outcome: deviation in fetal growth velocity (change in zscore between 20-26 weeks and birth) |
| Secondary | To evaluate the effect of the treatment on pregnancy outcome | Adherence/acceptability: missed doses and undesirable effects of allocated treatmentSecondary fetal growth outcome:Comparison of third trimester fetal growth velocity between treatment groups and in prespecified subgroups; number of small for gestational age infantsSecondary maternal outcomes: gestational weight gain, rates of adjuvant insulin therapy, pre-eclampsia, mode of birth, post-partum haemorrhage, shoulder dystocia. Secondary infant outcomes: apgar score, admission to neonatal intensive care, birthweight/birthweight centile, ponderal index  |
| Exploratory | To investigate the effect of metformin treatment on placental function and measures of maternal cardiometabolic health | Per protocol analysis: (comparison of third trimester fetal growth between groups)Longitudinal changes in angiogenic markers (sFlt, PlGF), maternal inflammatory (hsCRP, IL-6) and metabolic (adiponectin) markers will also be comparted between treatment groups.Cord blood C-peptide and erythropoietin (marker of intrauterine stress). |

**Trial Flow Diagram**



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# BACKGROUND AND RATIONALE

**Importance**: Amongst women with poor cardiometabolic health embarking on pregnancy, hyperglycaemia is a very common feature. The prevalence of hyperglycaemia is increasing across Europe, alongside increasing rates of older maternal age, obesity and hypertension. Gestational diabetes (GDM) rates have recently been estimated at 5.4% (3.8-7.8)1 and the prevalence of type 2 diabetes has doubled (0.5-1.1% between 2008 & 2012)2. As a result of the fact that the majority of women with hyperglycaemia have other cardiometabolic risk factors (family history, obesity, dyslipidaemia, hypertension), compared to healthy subjects these women have a 3-4 fold increased risk of pregnancy hypertension (7.4%)3. Rates of pre-eclampsia in women with type 2 diabetes have been reported to be as high as 31%4 and women with a combination of diabetes and vascular disease are six times more likely to develop fetal growth restriction (FGR)5.

The short and long-term impacts of prematurity and growth restriction in this group are much greater than macrosomia6. This means that whilst fetal macrosomia is the common pathology in women with hyperglycaemia, a very important minority (~3%)7), will conversely develop severe placental disease leading to FGR requiring early preterm delivery to prevent stillbirth8. An additional 20% will have a small for gestational age (SGA, <10th centile) baby and 12-18% will develop pre-eclampsia3, 7. Current practice is to offer metformin to all women with hyperglycaemia irrespective of potential risk factors for placental disease9, 10, but the effect of metformin on placental function and fetal growth remains uncertain11. A recent Canadian RCT of women with type 2 diabetes demonstrated increased rates of SGA in women treated with metformin12.

The effect of metformin on cellular metabolism has not been fully explained and remains controversial; metformin has been shown to disrupt mitochondrial respiration13, 14, alter redox status15}, impair tumour growth16} and cellular proliferation under hypoxic and nutrient deficient conditions17. All of these actions suggest that metformin could negatively affect placental function particularly in the context of oxidative stress and hypoxia, although this has not been tested directly. Conversely, metformin has been demonstrated to have significant, anti-inflammatory properties in the systemic vasculature18 18, 19 and in trophoblast cell lines20. There is some circumstantial evidence from the clinical trials, which have used metformin to limit fetal growth in women with hyperglycaemia, that metformin reduces the risk of gestational hypertension17, 21. However, the effect on the rate of pre-eclampsia, was not clear22 which may reflect different disease aetiologies between some types of pre-eclampsia and gestational hypertension. The effect of metformin on both maternal cardiometabolic health and placental function therefore warrants further investigation so that this therapy can be targeted to the women who will benefit most11.

Given the uncertainty regarding the potential benefits (improvement in maternal metabolic health and reduction in hypertensive disease) but potential negative effects on placental function (reduction in fetal growth and antiproliferative cellular actions), highlighted above and by a recent expert review11, a trial of metformin in women with hyperglycaemia and risk factors for placental disease is urgently needed. During the course of this trial, metformin will continue to be offered to women with type 2 diabetes and GDM who do not have risk factors for placental disease and/or where the baby is ≥50th centile after 24 weeks, where the overriding goal of therapy is the prevention of fetal macrosomia and its associated complications.

No previous studies have investigated the effect of metformin on placental function, fetal growth and maternal cardiometabolic health in women with hyperglycaemia and concurrent risk factors for placental disease. This study is made possible through access to a large population of high-risk pregnancies across Manchester (3 hospital sites serving 18,000 births per year) and the specialist translational clinic infrastructure which incorporates 3D volumetric ultrasound fetal growth assessment. Our group has pioneered the use of volumetric ultrasound techniques to improve the detection of fetal growth abnormalities23, 24. Previous studies investigating hypoglycaemic agents in pregnancy have used birthweight as the primary outcome, which provides only a crude estimate of fetal growth. In pregnancies where there are conflicting exposures influencing fetal growth and placental function (e.g. hypertension and hyperglycaemia) absolute birthweight is not sufficient to detect subtle, but clinically significant changes in fetal growth and placental function. To address this limitation, in this study longitudinal measures of fetal growth will be used to quantify the deviation in fetal growth in the third trimester using fetal growth trajectory predictions based on second trimester fetal growth measurements from the same fetus23. This will provide a much more sensitive assessment of the effect of metformin on fetal growth; the use of a continuous measure as a primary outcome also makes the study much more efficient as it requires a smaller sample size. Furthermore, longitudinal angiogenic markers will be measured to determine whether metformin has a measurable effect on placental function.

As it is routine clinical practice to offer metformin to women with hyperglycaemia, the intervention in this study will be to withhold metformin and manage hyperglycaemia with diet/insulin alone. A randomised study is essential to avoid treatment-selection bias and the study is necessarily open-label to aid the ongoing management of hyperglycaemia.

# AIMS AND OBJECTIVES

## Research question

In women with diabetes in pregnancy and risk factors for placental disease, what is the effect of withholding treatment with metformin versus usual care (including metformin) on fetal growth and maternal cardiometabolic health during pregnancy?

## Aim

To evaluate the effect of metformin on fetal growth, placental function and maternal cardiometabolic health.

## Objectives

### Primary objective:

* To evaluate if withholding treatment with metformin in women, with type 2 diabetes or gestational diabetes (GDM) pregnancy AND risk factors for placental disease, affects fetal growth

### Secondary objectives:

* To investigate the effect of metformin treatment on placental function and measures of maternal cardiometabolic health

## Primary endpoint

Deviation in fetal growth between second trimester scans (20-26 weeks) and birth (defined by change in gestation-adjusted z score)

## Secondary endpoints

* Adherence and acceptability of the intervention
* Measures of cardiometabolic health and diabetes control
* Development of pregnancy complications
* Assessment of neonatal size and condition at birth

# TRIAL DESIGN AND SETTING

## Trial Design

This is an open label randomised controlled trial (RCT) comparing fetal growth trajectory and placental function in women treated with or without metformin.

## Trial Setting

The study will be conducted within Manchester University NHS Foundation Trust (MFT) (single site). Women will be identified in antenatal clinics at three hospital sites within MFT, St Mary’s Oxford Rd, St Mary’s Wythenshawe, North Manchester General Hospital and provided with information regarding the study. Confirmation of eligibility, consent and all study visits will take place within the Maternal & Fetal Health Research Centre, St Mary’s Oxford Rd. Pregnancy outcome data will be collected following review of clinical records by study midwives within MFHRC with assistance from CRN research staff at each of the identification hospital sites.

Participants will continue to receive the standard pathway of care throughout the course of the trial, with the exception of omission of metformin therapy for those participants randomised to the intervention arm.

Trial site activities for NHS organisations in England may only commence once HRA approval has been issued and the sites have confirmed their capacity and capability to take part. Trial site activities for organisations in Northern Ireland, Scotland and Wales may only commence once NHS permission is granted by the research site.

## Assessment and management of risk

This trial protocol has been assessed by the Medicines and Healthcare products Regulatory Agency and confirmed not to be a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and therefore no submission to the MHRA is required (see appendix).

Metformin and insulin are both recommended as an option for the treatment of diabetes in pregnancy. In standard clinical practice, metformin is offered as first line therapy. Maternal and fetal safety is affected by maternal hyperglycaemia and therefore the treatment of maternal hyperglycaemia is key to the safety of the trial. Maternal glycaemia will be monitored using HBGM as per our standard clinical practice and hyperglycaemia managed with additional insulin in both treatment groups as necessary.

# TRIAL ELIGIBILITY CRITERIA AND CONSENT

## Inclusion Criteria

1. Singleton pregnancy between 6+0 and 30+0 weeks’ gestation inclusive
2. Aged 18 years or over and willing and able to give informed consent
3. Diagnosis of diabetes in pregnancy
	1. Type 2 diabetes diagnosed before pregnancy and requiring pharmacological treatment

OR

* 1. Type 2/GDM diagnosed <24 weeks’ gestation: abnormal glucose tolerance testa, abnormal HBGMb and/or HbA1C ≥42mmol/L

OR

* 1. GDM (diagnosed 24-30 weeks): HbA1C ≥39mmol/L and/or abnormal glucose tolerance testa
1. Abnormal HBGMb (≤30 weeks)
2. Presence of at least one risk factor for placental disease
	1. BP ≥130 and/or ≥80mmHg (clinic blood pressure)
	2. pulse wave velocity ≥ 9m/s
	3. age ≥35 years
	4. nulliparous
	5. pre-eclampsia and/or small for gestational age (<10th centile) in a prior pregnancy
	6. mean uterine artery PI ≥95th centilec
	7. placental growth factor <10th centilec
3. EFW ≤50th centile (if ≥22 weeks)c

a. Abnormal glucose tolerance test: fasting glucose ≥5.3mmol/L and/or 2 hour ≥8.5mmol/L

b. Abnormal Home Blood Glucose Monitoring (HBGM): 3 abnormal readings (fasting blood glucose ≥5.3mmol/L, 1 hour post meal ≥7.8mmol) in one week

c. To be confirmed/measured at the baseline visit

## Exclusion Criteria

1. Medical contraindication to metformin
2. Known diagnosis of Type 1 diabetes
3. Multifetal pregnancy
4. Prior pregnancy complicated by shoulder dystocia

## Screening of participants

Women with type 2 diabetes and GDM, who have concomitant risk factors for the development of placental disease, for whom metformin would be routinely recommended will be approached to participate in the study.

In the antenatal service, women with diabetes are routinely referred to a hospital antenatal clinic where they will be approached by a member of the research team or the clinical care team (midwife or obstetrician). Women will be approached during their routine hospital appointments and will be provided with a verbal and written explanation of the trial. A Participant Information Sheet (PIS) will be provided to facilitate this process.

Women with both type 2 diabetes diagnosed before pregnancy and women with diabetes diagnosed during pregnancy, who meet the above inclusion criteria, will be approached. Women will fall into one of the three categories described below.

1. Women with a diagnosis of type 2 diabetes before pregnancy are referred to the diabetes antenatal service between 6-12 weeks. It is usual practice to commence home blood glucose monitoring (HBGM) at this first visit and to discuss dietary modifications. HBGM is usually carried out for around 1 week prior to the commencement of treatment. Women will be provided with written and verbal information about the study at this appointment and offered an appointment in the research clinic within a week. At this appointment, willingness to participate in the study will be confirmed along with eligibility. HBGM will be reviewed and treatment discussed as per routine clinical practice guidelines (see below).
2. Women who are identified at their first pregnancy contact (booking) as having risk factors for the development of gestational diabetes (GDM) are assessed and offered a number of screening tests dependent on their level of risk. Women with GDM in a previous pregnancy are offered an early (12-16 weeks) glucose tolerance test; if this is abnormal then HBGM is recommended. Women can also choose to begin HBGM at booking (as above for women with a diagnosis of type 2 diabetes). In addition, all women with risk factors for the development of GDM (prior GDM, BMI>30, high risk ethnic background, family history of diabetes) are offered an HbA1C in early pregnancy; if this is abnormal (≥42mmol/L) then HBGM is recommended. In this group of women, where a diagnosis of diabetes is made in early pregnancy, procedures for invitation into the study will be the same as those for women with type 2 diabetes, i.e. verbal and written information regarding the study will be provided at or before HBGM is commenced and a research clinic appointment offered within 1 week.
3. Women with risk factors for GDM (without prior GDM) are invited for a glucose tolerance test at 24-28 weeks’ gestation. Women with a positive result (HbA1C ≥39mmol/L and/or fasting 5.3mmol/L and/or 2 hour 8.5mmol/L) are invited to commence HBGM within 1 week of the test. Women who are eligible for the study will be provided with verbal and written information as above and offered an appointment in the research clinic within 1 week.

Amongst women with a diagnosis of diabetes (as described above), eligibility for the trial, based on the presence of one of more risk factors for placental disease, will be identified (where possible) prior to approach of the woman.

1. Maternal age – identified from woman’s pregnancy record
2. Maternal blood pressure 130 and/or ≥80mmHg (routine measurements) identified from woman’s pregnancy records
3. Pulse wave velocity 9m/s measured routinely in specialist antenatal clinics (MAViS[[1]](#footnote-2) and VELOCTY[[2]](#footnote-3))
4. Prior history of pre-eclampsia ± small for gestational age (<10th centile) in a prior pregnancy – identified from woman’s pregnancy record
5. Nulliparous (no previous ongoing pregnancy beyond 24 weeks)
6. Mean uterine artery PI ≥95th centile - measured routinely in the research clinic1,2
7. Placental growth factor <10th centile – measured routinely in the research clinic1,2

All women meeting the inclusion criteria will be invited to an appointment in the Maternal & Fetal Health Research Centre Clinical Research Unit.

For women with a diagnosis of diabetes in whom a risk factor for placental disease is not confirmed at the initial screen, a referral to the research clinic can still be made if the woman is keen to participate in the study. Additional measurements will be offered in the research clinic to confirm eligibility. Women not meeting the eligibility criteria will be returned to routine diabetes antenatal care.

## Confirmation of eligibility

Eligibility will be confirmed by a medically qualified practitioner during the first study visit which will take place in the Maternal & Fetal Health Research Centre, St Mary’s Hospital (Oxford Rd Campus).

## Informed consent

Following confirmation of eligibility, the aims, trial treatment, anticipated benefits and potential risks of taking part in the study will be discussed with the participant. It will be made clear that participation is voluntary, and that the woman is free to decline to take part and may withdraw from the trial at any time. After all queries have been addressed and the clinical team is confident the participant understands the trial and all requirements, participants will be consented onto the trial. It is essential that full details of the discussion between the Investigator and the participant are clearly documented in the participant’s record.

An appropriately trained healthcare professional who is GCP trained and experienced and who has been delegated by the PI to undertake this activity (and this delegation is clearly documented on the delegation log) will obtain written informed consent for participation in the trial (following confirmation of eligibility by a medically trained individual). Participants will be consented prior to any trial-related procedures being undertaken.

If the woman wishes to participate in the trial and has been confirmed as eligible to participate by a medically trained individual, they will be asked to provide written informed consent. The consent form will include a statement to explain thatdirect access to maternal and child medical records is required for participation. We will also request consent for electronic data linkage between routinely collated electronic data records (for the woman and the baby) to ascertain future outcomes without participant recall, as well as to establish a ‘consent-to-contact’ to facilitate recall for future research. A woman will be free to decline provision of expanded consent for ‘consent-to-contact’. An appropriately trained and delegated healthcare professional will then sign and date the ICF. A copy of the fully signed consent form will be given to the woman, a copy will be filed in the medical notes, and the original wet-ink signed copy will be placed in the Investigator Site File (ISF).

Throughout the trial, the woman will have the opportunity to ask questions. If new evidence results in significant changes in the risk/benefit assessment, the participant information sheet and associated consent form will be reviewed and updated if necessary. If the participant information and consent form is updated, all participants (including those already being treated), would be informed of the new information, given a copy of the revised documents and asked to re-consent to continue in the trial where relevant.

The right of the participant to refuse to participate in the trial without giving reasons will be respected. After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/ she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis. Similarly, the participant will remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment.

Where English language is limited, a telephone interpreter (via the hospital BIG WORD service) may be used to translate the study materials and ensure the woman understands all that is involved with participation prior to signing consent.

Details of all women approached will be recorded on the screening log. With the woman’s consent other relevant healthcare professionals will also be informed that they are taking part in the trial (GP letter and letter inserted into handheld records).

## Trial Randomisation

Following confirmation of eligibility and consent, randomisation will occur via a secure online randomisation system. Unique log-in usernames and passwords will be provided to those who require access to the online system and who have been delegated the role of randomising women into the trial as detailed on the delegation log. The online randomisation system will be available 24 hours a day, 7 days a week, although it is anticipated that randomisation will only occur within standard working hours.

After eligibility has been confirmed by a delegated clinician and informed consent has been received, the woman can be randomised into the trial.

Women will be randomised at the level of the individual participant in a 1:1 ratio to either no metformin or standard care (including metformin). A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

* Type of diabetes (diagnosed < or > 24 weeks)
* Risk factor for placental disease (uteroplacental or maternal risk factor)
* gestational age (6+0 to 11+6, 12+0 to 23+6, 24+0 to 30+0 weeks’ gestation)

Following randomisation, a confirmatory e-mail will be sent to the randomising clinician, site Principal Investigator (PI), lead trial midwife and trial manager.

## Informing the participant’s GP

Information on the prescription of the relevant diabetes medications will be entered into the handheld paper maternity record as in usual clinical care, as the standard way of communicating with GPs and other relevant healthcare professionals (e.g. community-based midwives).

## Trial blinding

This is an open-label trial and, all trial participants, care providers, outcome assessors and data managers will be unblinded to allocation.The open-label design is to ensure that women are effectively and safely treated, with healthcare professionals and women aware of their treatment allocation. Any appropriately trained healthcare professional may up- or down-titrate metformin treatment (in the standard care arm) and add insulin treatment as clinically indicated (participants in either arm).

We have considered other designs but given the dynamic nature of glycaemic control in pregnancy and the need to titrate medications alongside blood glucose readings, an alternative would not be feasible or acceptable. It would be unfeasible to mask those delivering clinical care or outcome assessors to trial allocation as maternity notes, by necessity, contain documentation of treatment.

# INTERVENTION

## Treatment(s) and Dosing Schedule

This trial aims to investigate the effect of withholding treatment with metformin for women with diabetes and concomitant risk factors for placental disease. All women included in the trial will require treatment for their diabetes with the aim of normalising blood glucose measurements. Women will be randomised to the **intervention arm** (diet & lifestyle ± insulin) or **usual care** (diet & lifestyle, metformin ± insulin). As an open-label trial, healthcare professionals and women will be aware of their allocation.

Following randomisation, the appropriately trained healthcare professionals will provide a prescription (as used in usual clinical care) to be dispensed from a pharmacy. Specific Trial Prescription Forms will not be used.

Medications will be dispensed as per routine care. Clinical care, including titration of treatment will be provided by the clinical research team (specialist midwives in conjunction with medical staff), who are trained and experienced in the management for diabetes in pregnancy through the established VELOCITY hybrid research clinic.

* **Intervention arm**: Diet and lifestyle advice as per routine care. Women will be prescribed long acting insulin (Levemir or Humulin I) and/or short acting insulin (Novorapid). Dose changes will be recommended to participants at a minimum of 3 day intervals according to HBGM.
* **Usual care arm**: Diet and lifestyle advice as per routine care. Women will be prescribed metformin 500mg bd titrated up to a maximum dose of 2.5g/day as per standard practice (dose increase of 500mg every 3 days). If women suffer gastrointestinal side effects following a dose increment, they will be advised to reduce to the previous dose for a further 3 days, before increasing again. If further side effects occur they will be advised to continue on the maximum tolerated dose. Additional long-acting insulin (Humulin I) and/or short acting insulin (Novorapid) will be prescribed by the clinical team if target blood glucose readings are not achieved two weeks after taking the maximum tolerated dose.

All care pathways detailed above (with the exception of omission of metformin therapy) follow the same principles and guidelines as our standard treatment of diabetes in pregnancy; i.e. frequency of monitoring, dose titration and escalation of treatment will not differ from routine care, set out by local and national (NICE) guidelines. Blood glucose targets (<5.3mmol/L fasting and <7.8mmol/L 1 hour post meal) will be the same for all participants, regardless of treatment allocation. It is anticipated that women in the intervention arm will require higher doses of insulin treatment to achieve the same blood glucose control.

## Drug Interaction or Contraindications

As no brand of metformin will be specified, and treatment is within usual clinical care, healthcare professionals will review drug interactions or contraindications within usual clinical practice.

## Accountability Procedures

No stock recording will be undertaken as all medications will be dispensed from usual care pharmacies. Usual clinical practice will be followed in which women are asked about tablets taken, side-effects and adherence. Adherence to treatment (participant recall of number of missed insulin injections and metformin tablets) and current insulin and metformin dose (in the preceding week) will be recorded on the CRF at each research visit.

## Treatment Modification

Usual clinical care will be provided (following local and NICE guidelines) and no trial specific treatment modifications are planned. Treatment should continue according to the allocated treatment arm with dose titrations based on glycaemic control and tolerance as per standard clinical guidelines.

## Discontinuation of Treatment

Stopping or switching diabetes treatments is a common part of usual clinical care in pregnancy. Some women allocated to usual care will not be able to tolerate metformin. The daily dose of metformin (0-2.5g), Levemir/Humulin I and Novorapid taken over the preceding week will be recorded at each study visit. Failure to tolerate metformin (usual care arm) will not be reported as an adverse event unless related to a reportable Serious Adverse Event. A woman can continue in the study (for collection of outcome data) after discontinuation of treatment.

## Treatment Supply and Storage

### Treatment Supplies

All drugs will be supplied by usual care pharmacies.

### Packaging and Labelling

No specific packaging or labelling will be required as usual care pharmacy supplies will be used.

### Drug Storage

Drugs will be stored within usual care pharmacies.

# TRIAL PROCEDURES

A schedule of procedures can be found on page 28.

All women meeting the inclusion criteria and expressing an interest in participating in the study will be invited to an appointment in the Maternal & Fetal Health Research Centre Clinical Research Unit. The clinic is staffed by obstetricians, diabetologists, specialist diabetes midwives and research midwives and provides routine clinical care as well as facilitating intervention trials and observational studies.

Following attendance at the research clinic appointment, if a woman decides not to participate in the study or does not meet the eligibility criteria, her follow up appointments will continue in the diabetes antenatal clinic. For women participating in the study, follow up appointments will take place in the research clinics.

## Baseline visit

Following confirmation of eligibility (including an ultrasound scan for women >16 weeks) and written consent and randomisation, baseline demographics including self-reported ethnicity, obstetric and medical history, medication history and estimated date of delivery will be recorded on the eCRF. Additional measurements including blood pressure, maternal weight and skinfold measurements will be recorded and research blood samples obtained.

## Study visits (every 4 weeks)

* Women will be invited to a study visit every 4±2 weeks after randomisation
* Where appropriate/possible visits will align with clinically-indicated pregnancy visits and take place at 8-14, 16-18, 22-24, 26-30, 30-34, 34-38 weeks’ gestation.
* Confirmation of willingness to continue in the trial will be confirmed by a member of the clinical research team
* Routine clinical care will be provided to women during their study visits from the multidisciplinary clinical research team.
* An ultrasound scan will be performed at each visit by a trained sonographer (midwife or doctor) within the clinical research team. Standard fetal biometry (triplicate measurements), liquor volume, umbilical and uterine artery Doppler will be measured and reported as per standard clinical care. Thigh volumes (triplicate) will be acquired using a 3D probe. This additional measurement adds one-two minutes to the scan.
* Additional measurements (as per the baseline visit) including blood pressure, maternal weight and skinfold measurements will be recorded and a blood sample obtained at each visit.
* Dose of insulin (long acting and short acting) and metformin and self-reported adherence with prescribed medication (number of missed doses) for the preceding 7 days will be recorded at each study visit. Undesirable effects (none, GI disturbance, troublesome local skin reactions) will be recorded at each study visit.
* Glycaemic control for the preceding 7 days will be summarised and recorded at each study visit; the mean fasting and mean post-meal glucose (for women using HBGM readings downloaded from their meter using Diasend) and time in range (% between 3.5-7.8mmol/L) for women using Libre sensors. Number of hypoglycaemic episodes (blood sugar <3mmol/L in the last 7 days) will also be recorded. HbA1C will be measured in line with standard clinical care once per trimester, or more frequently if indicated.
* A review of pregnancy complications (e.g. development of pre-eclampsia/hypertension, obstetric cholestasis), medication change (commenced antihypertensive, increased antihypertensive, other) and hospital attendances between visits (day unit attendance, hospital admission (days) and whether related to maternal diabetes (Y/N))
* At the 30-34 weeks’ visit, women will be asked to fast prior to their appointment in order to collect blood samples for fasting insulin, glucose and lipid measurements.

## After birth

* The development of pregnancy complications (e.g. development of hypertension/pre-eclampsia) will be captured at each study visit
* Pregnancy complications and birth outcomes will be captured from the birth records
* The placenta will be collected at birth (where possible) and processed within 4 hours
* A cord blood sample will be collected and stored in the fridge for up to 72 hours
* Measurements will be obtained from the infant prior to hospital discharge (where possible) or within the first 5 days of birth by a member of the clinical research team. Measurements will include head and abdominal circumference, crown-heel length, skin fold measurements and weight.

# OUTCOME MEASURES

Clinical data will be collected during the antenatal period and birth up to primary hospital discharge or 28 days post-birth, whichever occurs sooner. Data on dosage, undesirable effects of the intervention, discontinuation of treatment, dose and glycaemic control in the preceding week will be captured at each study visit. Data collection for the trial will be up to primary hospital discharge only.

Data collected will include baseline demographic and pregnancy characteristics, maternal, birth and neonatal outcomes and entered onto a secure online study-specific database. It is anticipated that the majority of babies will be delivered in the hospital site where they were booked for antenatal care; we have successfully previously utilised the CRN network to locate outcomes for babies delivered at other units. Outcomes will be collected by the MFHRC research midwives by contacting the relevant hospital research midwives.

## Primary Outcome

Third trimester fetal growth velocity will be assessed by change in fetal growth zscore between 20-26 weeks (average) and birth.

At each scan the estimated fetal weight (EFW) will be calculated using standard 2D biometry and fractional thigh volume (TVol) measurements using a standard formula 25 and converted to a zscore 26. The delta change in zscore between the average zscore of scans performed between 20-26 weeks and the birthweight zscore will be calculated.

In order to verify the primary outcome, the eCRF will capture the TVol measurement and the EFW at each scan as well as recording the 2nd trimester and 3rd trimester deviation scores. The source data (scan report) will verify the 2D biometry.

## Secondary Outcomes

Secondary outcomes will be reported as per standard for pregnancy intervention trials. Reporting and analysis of secondary outcomes will be described in full in the statistical analysis plan, to avoid issues of multiple testing not all secondary outcomes will be compared between treatment groups. Where appropriate, outcomes will be presented with a treatment effect and confidence intervals, other outcomes will be presented with summary statistics only.

Prespecified secondary outcomes:

### Adherence/Acceptability

* Number of missed doses– calculated as an average over pregnancy from the number of missed doses reported in the 7 days prior to each study visit (adjusted for number of study visits)
* Undesirable effects of allocated treatment (number of women reporting undesirable effects associated with metformin and/or insulin/number of women receiving metformin or insulin treatment)
* Treatment satisfaction with allocated medication regime (questionnaire)
* Acceptability of allocated medication regime (questionnaire)

### Secondary fetal growth research outcomes

* Distribution of fetal growth zscores between treatment groups and within prespecified subgroups
* Comparison of fetal growth zscores (conventional Hadlock formula EFW without TVol measurement) between treatment groups and within prespecified subgroups
* Fetal growth velocity measured by growth potential realisation index (GPRI). (IGAP). <https://igap.research.bcm.edu/> This online tool uses second trimester growth measurements to predict 3rd trimester growth for an individual fetus. The percentage deviation from the predicted growth is calculated and reported as GPRI.
* Number of small and large for gestational age infants (defined using birthweight zscore)

### Standard secondary maternal outcomes

* Gestational weight gain (difference between baseline and 30-34 week visit weight adjusted for number of weeks)
* Episodes of severe hypoglycaemia (blood glucose < 3mmol/L) – (total number reported over the treatment duration reported at each study visit)
* Mean (fasting and 1 hour post meal) daily glucose and % time in target – captured from HBGM and/or CGM sensors at each study visit and summarised for each trimester
* Maximum achieved dose of metformin (standard care arm only)
* Total insulin dose (units/kg/day) at final study visit (short and long acting insulin reported separately)
* Mean change in insulin dose (units/day) from baseline to last study visit
* Need for antihypertensive therapy – study visits and pregnancy outcome case note review
* Pre-eclampsia (defined according to ISSHP guidelines) - study visits and pregnancy outcome case note review
* Indicated delivery (induction of labour or prelabour rupture of membranes (PROM) with stimulation of labour or pre-labour Caesarean section)- pregnancy outcome case note review
* Mode of onset of birth (spontaneous, induction of labour, PROM with stimulation of labour, pre-labour Caesarean section) - pregnancy outcome case note review
* Indication for onset of birth - pregnancy outcome case note review
* Mode of birth - pregnancy outcome case note review
* Post-partum haemorrhage (blood loss >1000mls) - pregnancy outcome case note review
* Shoulder dystocia - pregnancy outcome case note review
* Total number of postnatal hospital inpatient days - pregnancy outcome case note review

### Neonatal outcomes – clinical birth outcomes obtained from case note review

* Fetal loss prior to 24 weeks’ gestation
* Fetal loss from 24+0 weeks’ gestation (stillbirth)
* Known early neonatal death (up to 7 days from birth)
* Known late neonatal death (between 7 and up to 28 days from birth)
* Gestational age at birth
* Birthweight
* Birthweight centile
* Birthweight zscore
* Neonatal unit admission (separation of baby from mother)
* Principal recorded indication for neonatal unit admission
* Length of stay in neonatal unit (and level of care)
* Apgar score (5minutes)
* Umbilical arterial pH at birth
* Need for additional resuscitation at birth: intubation in the delivery room, resuscitation drugs or chest compressions
* Need for respiratory support
* Type of respiratory support needed
* Need for treatment for neonatal hypoglycaemia
* Lowest blood glucose measurement
* Neonatal seizures
* Intracranial haemorrhage
* Necrotising enterocolitis
* Breastfeeding at discharge

### Exploratory outcomes – additional research outcomes

* Longitudinal changes in angiogenic markers (sFlt, PlGF) – measured in research blood samples (batch analysis end of study)
* Maternal skinfold measurements (delta change from baseline visit adjusted for gestation)
* HOMA-IR (measured at 30-34 weeks) - measured in research blood samples (real time in the biochemistry lab)
* Maternal metabolic/inflammatory markers (hsCRP, IL-6, adiponectin) - measured in research blood samples (batch analysis end of study)
* Ponderal index (fetal weight in grams X 100/(fetal length in centimeters)
* Neonatal measurements within 72 hours of birth (Crown-rump, crown-heel lengths, weight, arm, thigh, head, abdominal circumferences, biceps, triceps, subscapular skinfold thicknesses)
* Cord blood C-peptide
* Erythropoietin (marker of intrauterine stress)27, 28

### Adverse events:

* Adverse event recorded (number of women and number of adverse events)

## END OF TRIAL

For regulatory purposes, the end of trial will be 28 days after the end of the pregnancy for the final participant. The declaration of end of trial form will be submitted to regulatory authorities. The trial team will notify the REC of the end of a clinical trial within 90 days of its completion.

## Schedule of Assessments

**Table 1:** Schedule of Assessments

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Procedures | Participant identification Antenatal clinics | Baseline visit | Intervention period (study visits every 4±2 weeks) | Fasting visit (30-34 weeks) | At/after birth |
| Routine antenatal visit | x | x | x | x |  |
| Eligibility check | x | x |  |  |  |
| Written informed consent |  | x |  |  |  |
| Randomisation |  | x |  |  |  |
| Collection of baseline characteristics (demographics, obstetric and medical history, medication) [completion of eCRF] |  | x |  |  |  |
| Confirmation of willingness to continue intervention [completion of eCRF] |  |  | x | x |  |
| Study visits every 4±2 weeks (including ultrasound scan, BP, weight, skinfold) [completion of eCRF] |  | x | x | x |  |
| Adherence with treatment: dose of insulin/metformin and self-reported number of missed doses in previous 7 days [completion of eCRF] |  | x | x | x | x |
| Summary of glycaemic control & number episodes of hypoglycaemia (preceding 7 days) [completion of eCRF] |  | x | x | x | x |
| Fasting blood samples (30-34 weeks only) |  |  |  | x |  |
| Acceptability questionnaire completion [hard copy] |  |  |  | x |  |
| Review of pregnancy complications / events [completion of eCRF] |  |  | x | x | x |
| Research blood samples[completion of sample log] |  | x | x | x | x |
| Safety reporting |  |  | x | x | x |
| Pregnancy outcome/case note review [completion of eCRF] |  |  |  |  | x |
| Collection of placenta and cord blood |  |  |  |  | x |
| Measurement of infant (within 5 days of birth) [completion of eCRF] |  |  |  |  | x |

## Participant Withdrawal

If women do not attend a research visit, they will be contacted by phone and invited to attend the following week. Women will be able to withdraw consent for further contact at any time without giving a reason and with no effect on their (or their baby’s) on-going care. In the event of discontinuation, consent to contribute their pregnancy outcome data to the trial will be sought, if women do not wish to submit their data they will be withdrawn from the study.

## Storage and analysis of samples

* Blood samples (EDTA plasma (4mls) and Serum (4.5mls)) will be collected at the baseline study visit and subsequent study visits.
* Samples will be centrifuged in the MFHRC and stored in 250µl aliquots at -80C. A sample log should be completed at the time of sampling.
* In addition to the research blood samples, at 30-34 weeks fasting insulin and glucose will be measured. These samples should be transported to the biochemistry lab at St Mary’s Hospital, Manchester Foundation Trust for immediate processing.
	+ At the end of the study, samples will be analysed in aliquots for the measurement of angiogenic markers, hsCRP, IL-6, adiponectin.
	+ Additional biomarkers related to cardiometabolic health may be measured.
	+ Samples will be transferred to the Tommy’s National Reproductive Health Biobank for storage following completion of the trial.
* For women giving birth at St Mary’s Oxford Rd, placentas will be collected after birth where possible. Placental tissue will be sampled within 4 hours of birth by research technicians within the MFHRC and stored within the Tommy’s National Reproductive Health biobank (18/WA/0356). Placentas will not be collected for women giving birth at other hospital sites.
* For women giving birth at St Mary’s Oxford Rd, cord blood samples (EDTA plasma and serum) will be collected by a midwife after birth (within 1 hour). Samples will be labelled and stored in the Delivery Suite fridge for up to 72 hours prior to collection, processing and storage by the MFHRC technical staff. Cord samples will not be collected for women giving birth at other hospital sites.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes, and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

# MANAGEMENT OF ADVERSE EVENTS

## Definitions

### Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the study has commenced, even if not considered to be related to the study. Medical conditions/diseases present before starting the study will only be considered as adverse events if they worsen after the start of the study. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events will be sought by non-directive questioning of the patient during the study. Adverse events also may be detected when they are volunteered by the patient or through physical examination, laboratory test, or other assessment. As far as possible each adverse event will be evaluated to determine:

* The severity (mild, moderate, severe)
* Its relationship to the investigational treatment
* Its duration
* Action taken (no action taken; study treatment temporarily interrupted; study treatment permanently discontinued; concomitant medication taken; non-drug therapy given; hospitalisation required)
* Whether it is **serious**, where a serious adverse event (SAE) is defined as one which:

 - Is fatal or life-threatening

 - Results in persistent or significant disability/incapacity

 - Constitutes a congenital anomaly/birth defect

- Requires prolonged hospitalisation (except where it is for routine treatment/monitoring, elective or pre-planned treatment not related to study, for social or respite reasons)

- Is medically significant i.e. defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see below).

All adverse events will be recorded in detail, reported to the Trial Steering Committee and treated appropriately. Such treatment may include changes in study treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation, or any other medically required intervention. Once an adverse event is detected it will be followed until its resolution, and assessments will be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the investigational treatment, the interventions required to treat it, and the outcome.

### Evaluation of AEs and SAEs

Seriousness, causality, severity and expectedness will be evaluated for each AE.

### Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined above (see definitions).

### Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions. All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study treatment will be considered as ARs/SARs. If concomitant or rescue/escape drugs are given, the Investigator must also make an assessment of whether the AE/SAE is likely to be related to an interaction between the study treatment and concomitant or rescue/escape drugs or whether the AE/SAE might be linked to either the study treatment or concomitant or rescue/escape drugs but cannot be attributed to only one of these drugs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the study treatment and concomitant or rescue/escape drugs, or any AE/SAE that cannot be attributed to only the study treatment or the concomitant or rescue/escape drugs will also be considered to be ARs/SARs .

**Unrelated:** where an event is not considered to be related to the study treatment.

**Possibly:** although a relationship to the study treatment cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

**Probably:** the temporal relationship and absence of a more likely explanation suggest the event could be related to the study treatment.

**Definitely:** The known effects of the study treatment or its therapeutic profile, or based on challenge testing, suggest that study treatment is the most likely cause.

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.

### Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the Adverse Event (AE) 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.

### Assessment of expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the Summary of Product Characteristics (SmPC).

## Serious Adverse Event (SAE) reporting

Any SAE will be reported by the Investigator (including a completed SAE form) within 24 hours of first knowledge to the Sponsor. The Investigator will ensure that the patient is appropriately treated. They will also determine whether the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction). If it is deemed to be a SUSAR it will be reported immediately to the sponsor. All Adverse Events including SAEs will be reported to the Trial Steering Committee. A Development Safety Update Report (DSUR) will be submitted by the sponsor (in conjunction with the Chief Investigator) to the Research Ethics Committee. Completed initial and follow-up Serious Adverse Event forms should be faxed to the sponsor on 0161 276 5766 and addressed ‘For the attention of the Quality Manager’ or emailed to saereporting@manchester.ac.uk.

### Regulatory Reporting Requirements

The sponsor, or their delegate, has a legal responsibility to notify the Regulatory Competent Authority and the Research Ethics Committee that approved the trial. Fatal or life threatening SUSARs will be reported no later than 7 calendar days, with a further 8 days for follow up information. All other SUSARs will be reported no later than 15 calendar days after the sponsor is first aware of the reaction.

### Follow up procedures

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to the sponsor. AEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

## Operational definitions for (S)AEs

The safety reporting period will commence from provision of informed consent and will continue until primary hospital discharge or 28 days post-birth (or pregnancy loss), whichever occurs sooner. AE/SAEs must meet the definition as described in section 8.1, with the exception of events below which **will not** be considered to be AEs/SAEs and do not require reporting.

The following are considered expected in this population of pregnant women or a result of the usual clinical care and as such will be recorded in the participant’s medical record (including where a woman offers information to a research team) but not reported as (S)AEs:

### Maternal events:

* Intolerance to metformin (usual care arm)
* Episodes of hypoglycaemia (not requiring hospitalisation)
* Admission in active labour
* Admission for cervical ripening or induction of labour
* Admission for caesarean section
* Admission for assessment for suspected fetal compromise, including poor growth, or reduced fetal movements
* Admission for the treatment of infection/sepsis
* Admission for monitoring for diabetes, hypertension or pre-eclampsia, antepartum haemorrhage, suspected preterm labour, pre-labour rupture of the membranes or other reasons for monitoring
* Admission for psychiatric or social reasons
* Admission for unstable lie or external cephalic version
* Admission for postpartum complications
* Known complications of pregnancy that are collected for every woman as part of outcome collection (including, but not limited to, pre-eclampsia, post-partum haemorrhage, postpartum haemorrhage requiring transfusion or hysterectomy

Maternal undesirable effects of allocated medication regime will be recorded at each trial visit.

### Fetal and neonatal events:

Known fetal and neonatal complications of pregnancy that are collected for every infant as part of outcome collection, including, but not limited to:

* Neonatal unit admission
* Miscarriage
* Congenital anomaly
* Preterm delivery (<37 completed weeks’ gestation)
* Neonatal complications (including but not limited to hypoglycaemia, seizures, encephalopathy, need for respiratory support, sepsis, intraventricular haemorrhage, confirmed infection, necrotising enterocolitis, retinopathy of prematurity, congenital anomaly, intraventricular haemorrhage)

Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, which does not lead to further complications, will not be considered as an adverse event.

## Reporting urgent safety measures

The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of the clinical trial against any immediate hazard to their health and safety.

An urgent safety measure is a procedure not defined by the protocol. Implementation may take place prior to authorisation by the regulatory authority and REC in order to protect clinical study participants from any immediate hazard to their health and safety.

If an immediate hazard to the health and safety of participants in MIMICH is detected, the sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

The CI and sponsor will together determine the appropriate course of action. Once the appropriate course of action has been determined, the CI must take the agreed action to ensure trial subjects are made safe.

The REC will be informed of Urgent Safety Measures by means of a completed substantial amendment form.

If MIMICH is temporarily halted for any reason, the sponsor must notify the Ethics Committees immediately and at least within 15 days from when the trial is temporarily halted. The notification should be made as a substantial amendment using the Notification of Amendment form and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt.

In this case the study may not recommence until authorised to do so by the responsible regulatory authority and REC.

## Events that require expedited (immediate) reporting

Although the following SAEs are expected to occur in this population they will still be required to be reported (expedited reporting):

* Maternal death
* Maternal hypoglycaemia requiring hospitalisation
* Stillbirth after 24 weeks’ gestation
* Neonatal death up to 28 days

# DATA HANDLING

## Source Data

In order to allow for the accurate reconstruction of the study and clinical management of the woman, source data will be accessible and maintained.

## Electronic Case Report Form Completion

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete electronic case report forms (eCRFs) will be trained to adhere to eCRF completion guidelines.

In all cases it remains the responsibility of the CI to ensure that the eCRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI, or delegate(s), on the eCRF.

## Participant completed Questionnaires

The acceptability of the trial intervention will be assessed using a questionnaire at 30-34 weeks gestation which will be transcribed onto the study database.

## Data Management

Confidentiality of participant data shall be observed at all times during the study. Personal details for each participant taking part in the research study and linking them to a unique identification number will be held locally on a trial Screening Log and Enrolment Log in the Investigator Site File (ISF) at each of the investigation centres. These details will not be revealed at any other stage during the study, and all results will remain anonymous. The unique trial identification for each participant will be used on the CRFs and any other trial documentation shared within the trial management team.

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the Data Management Manual. Coding and validation will be agreed between the trial’s manager, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Electronic data will be stored on password-protected computers. All paper records will be kept in locked filing cabinets, in a secure office at each of the investigation centres. Only members of the research team and collaborating institutions will have password access to the anonymised electronic data. Only members of the research teams will have access to the filing cabinet. Paper copies of the data will be stored for 15 years.

## Access to data

Direct access to the source data will be provided for monitoring, audits, REC review during and after the study. Appropriate procedures agreed by the Chief Investigator and TMG will be put in place for data review, database cleaning and issuing and resolving data queries.

## Archiving

Archiving will be authorised by the sponsor following submission of the end of trial report. Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Each participating centre will be responsible for archiving trial documents at their site, including but not limited to, participant medical notes and investigator site files.

These documents shall be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for 15 years from the end of the trial. The medical files of trial participants shall be retained in accordance with both national legislation and with the minimum/maximum period of time permitted by the hospital, institution or private practice.

All other essential documents and the study data set will be archived by the University of Manchester for 7 years from the date of the final publication in a way that will facilitate any audit and inspection. Documents should be securely stored and access restricted to authorised personnel. Destruction of essential documents will require authorisation from the Sponsor.

# TRIAL STATISTICAL CONSIDERATIONS

## Sample Size

In a comparison of women with Type 2 diabetes treated with metformin recruited to the VELOCITY study, the mean delta zscore between the second trimester and birth was -0.51 (SD 1.1) for women with a placental disease risk factor (n=34) and 0.30 (SD 0.9) in women without a risk factor (n=45). A sample size of 190 women (95 in each group) will provide 80% power to detect a clinically significant difference in delta zscores of 0.41 (SD 1.0) between the treatment groups; this difference would reflect a rightward shift in the birthweight distribution in women in whom metformin was withheld to a mean of -0.1.

An adjusted analysis of the effect of the intervention (withholding metformin) on fetal growth will include covariates (mean daily glucose, time in target) which are known to influence fetal growth to improve the precision of the treatment effect as appropriate29. Change in fetal weight zscore provides a continuous measure of late pregnancy growth trajectory derived from early fetal biometry and 3D volumetric measurements and therefore the fetus is its own control. Importantly, this removes the need to adjust for infant sex. Furthermore, as the measurement of fetal weight zscores using 3D fetal thigh volumes, and therefore calculation of delta zscores is done after birth, the risk of bias is minimised. In the MiTy trial, a comparison of metformin vs no metformin in unselected women with type 2 diabetes, the difference in birthweight zscore was -0.28 (-0.45 to -0.10).

Recruitment figures have been based on attendances to the Manchester Antenatal Vascular Service (MAViS) clinic, which provides care for women with cardiometabolic disease, and the diabetes service across Manchester Foundation Trust. Allowing for the fact that the proposed study will draw from a population of 18,000 pregnancies per annum, eligible women will include those with type 2 diabetes (n≈108) and women who develop GDM with additional risk factors for placental disease (n≈420). A recruitment rate of 50% would yield an available cohort of approximately 225 women (10% drop out). Based on figures from the MAViS cohort, 20% would be expected develop a small for gestational age (SGA<10th centile) and 12-18% pre-eclampsia.

## Analysis of Outcomes

A separate Statistical Analysis Plan will be produced and will provide a more detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to the intervention versus usual care. In the first instance, all analyses will be based on the intention to treat (ITT) principle, i.e. all participants (and all babies of participants) will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. The protocol ITT dataset will comprise all women who provided data for the primary outcome. An ITT analysis will be undertaken for the primary outcome with an exploratory analysis based on an on treatment population.

For all outcome measures, appropriate summary statistics and treatment effects (e.g. mean differences, relative risks) will be presented, along with 95% confidence intervals and p-values as specified below. Treatment effects will be adjusted for the minimisation variables listed in section 6.2 where possible. No adjustment for multiple comparisons will be made.

## Primary Outcome

Fetal growth velocity will be assessed by change in fetal growth zscore between 20-26 weeks (average) and birth.

Treatment arms will be compared using linear regression models with categorical variables for each of the matching parameters used in the randomisation process and for the treatment unit.

## Secondary Outcomes

Secondary outcomes which are binary will be analysed using analogous log binomial regression models and results presented as adjusted risk ratios with 95% confidence intervals. Continuous outcomes (e.g. gestational age at birth, birthweight centile) will be analysed using linear regression models if the outcome is sufficiently normally distributed (or where data can be suitably transformed) and results presented as differences in means with 95% confidence intervals. For skewed continuous outcomes, unadjusted median differences and 95% confidence intervals will be presented.

For adverse events these data will be presented by randomised allocation.

## Subgroup Analyses

Exploratory subgroup analyses will be undertaken on variables used in the minimisation algorithm, and will be limited to the primary outcome. Tests for statistical heterogeneity (by including the treatment group by subgroup interaction parameter in the regression model) will be presented alongside the effect estimate and 95% CI within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

## Missing Data and exploratory analyses

Every attempt will be made to collect full follow-up data on all participating women; it is thus anticipated that missing data will be minimal. Women with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This may include a multiple imputation approach. Full details will be included in the Statistical Analysis Plan.

An exploratory analysis will be undertaken for the primary outcomes based on a on treatment analysis population (women adherent within their treatment allocation from randomisation to birth, for whom outcome data are available). For the primary outcome, this will allow us to examine the robustness of the conclusions.

## Planned Interim Analysis

Interim analyses of safety for presentation to the independent TSC will take place during the study. This is likely to include full assessment of safety (SAEs) at least at annual intervals. Details of the agreed plan will be written into a TSC Charter.

## Planned Final Analyses

The primary analysis for the study will occur once all participants have had their primary hospital discharge or 28 days post-birth, whichever occurs sooner and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the primary hospital discharge or 28 days post-birth (whichever occurs sooner). No analysis will be conducted until the trial database has been locked and approved for analysis by the study Sponsor.

#  MONITORING

A trial Monitoring Plan will be developed and agreed by the Sponsor and TMG. The plan will be based on the trial risk assessment, which may include on site monitoring. The procedures and anticipated frequency for monitoring will be documented in the Monitoring Plan.

## Remote Monitoring

Essential documents will be requested periodically and reviewed remotely by the Clinical Trials Monitor. Details of the documents required and the frequency of the requests will be detailed in the Monitoring Plan.

## On-Site Monitoring

On-site monitoring will be defined using a risk-based strategy and a risk assessment will be completed by the Sponsor or delegate team as part of the site set-up process to ascertain the frequency and level of monitoring required (although additional monitoring may be conducted if necessary).

The purpose of these visits is:

* To verify that the rights and well-being of participants are protected.
* To verify accuracy, completion and validity of reported trial data from the source documents.
* To evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol, GCP and with the applicable regulatory requirements

# TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

## Role and Responsibilities

### Sponsor

The trial will be sponsored by the University of Manchester. The responsibilities of the sponsor are as defined in 9.10 of the UK Policy Framework for Health and Social Care Research, V3.3. In line with this requirement, the Chief Investigator will ensure that all involved in the research project understand and discharge their responsibilities in accordance with the agreed protocol and any management, ethical and regulatory approvals.

Responsibilities of the sponsor are detailed in the. The University of Manchester, as the sponsor, has delegated a number of these responsibilities as detailed in 9.10 of the UK Policy Framework for Health and Social Care Research, V3.3 the Delegation of Responsibilities section of the research agreement signed between the Sponsor and CI.

The sponsor has legal responsibilities that cannot be delegated.

### Funder

This trial is funded by the European Research Council. The roles and responsibilities of the funder are defined within the Investigator-Sponsor Funding Agreement.

## Oversight Committees

### Trial Management Group

A Trial Management Group (TMG) will be established and will include those individuals responsible for the day-to-day management of the trial including the Chief Investigator (CI), co-investigators and identified collaborators, Principal Investigators, sponsor, the trial statistician and trial manager(s). Notwithstanding the legal obligations of the sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial including monitoring overall progress to ensure the protocol is adhered to and to take appropriate action to safeguard the participants and the quality of the trial.

The TMG will meet to discuss progress at least quarterly once the trial is actively recruiting. Minutes will be taken at TMG meetings and copies of the minutes will be filed in the Trial Master File (TMF). The clinical trial manager (CTM) and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TMG meetings are available on request.

### Trial Steering Committee

A Trial Steering Committee (TSC) will be established and will include an independent chair, at least two other independent members (including a statistician), a PPI representative(s), and the CI. The role of the TSC is to take responsibility for safety monitoring and the scientific integrity of the trial, the scientific validity of the trial protocol, assessment of the trial quality and conduct (to ensure the trial is being conducted in accordance with the principles of GCP and the relevant regulations) as well as for the scientific quality of the final trial report. Decisions about the continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

The TSC will meet once ethics approval has been given and before the trial begins recruitment. Once the trial has started the TSC should meet annually to monitor the progress of the trial although there may be periods when more frequent meetings are necessary. Meetings should be organised by the CI and trial manager. Minutes will be taken at TSC meetings and copies of the minutes will be filed in the TMF and made available to the sponsor. The CTM and CI will ensure that all the relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TSC meetings are available on request. The Committee’s terms of reference, roles and responsibilities will be defined in a charter issued by the CTM.

Additional meetings may be called if recruitment is much faster than anticipated and the TSC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The TSC will convey any relevant findings to the funders. The TSC may consider recommending the discontinuation of the trial if any issues are identified which may compromise participant safety.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Research Ethics Committee (REC) review and reports

Before the start of the trial, an application will be submitted to the Health Research Authority (HRA) for approval. Approval will also be sought from a REC for the trial protocol, informed consent forms and other relevant trial documents e.g. GP information letters.

Amendments will be submitted with the oversight of the trial sponsor. Substantial amendments that require REC review will not be implemented until the REC grants a favourable opinion for the trial and local R&D approval is secured.

In addition:

* All correspondence with the REC will be retained in the Trial Master File/ Investigator Site File.
* An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.
* The Chief Investigator and sponsor will notify the REC of the end of trial. If the trial is ended prematurely or temporarily halted, the Chief Investigator and sponsor will notify the REC, including reasons for the premature termination.
* Within 12 months of declaration of the end of the trial, the Chief Investigator/sponsor will submit a final report with the results, including any publications/abstract, to the REC.

## Regulatory Compliance

The trial will not commence until all approvals are in place. The protocol and trial conduct will comply with the UK Policy Framework for Health and Social Care Research and any relevant amendments. The Chief Investigator and sponsor will submit a final report to the HRA and funder with the results within 12 months of the declaration of the end if the trial.

## Local Capability and Capacity Review

Before any participating site can enrol participants into the trial, the Chief Investigator/ Principal Investigator or designee will apply for confirmation of local capability and capacity from the site’s Research & Development (R&D) department.

## Peer review

The trial has been peer reviewed through award of a Consolidator Fellowship to Professor Jenny Myers by the European Research Council. The application was peer reviewed by nine external referees and awarded post interview. The trial protocol and associated participant facing documentation has been externally reviewed by the ERC Ethics review board.

## Public and Participant Involvement

Members of the Maternal & Fetal Health Research Centre User Group have reviewed the funding application summary, the trial flow chart and associated participant facing documentation. The user group have commented on aspects of the trial design and reviewed and improved the language used in the documentation. Material produced to disseminate the results of the trial results will be disseminated following review by the user groups and other patient organisations – e.g. Diabetes UK.

## Protocol compliance

As stated in the UK Clinical Trials Regulations, planned deviations or waivers to the trial protocol are not permitted, unless the deviation/non-compliance is being performed as an urgent safety measure to protect a participant from immediate harm.

Accidental protocol non-compliances can happen at any time. Non-compliances vary in incidence and impact and are classified accordingly as minor, major or as a serious breach. The sponsor will subsequently advise on any further action or information required.

The trial team will maintain a log of all protocol non-compliances to enable these events to be monitored for frequency.

## Data protection and participant confidentiality

Trial participants will be identified by the clinical trial team by an unique identifier, initials and date of birth.

Representatives from the sponsor trial monitoring team and the regulatory authorities will be required to have access to participants’ notes for quality control and assurance purposes but participants should be reassured that their confidentiality will be respected at all times. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

All Investigators and trial site staff involved with the trial must comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. The Sponsor’s host institution will be the data custodian.

Participant notes and trial files at site must be kept in a secure storage area with limited access. Computers used to collate the data will have access restrictions via user names, passwords and the use of encrypted digital files and storage media.

Published results will not contain any personal data that could allow identification of individual participants.

Any personal data recorded will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain.

## Financial and other competing interests

No members of the research team, investigator teams or the trial sponsor have any financial or other competing interests that might influence the trial design, conduct or reporting. All oversight committee members will be asked to disclose any potential conflicts of interests as part of the membership agreement. If any financial or other competing interests are identified during the course if the trial, this information will be declared and will be stored in the TMF.

## Indemnity

The University of Manchester will act as the Sponsor for this trial. The UoM has in place Clinical Trials indemnity coverage for this study which provides cover to the University for harm which comes about through the University’s, or its staff’s, negligence in relation to the design or management of the study and may alternatively, and at the University’s discretion, provide cover for non-negligent harm to participating women. The insurance cover is limited at £1M for birth defect or fetal injury.

The participating site will be liable for clinical negligence and other negligent harm to participants who are taking part in the trial and are covered by the duty of care owed to them by the site concerned. For all participating sites that are part of the NHS, the NHS indemnity scheme will also apply.

## Amendments

Any changes in research activity will be reviewed and approved by the Chief Investigator. With the oversight of the Sponsor, the subsequent amendment will categorised as a substantial or non-substantial. Any required changes to the CTA or the documents that supported the original application for the CTA and/or ethical approval will be submitted as an amendment to the appropriate ethical and regulatory authorities by the trial team. Substantial amendments will not be implemented until the HRA grants approval of the study.

The trial team will maintain an amendment history tracker to ensure the most recent version of the protocol and supporting documents is used at all times.

## Post-trial care

As diabetes treatment is often switched immediately after birth (and therefore extended postnatal data are unlikely to reflect effects of the intervention), outcomes will be collected up to birth and data collection up to primary hospital discharge or 28 days post-birth, whichever occurs sooner. The decision to continue or switch diabetes medications after birth will sit entirely with clinicians within the woman’s usual care team.

## Access to the final trial dataset

Individuals with access to the full dataset will include the trial statistician and data manager. The CI will have access to the full dataset after database lock. The CI’s Institution will be the overall owner of the study data. Site investigators will not have access to the full data set and must not use, disseminate or publish any trial data without the prior written consent of the TMG and TSC.

# DISSEMINATION POLICY

The trial data will be owned by the University of Manchester. The trial data will be analysed in line with statistical analysis plan, tabulated and summarised in a Final Study Report. The study report will be accessed on request to the CI. Any data collected as part of the trial will only be published following approval by the CI and Sponsor.

The funders of the study will be acknowledged in any publications arising from the trial.

A plain English summary of the trial findings will be published via the MFHRC website and disseminated through other partner charity media platforms e.g. Diabetes UK, Tommys.

Participants can request specific results through direct request to the CI after completion of the Final Study Report.

An anonymised participant level dataset will be accessible as set out in the data management plan.

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#  APPENDICES

## Appendix 1

Confirmation email from the MHRA that a clinical trial authorisation is not required.



1. 1 Women with a history of hypertensive complications in a previous pregnancy or with a history of hypertension outside of pregnancy are referred to the MAViS clinic at 12-16 weeks [↑](#footnote-ref-2)
2. 2 Women with a diagnosis of diabetes before pregnancy are referred to the VELOCITY clinic at 12-16 weeks [↑](#footnote-ref-3)