

# METAFOR: studying delayed-release metformin to control blood sugar levels for women with gestational diabetes

<b>Submission date</b> 09/12/2022	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 11/07/2023	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 29/04/2024	<b>Condition category</b> Pregnancy and Childbirth	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

We will address the unmet clinical need for an effective, well-tolerated, and safe drug therapy for women with gestational diabetes, the most common pregnancy complication.

Metformin IR (immediate release) is widely used as first-line drug therapy in the UK to control blood sugar levels and has significant advantages over other available drug therapies for women, including that it is a tablet and it helps limit pregnancy weight gain.

However, standard metformin IR has poorly tolerated side effects including nausea and diarrhoea. It also freely crosses the placenta, and emerging evidence suggests the potential for adverse child health outcomes including obesity.

We plan to perform a three-arm pilot proof-of-principle trial consisting of two non-randomised arms and one crossover randomised controlled arm involving 50 women using a new “delayed-release” (DR) metformin tablet which we hypothesise will substantially reduce levels of metformin in the mother’s blood and will reduce transfer of metformin across the placenta compared to metformin IR tablets, minimising the potential for adverse effects of metformin exposure for the child.

We also aim to assess whether this metformin DR preparation compared to metformin IR is a feasible and acceptable alternative to other drug therapy for women with gestational diabetes and will have fewer side effects, which will encourage women to take their treatment regularly, thus improving their blood sugar control and avoiding the need for insulin injections.

Our findings will support an application for a larger DR delayed-release as a treatment to optimise the management of gestational diabetes with the fewest side effects for mother and baby.

### Who can participate?

Women who are pregnant and experiencing gestational diabetes.

Please note: We use the term 'women' in our participant information and protocol to refer to those who are pregnant, and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive.

What does the study involve?

Please refer to the participant information sheets for this information (to be uploaded at a later date).

What are the possible benefits and risks of participating?

**Benefits:**

There are no immediate benefits of taking part in this study. However, the findings will be important in helping find an effective and well-tolerated treatment for gestational diabetes. If this is shown to be the case, we hope that this will benefit lots of pregnant women in the future.

**Risks:**

We are aware that participants in this study will give up their valuable time for participation. Other than that, the major risk and burden relates to the potential adverse effect of the IMP. Metformin treatment holds significant advantages for women but has poorly tolerated side effects and freely crosses the placenta with increasing concern regarding the potential for adverse long-term offspring health outcomes. Delayed-Release metformin (Metformin DR) is a new formulation of metformin hydrochloride designed to reduce systemic metformin exposure while retaining efficacy in maintaining normoglycaemia.

Study-specific blood tests will also be performed on all women at baseline, and as per individual sub-study protocols. Blood tests at baseline include: full blood count, kidney and liver function, random venous glucose, and HbA1C. Risk is minimised in this study by ensuring normal renal and liver function in all women prior to randomisation.

Metformin levels will also be assessed in all blood tests taken after ingestion of the IMP.

Where is the study run from?

University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?

June 2022 to May 2024

Who is funding the study?

Chief Scientist Office (UK)

Who is the main contact?

Dr Anna Heye, METAFOR.trial@ed.ac.uk

Dr Rebecca Reynolds, r.reynolds@ed.ac.uk

**Study website**

<https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/metafor>

## Contact information

**Type(s)**

Scientific

**Contact name**

Dr Anna Heye

**Contact details**

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**Type(s)**

Principal Investigator

**Contact name**

Prof Rebecca Reynolds

**ORCID ID**

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**Additional identifiers****EudraCT/CTIS number**

2022-001240-24

**IRAS number**

1004070

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

AC21117, IRAS 1004070

**Study information****Scientific Title**

METAFOR Study Pilot: Metformin Antenatal Formulations Study Pilot: an open-label feasibility study

**Acronym**

METAFOR

## **Study objectives**

### **Primary objectives:**

In this study we aim to test whether a new “delayed-release” metformin tablet is a feasible and acceptable alternative for women with gestational diabetes. This will be a first-in-pregnancy usage of metformin DR and we hope to see if women will be willing to take a new formulation of metformin in pregnancy.

### **Secondary objectives:**

1. To explore acceptability and tolerability of metformin delayed-release (DR) in pregnancy
2. In studies of people who are not pregnant, the new metformin tablet has fewer side effects than regular metformin tablets. If this is the case for pregnant women, it would make it easier for women to take their treatment regularly, thus improving their blood sugar control and avoiding the need for insulin injections
3. To demonstrate that metformin DR lowers blood sugar levels in women with gestational diabetes with similar effects to metformin IR. Due to the delayed release formulation we think there will be reduced levels of metformin crossing the placenta to the baby.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Approved 16/06/2023, East of England - Cambridge East Research Ethics Committee (2 Redman Place, London, EC20 1JQ, UK; Tel: not provided; CambridgeEast.REC@hra.nhs.uk), ref: 23/EE/0012

## **Study design**

Interventional randomized cross over trial

## **Primary study design**

Interventional

## **Secondary study design**

Randomised cross over trial

## **Study setting(s)**

Hospital

## **Study type(s)**

Treatment

## **Participant information sheet**

Not available in web format, please use the contact details to request a patient information sheet.

## **Health condition(s) or problem(s) studied**

Gestational diabetes in pregnancy

## **Interventions**

ARM 1 (Non-randomised):

Population: 20 pregnant women diagnosed with gestational diabetes with singleton pregnancies

and a clinically documented plan to have birth by elective Caesarean section  $\geq 37$  weeks' gestation.

Duration of treatment phase: 24 hours

Treatment allocation: On receipt of a trial specific prescription, Pharmacy will dispense 4 Metformin DR 900mg tablets (1 to be taken by participant, 3 provided as an overage).

Dose: One Metformin DR 900mg tablet orally within 3 to 8 hours prior to planned Caesarean section

Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

#### ARM 2 (Non-randomised):

Population: 10 pregnant women diagnosed with gestational diabetes with singleton pregnancies between  $\geq 28+0$  and  $\leq 36+0$  weeks gestation. Only patients from the Edinburgh Royal Infirmary, NHS Lothian site will be recruited to this arm of the study. Arm 2 requires a day admission to the Clinical Research Facility Trials Unit and a single dose of metformin DR with serial blood sampling.

Duration of treatment phase: 24 hours

Treatment allocation: On receipt of a trial specific prescription, Pharmacy will dispense 4 Metformin DR 900mg tablets (1 to be taken by participant, 3 provided as an overage).

Dose: One Metformin DR 900 mg tablet to be taken orally with or after breakfast and 1.5 hours (-1+2 hours) prior to commencement of blood sampling at clinical research facility.

Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

#### ARM 3 (Randomised crossover, web-based randomisation system allocated at 1:1 ratio):

Population: 20 pregnant women diagnosed with gestational diabetes with singleton pregnancies documented in the patients' medical notes to be adequately treated with metformin  $< 36+0$  weeks pregnant.

Duration of treatment phase: 2 weeks

Treatment allocation:

Once the crossover randomisation allocation has been generated, the next available IMP pack (8 Metformin DR 900mg tablets) for Arm 3 will be dispensed on receipt of a prescription (7 to be taken by participant, 1 provided as an overage). They will be randomised to:

- Continue to take their own normal standard prescribed daily dose of Metformin IR for first 7 days and then given the IMP Metformin DR 900mg tablet daily for 7 days at the follow-up visit OR
- Be given the IMP Metformin DR 900mg tablet daily for the first 7 days and at the follow up visit at 7 days advised to take their own normal standard prescribed daily dose of Metformin IR for 7 days.

Dose: One Metformin DR 900mg tablet once a day for 7 days

Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

#### Intervention Type

Drug

#### Phase

Phase II

#### Drug/device/biological/vaccine name(s)

Metformin

### **Primary outcome measure**

Fetal metformin exposure measured by the maternal: fetal serum metformin ratio using paired maternal and umbilical cord blood samples at delivery by elective Caesarean section in Arm 1 up to 3 months following delivery, data extracted from record of mother and baby.

### **Secondary outcome measures**

Up to 3 months following delivery, data extracted from record of mother and baby:

Arm 1:

- 1.1. Placental metformin level at delivery
- 1.2. Placental metformin transporter levels at delivery
- 1.3. Maternal plasma metformin level at delivery
- 1.4. Fetal serum metformin level at delivery
- 1.5. Fetal arterial:venous metformin ratio at delivery
- 1.6. Detection of metformin in maternal serum 24 hrs post-delivery

Arm 2:

- 2.1. AUC of maternal serum metformin levels in the third trimester.
- 2.2. Pharmacokinetic parameters of metformin in maternal blood, including peak serum concentration, half-life, bioavailability, renal clearance
- 2.3. Metformin concentrations in maternal urine

Arm 3:

- 3.1. Percentage of eligible participants recruited i.e. number who agree to take part out of all eligible participants who are approached.
- 3.2. Side-effects of treatment by questionnaire
- 3.3. Acceptability of treatment by questionnaire
- 3.4. Concordance with treatment by questionnaire
- 3.5. Percentage maternal blood glucose readings within local clinical target range
- 3.6. Need for additional gestational diabetes therapy at the end of 1 week of metformin DR/IR
- 3.7. Average plasma glucose concentration

### **Overall study start date**

01/06/2022

### **Completion date**

16/01/2024

### **Reason abandoned (if study stopped)**

Lack of staff/facilities/resources

## **Eligibility**

### **Key inclusion criteria**

1. Women who are pregnant with singleton pregnancy
2. Women with a documented diagnosis of gestational diabetes in their current pregnancy  
EITHER/OR Women who are documented to be currently treated for gestational diabetes due to a documented history of gestational diabetes in a previous pregnancy
3. Women who are able to give written informed consent to participate

In addition:

**Arm 1:**

1. Planned for elective Caesarean section at  $\geq 37$  weeks gestation
2. Women with gestational diabetes documented to be treated with diet alone

**Arm 2:**

1. Women who are in the third trimester of pregnancy ( $\geq 28+0$  weeks and  $\leq 36+0$  weeks gestation at consent)
2. Women with gestational diabetes documented to be treated with diet alone

**Arm 3:**

1. Women  $\leq 36+0$  weeks pregnant at randomisation
2. Women with gestational diabetes documented to be treated with diet and standard metformin IR (standard dose 1000 mg once daily or 500 mg twice daily)

Please note: We use the term 'women' on this site and in the study protocol to refer to those who are pregnant, and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive. Our participant-facing study documents utilise appropriate gender-inclusive language.

**Participant type(s)**

Patient

**Age group**

Adult

**Sex**

Female

**Target number of participants**

50

**Key exclusion criteria**

1. Pre-existing diabetes mellitus
2. Taking glucose-lowering agents other than metformin (insulin, glibenclamide)
3. Previous delivery of a baby  $< 3$ rd centile by weight or previous serious adverse pregnancy outcome (e.g. stillbirth or early neonatal death)
4. Known sensitivity to metformin hydrochloride or any of the known excipients.
5. Documented acute clinical condition at the time of study entry with the potential to alter renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock and intravascular administration of contrast agents.
6. Known diagnosis or documented clinically suspected acute or chronic diseases that may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency, acute alcohol intoxication and alcoholism.
7. High risk of operative blood loss  $> 1$  litre at Caesarean section, e.g. placenta praevia,  $> 2$  previous Caesarean sections
8. Currently lactating
9. Known fetal anomaly
10. Multiple pregnancy
11. History of, or currently clinically suspected, liver failure or dysfunction at the time of trial

entry

12. History of, or currently clinically suspected, severe renal failure or dysfunction at the time of trial entry\*\*

13. History of, or currently clinically suspected, (any type of) acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

14. Previous known severe renal failure (GFR < 45 mL/min)\*\*

15. Already enrolled in another randomised clinical trial involving IMP.

16. Taking prescribed drug known to affect renal function or result in haemodynamic change

17. Receiving investigation using iodinated contrast agent

In addition:

Arm 3:

18. Women who have two or more routine blood glucose values out of range at the same time point on consecutive days, within the 14 days prior to consent, without a valid reason in the opinion of the PI.

19. Women who regularly fail to check glucose by finger prick on 2 or more times per day

**Date of first enrolment**

06/09/2023

**Date of final enrolment**

03/12/2023

## Locations

**Countries of recruitment**

England

Scotland

United Kingdom

**Study participating centre**

**Royal Infirmary of Edinburgh at Little France**

51 Little France Crescent

Old Dalkeith Road

Edinburgh

Lothian

United Kingdom

EH16 4SA

**Study participating centre**

**The Rosie Hospital**

Addenbrookes Hospital

Robinson Way



Cambridge  
United Kingdom  
CB2 0Sw

## Sponsor information

### Organisation

University of Edinburgh

### Sponsor details

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### Sponsor type

University/education

### Website

<http://www.ed.ac.uk/home>

### ROR

<https://ror.org/01nrxf90>

### Organisation

NHS Lothian

### Sponsor details

The Queens Medical Research Institute  
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### Sponsor type

Hospital/treatment centre

### Website

<http://www.nhslothian.scot.nhs.uk/Pages/default.aspx>

**ROR**

<https://ror.org/03q82t418>

## **Funder(s)**

### **Funder type**

Government

### **Funder Name**

Chief Scientist Office, Scottish Government Health and Social Care Directorate

### **Alternative Name(s)**

Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

### **Funding Body Type**

Government organisation

### **Funding Body Subtype**

Local government

### **Location**

United Kingdom

## **Results and Publications**

### **Publication and dissemination plan**

Peer reviewed scientific journals

Conference presentation

Publication on website

Submission to regulatory authorities

Pilot data will be generated from the proposed work. The data will be available by request after completion of analyses by the study team. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion). It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

### **Intention to publish date**

30/11/2024

### **Individual participant data (IPD) sharing plan**

After publication, anonymised patient level study data may be shared with other researchers on reasonable request in writing to the Chief Investigator, Professor Rebecca Reynolds (R.Reynolds@ed.ac.uk).

## IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Plain English results</a>			29/04/2024	No	Yes