CHIEF SCIENTIST OFFICE

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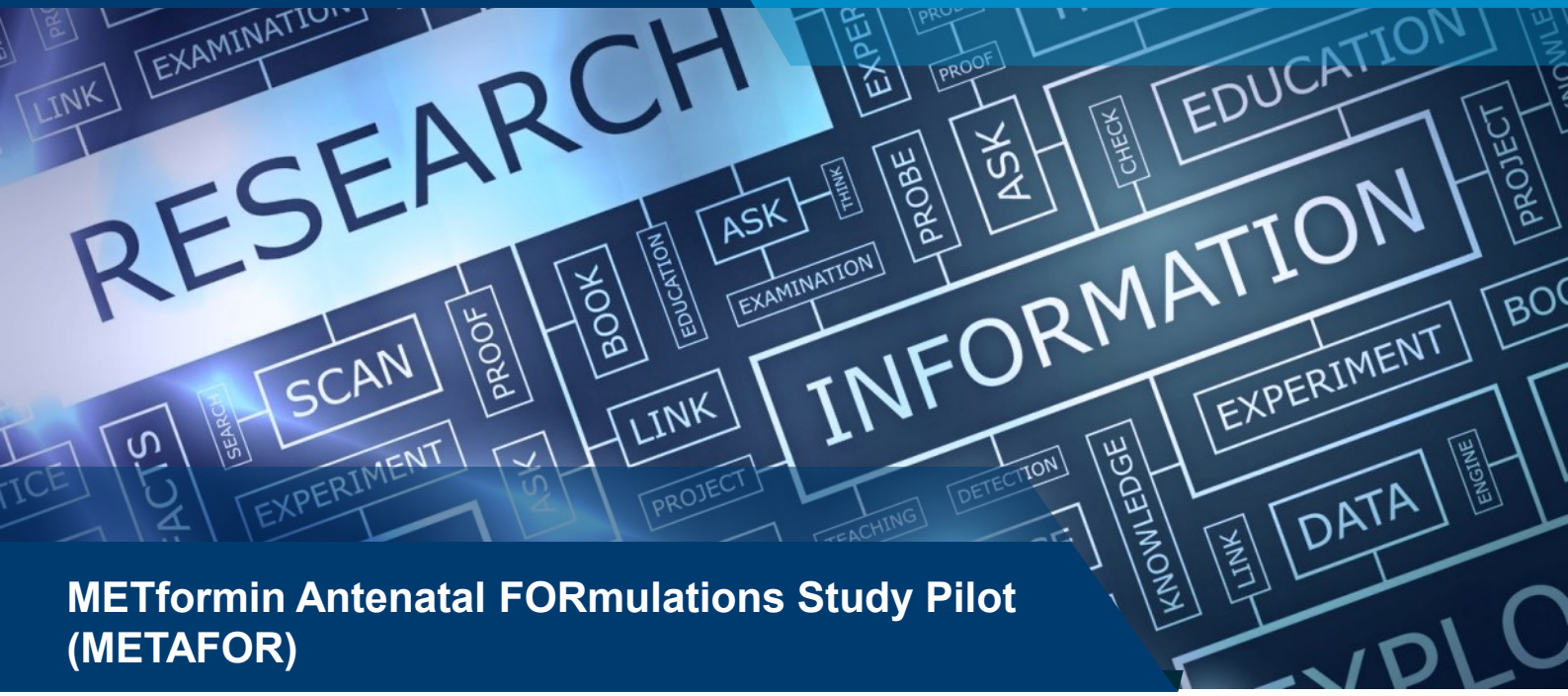
RESEARCH PROJECT BRIEFING



METformin Antenatal FORmulations Study Pilot (METAFOR)

AIMS

The METAFOR study aimed to optimise drug therapy for pregnant women and birthing people with gestational diabetes (GDM), the most common pregnancy complication, affecting around 1 in five pregnancies. The first-line drug therapy in the UK, Metformin IR (immediate release), is widely used and effective in controlling blood sugar levels and limiting gestational weight gain in people with GDM. However, it also has poorly tolerated side effects, including nausea and diarrhoea, and freely crosses the placenta. Emerging evidence suggests that the resulting fetal metformin exposure can cause adverse child health outcomes including obesity.

METAFOR aimed to test 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, thus minimising the potential for adverse effects of metformin exposure for the child. We also aimed to assess whether the metformin DR preparation is a feasible and acceptable alternative to metformin IR for women with GDM and will have fewer side effects.

KEY FINDINGS

- Due to unforeseen and unavoidable delays during the initial phase of this project (largely caused by lengthy discussions regarding the drug supply agreement as well as exceptionally long MHRA review timelines), the trial opened to recruitment approximately 12 months behind schedule.
- The original batch of study drug expired in December 2023 and we were unable to source additional study drug. Consequently, the trial had to be terminated early after being open to recruitment for only approximately three months.
- During that time, 234 women were screened between two study sites, 16 women were approached and one participant was recruited to trial Arm 1.
- Data from the one participant supported minimal placental transfer of metformin DR.

WHAT DID THE STUDY INVOLVE?

METAFOR was an open-label pilot proof-of-principle trial consisting of three linked arms.

- Arm 1: non-randomised design (both participants and researchers know that metformin DR is taken), including 20 pregnant women diagnosed with GDM scheduled for elective Caesarean section at ≥37 weeks gestation. Participants were to take one metformin DR 900 mg tablet on the morning of delivery by Caesarean section with blood, umbilical cord and placenta sampling.
- Arm 2: non-randomised design, including 10 pregnant women with GDM between ≥28+0 and ≤36+0 weeks gestation. Participants were to take one metformin DR 900mg tablet prior to commencement of serial blood and urine sampling at a clinical research facility.
- Arm 3: randomised crossover design (the order of which tablet is taken is assigned randomly), including 20 women with GDM who are adequately treated with metformin IR at <36+0 weeks pregnant. Participants were to be randomised to continue their own standard care dose of metformin IR for 7 days week, followed by 7 days of metformin DR 900mg or vice versa.

For all arms, postnatal data was to be collected from the medical records of both mother and baby at 28 days post-delivery.

Pregnant women attending antenatal diabetes clinics and the Lothian Maternity Voices Partnership were involved in the design of the trial and drafting of study documents. Pregnant women were also involved in the delivery of the work.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

We experienced unforeseen delays during the initial phase of this project, largely caused by lengthy discussions regarding the Drug Supply Agreement as well as exceptionally long MHRA review timelines. Despite those early challenges, we successfully obtained approvals for the study and by early November 2023 two trial sites in two hospitals were open to recruitment (approximately 12 months later than originally planned).

In early December 2023, recruitment was suspended as the initial supply of study drug had expired. We have made extensive efforts to obtain additional study drug supply with a longer expiry date, but this was not possible.

While the study was open to recruitment, 234 women were screened during routine appointments between the two sites. 187 of 234 of screened women were ineligible, mostly due to having pre-existing diabetes (n=68) or being treated with other glucose-lowering agents such as insulin (n=42). Of 47 eligible women, 31 were not approached due to the drug expiry date (n=16) or change in clinical circumstances). 16 eligible women were approached, 15 of whom declined to take part in the study. This is in line with our original assumption that approximately 1 in 20 eligible women will consent to be part of the study. One woman consented to take part in trial Arm 1 and completed the study.

Since this trial was terminated early with n=1 participant, there has been no formal analysis. However, the participant's cord venous serum and cord arterial serum concentrations were 3 and 4.5 times lower, respectively, than paired maternal serum samples. This contrasts with our pre-existing data collected from women taking metformin IR where that cord serum concentrations were approximately twice as high as maternal serum samples. This thus supports our hypothesis that the placental and fetal metformin levels are significantly reduced with metformin DR when compared to metformin IR.

WHAT IMPACT COULD THE FINDINGS HAVE?

- METAFOR was a pilot trial. While we were not able to complete recruitment and achieve the study objectives, we gained valuable experience with regards to realistic set-up timelines and screening rates. Moreover, we gathered feedback from sites on the study documentation and procedures.
- We strongly believe that the research question remains valid and important. Our preliminary data also supports our overall hypothesis. Therefore, we hope to re-visit this work at some point in the future if a secure study drug supply chain can be identified. Future studies will greatly benefit from the lessons learnt during this project.

HOW WILL THE OUTCOMES BE DISSEMINATED?

While it will not be possible to publish any results, we will consider summarising our approach and lessons learned in an article. A brief summary will also be posted on the publicly available ISRCTN register.

CONCLUSION

Due to delays during the set-up phase and resulting expiry of the study drug, this project had to be terminated early. Nevertheless, we have demonstrated that the trial procedures are deliverable. We have gained experience with regards to realistic set-up timelines, gathered feedback from site teams on the study documentation and collected screening data, all of which will be valuable information for future grant applications and trial designs when a new supply of metformin DR can be secured.

RESEARCH TEAM & CONTACT

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Additional Information

The terms 'women' and ‘birthing people’ are used in this trial 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.

The study drug used in this trial was provided by Anji Pharmaceuticals Inc, 245 Main Street | Cambridge, MA 02142, USA