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Does metformin prolong pregnancy in preterm pre-eclampsia? A study protocol for a South African, hospital-based double-blind, randomised, placebo-controlled trial

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ABSTRACT

Introduction Preterm pre-eclampsia is a leading cause of maternal morbidity and mortality. The Pre-eclampsia Intervention 2 (PI 2) trial suggested that metformin sustained release (XR) may prolong gestation by a week in pregnant women undergoing expectant management (7.6 days, geometric mean ratio 1.39, 95% CI 0.99 to 1.95; p=0.057). These findings should be confirmed with a larger sample size, and we need to know if such a prolongation improves neonatal outcome. Here, we describe the protocol for such a follow-up trial.

Methods The PI 3 trial is a phase III, intention-to-treat, double-blind, placebo-controlled randomised clinical trial to assess if metformin XR can prolong gestation and improve neonatal outcomes in women undergoing expectant management for preterm pre-eclampsia. We will recruit women who are between 26+0 and 31+6 weeks pregnant. Women will be randomised to receive either 3 g metformin XR or an identical placebo in divided daily doses. The primary outcome is prolongation of pregnancy. Secondary outcomes are neonatal birth weight and length of neonatal care admission (an indicator of neonatal health at birth). All other outcomes will be exploratory. We will record tolerability and adverse events. We plan a sample size of 500 participants to be powered for the primary and secondary outcomes.

Ethics and dissemination PI 3 has ethical approval (Health Research Ethics Committee 2, Stellenbosch University, Protocol number M21/03/007, Project ID 21639, Federal Wide Assurance Number 00001372, Institutional Review Board Number IRB0005239), and is registered with the Pan African Clinical Trial Registry (PACTR202104532026017) and the South African Medicine Control Council (20211211). Data will be presented at international conferences and published in peer-reviewed journals.

Trial registration number PACTR202104532026017)

ARTICLE FOCUS

⇒ Protocol of a phase III clinical trial to confirm whether metformin sustained release (XR), administered to women with preterm pre-eclampsia, can safely prolong gestation and improve neonatal outcomes compared with placebo.

KEY MESSAGES

⇒ Our previous study (PI 2) showed metformin XR may prolong gestation in women managed expectantly with preterm pre-eclampsia.

⇒ This study aims to confirm or refute whether metformin XR prolongs pregnancies complicated by preterm pre-eclampsia.

STRENGTHS AND LIMITATION OF THIS STUDY

⇒ This is a protocol for a randomised, double blind, placebo-controlled clinical trial where we plan to recruit 500 participants. This will provide sufficient power to evaluate the outcomes of prolongation of gestation (primary outcome), neonatal birth weight and length of neonatal admission (secondary outcomes).

⇒ This trial will be run at a single-referral hospital.

INTRODUCTION

Pre-eclampsia is a pregnancy specific disorder that presents with hypertension and multiorgan injury.[1] Globally, it is a leading cause of maternal mortality responsible for more than 60 000 maternal deaths per year, and many more fetal and neonatal losses.[1–3] Preterm pre-eclampsia, a severe variant, often results in iatrogenic preterm birth with the associated risks for the neonate of severe disability including cerebral palsy, intracerebral haemorrhage, retinopathy of prematurity, chronic lung disease and death.[4 5] When pre-eclampsia is diagnosed, there are two options: delivery or expectant management. The consequences of preterm birth are balanced against the risks of serious complications of

pre-eclampsia for the mother. Expectant management can only be offered when both the mother and fetus are stable.

Until recently, there have been no treatment options for prolonging pregnancy for women undergoing expectant management of preterm pre-eclampsia. Antithrombin III, given as an intravenous infusion, and esomeprazole, 40 mg orally per day, did not show a prolongation of pregnancy in clinical trials.[6 7] Sildenafil, 50 mg three times a day, showed a possible 4 day prolongation, but more recent pregnancy trials using this drug have raised concerns about significant fetal and neonatal risks.[8 9] This makes the further consideration of sildenafil to treat pre-eclampsia unlikely.

In 2021, we published the Pre-eclampsia Intervention 2 trial (PI 2) where we reported sustained release (XR) oral metformin (commonly used to treat diabetes in pregnancy) may prolong pregnancy in preterm pre-eclampsia in a trial of 180 women.[10] Metformin XR was associated with a median difference of 7.6 days prolongation of pregnancy, compared with placebo (geometric mean ratio 1.39, 95% CI 0.99 to 1.95; p=0.057).[10] Among women who continued to take the trial drugs at any dose, the median prolongation in the metformin arm was 9.6 days longer. For those who took the full dose of metformin XR, prolongation of gestation was 11.5 days longer.[10] There were also trends towards a higher birth weight in the metformin arm and a shorter length in neonatal hospital stay. This trial suggests that metformin XR may prolong gestation in women with preterm pre-eclampsia. However, a larger trial is needed to confirm, or refute these findings. Here we report a protocol of a larger trial, the PI 3 trial, which is powered to detect differences in prolongation of gestation, birth weight and length of neonatal admission.

OBJECTIVES

To determine whether metformin XR, compared with placebo, can prolong pregnancy and improve neonatal outcomes in women with preterm pre-eclampsia diagnosed between 26+0 and 31+6 weeks' gestation.

METHODS

The full protocol is available in the online supplemental information.

Study design

Single-centre, phase III, double-blind, placebo-controlled randomised trial.

Duration of the trial

We anticipate that it will take 6 years to complete the trial (2022–2028), based on recruitment rates of our previous trials.[7 10]

Confidentiality

Patient confidentiality will be protected according to the regulations set forth by Stellenbosch University's Human Research Ethics Committee or Institutional Review Board (IRB). Participants are free to withdraw from the study at any time and this will not affect clinical care. In the event of withdrawal, we will ask permission to use participant's clinical information and laboratory samples collected thus far in subsequent analyses.

Data management

Data will be collected prospectively using a research electronic data capture (REDCap) database hosted at Stellenbosch University.[11] Data entry and checking will be continuous, and queries will be addressed contemporaneously to ensure clarification without delay. All data will be double checked for accuracy and cleaned. Any queries will be addressed by reviewing source documents. The database will be locked before unblinding.

Study population

Pregnant women diagnosed with pre-eclampsia at a gestational age between 26+0 weeks and 31+6 weeks who are being managed expectantly for preterm pre-eclampsia by the Obstetric Special Care Unit, at Tygerberg hospital (Western Cape Provence of South Africa) will be invited to participate. To be eligible for inclusion, the treating clinicians must agree that the patient is suitable for expectant management of preterm pre-eclampsia and that delivery is not immediately required or anticipated in the next 48 hours.

Inclusion criteria

We will include women with a singleton pregnancy with preterm pre-eclampsia or chronic hypertension with superimposed pre-eclampsia, all defined according to the International Society for the Study of Hypertension In Pregnancy (ISSHP).[12] We will also require the presence of significant proteinuria (more than 300 mg in a 24-hour urine collection). Tygerberg hospital is a referral centre servicing a population of over 2 million people. The Obstetrics Department only manages complicated pregnancies (such as those affected by preterm pre-eclampsia) and delivers more than 8000 women per year.

Gestational age will be determined by either last normal menses dates (if the woman is certain of her last menstrual period) or by an early, or mid trimester pregnancy ultrasound. If the gestational age is uncertain, we will recruit participants with an estimated fetal weight between 500 and 1800 g, determined by ultrasound performed at presentation. A full list of inclusion criteria is provided in box 1 and are the same as the PI 2 trial.[13]

Exclusion criteria

We will exclude the following women from the trial: those who do not qualify for expectant management (delivery is anticipated in the next 48 hours) are already using metformin or have contraindications to using metformin.

Box 1 Inclusion criteria

A diagnosis of one of the following and the attending clinician believes that there would be benefit from expectant management:
⇒ Pre-eclampsia.
⇒ Gestational hypertension with evidence of pre-eclampsia.
⇒ Pre-existing hypertension with evidence of pre-eclampsia.
⇒ Unclassified proteinuric hypertension.
AND all the following are present:
⇒ Gestational age between 26+0 weeks and 31+6 weeks.
⇒ Singleton pregnancy.
⇒ The managing clinicians have made the assessment to proceed with expectant management and that delivery is not expected within 48 hours.
⇒ Managing clinician and neonatologist believe that the fetus could potentially be delivered in a viable condition.
ALSO:
⇒ The mother must be able to understand the information provided, with the use of an interpreter if needed, and must be able to give informed consent.
⇒ Patient will be admitted to hospital for expectant management and standard care.
⇒ Mother must be older than 18 years of age.

Box 2 Exclusion criteria

Any of the following at the initial assessment:
Patient is unable or unwilling to give consent.
Established fetal compromise that necessitates delivery.
Suspicion of a major known fetal anomaly or malformation.
The presence of pre-eclampsia with:
⇒ Eclampsia.
⇒ Severe hypertension (systolic blood pressure greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 110 mm Hg that cannot be controlled with antihypertensive medication within 48 hours of admission).
⇒ Cerebrovascular event.
⇒ Posterior reversible encephalopathy syndrome (PRES).
⇒ Severe renal impairment (creatinine level ≥125 µmol/L or a need for dialysis).
⇒ Signs of left ventricular failure which include pulmonary oedema requiring treatment or oxygen saturations of less than 90% caused by left-sided heart failure.
⇒ Disseminated intravascular coagulation.
⇒ Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.
⇒ Liver transaminases>500 IU/L.
⇒ Fetal distress on cardiotocography.
⇒ Liver haematoma or rupture.
⇒ Fetal distress on cardiotocography.
⇒ Severe ascites on ultrasound as defined by the sonographer.
⇒ Renal disease or dysfunction, suggested by a creatinine level greater than or equal to 125umol/L umol/L.
⇒ Known hypersensitivity to metformin.
⇒ Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
Contraindications for expectant management of pre-eclampsia.
Current use of metformin or a clinical indication for the use of metformin.
Contraindications to the use of metformin.
Current use of a drug that may be affected by metformin: glyburide, furosemide, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin.

We will also exclude women with diabetes. The exclusion criteria are similar to the PI 2 trial (box 2).[13]

Participant enrolment

Potential participants will be identified after they are admitted to Tygerberg Hospital with a diagnosis of preterm pre-eclampsia and deemed suitable for expectant management by the Obstetric Special Care Unit (ie, their disease is not so severe as to require immediate birth).[13] A trial information leaflet and a consent form will be given to potential participants (see online supplemental material). Written informed consent will be obtained before recruitment.

Randomisation and allocation concealment

Women will be randomised to metformin XR or an identical placebo in a 1:1 ratio. We will use an online, web-based sequence generator system, managed by TASK (a South African headquartered, multinational clinical research institute: https://www.task.org.za/). Researchers and participants will be blinded until the database has been locked.

Gestation at enrolment may be a potential predictor for the outcome. To ensure that treatment group allocation is balanced, we will stratify by gestational age. Stratum 1 will include gestational ages between 26+0 up to and including 28+6 weeks gestation. Stratum 2 will include gestational ages from 29+0 up to and including 31+6 weeks gestation.

Once women are randomised, the allocated treatment pack will be dispensed to the participant. All treatment packs will be identical and will contain either active tablets or placebo. The researchers will have no access to the randomisation list. This process will ensure that there is allocation concealment throughout the conduct of the trial. Only the trial pharmacist who packages the trial medication will have access to the randomisation listing.

Active and placebo tablets will be produced in bulk by Merck Healthcare, KGaA, Darmstadt, Germany (https://www.merckgroup.com/en) and supplied to the trial pharmacy (https://www.task.org.za/services/clinical-pharmacy/). The trial pharmacy will be responsible for packaging and labelling the trial medication according to the requirements of the South African Health Products Regulatory Authority (SAHPRA) (https://www.sahpra.org.za/). Treatment packs will be delivered to the trial site where they will be kept in a locked, temperature-monitored storage area until they are dispensed after randomisation.

Once a participant has been included and randomised, they will receive a treatment pack and diary. Each pack will contain treatment for 3 weeks. A second treatment pack will be available for each participant if needed. This will be used if they remain pregnant for more than 3 weeks, or if the original treatment pack is lost or damaged. The packs will either contain 500 mg metformin XR or identical placebo tablets. They will be identical in shape, colour,

weight and feel. The treatment pack will be labelled with the participants name and trial number. Participants will start by taking one tablet three times a day. If they develop side effects, the dose will be decreased until the drug is tolerated. If the participant is able to increase the dose, it will be increased to a maximum of two tablets three times a day until birth. Each participant will be given a treatment diary to monitor compliance and side effects. Research nurses will monitor the treatment diary daily.

Metformin XR may interact with certain medications like dolutegravir and rifampicin. Dolutegravir is an integrase inhibitor used in a fixed highly active antiretroviral therapy combination called TLD (Tenofovir Disoproxil Fumurate (TDF), Lamivudine (3TC) and Dolutegravir (DTG)). TLD is used as first-line treatment to treat HIV/AIDS in South Africa. In pharmacokinetic studies, dolutegravir increases metformin plasma exposure, possibly by organic cation transporter 2 inhibitions.[14] For this reason, if a participant is taking TLD, she will be limited to a maximum dose of 1500 mg Metformin XR daily.

Rifampicin is used to treat tuberculosis which is endemic to South Africa. Pharmacokinetic studies have shown that metformin exposure is increased when coadministered with rifampicin.[15] It is hypothesised that the increased exposure is due to increased absorption as renal clearance and tubular secretion were unaffected by rifampicin. Because of the increased exposure, we will also limit women who are taking rifampicin to a maximum dose of 1500 mg Metformin XR daily.

Once the infant is born, the treatment pack will be collected, and a pill count will be performed.

Cointerventions

Participants will remain under the care of the Obstetric Special Care management team. The study will not interfere with routine care provided for women with preterm pre-eclampsia, including the decision to deliver the pregnancy. Management for preterm pre-eclampsia involves admission to hospital with close maternal and fetal surveillance. The Obstetric Special Care Unit follows a strict protocol for expectant management for preterm pre-eclampsia. Maternal surveillance includes 4 hourly blood pressure measurement, two times daily clinical assessment, daily urinalysis and two times weekly assessments with blood tests that monitor signs of disease progression (full blood count, renal function tests and hepatocellular enzymes if haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is suspected). Fetal surveillance includes 6 hourly cardiotocography. Ultrasound assessments are done every 2 weeks (or more frequently if clinically indicated) to assess fetal growth.[16]

Indications for delivery will be a clinical decision (made independently from the research team) and may include inability to achieve blood pressure control, the development of major maternal or fetal complications or intrauterine fetal death. At Tygerberg hospital, it is part of the protocol to end expectant management at 34 weeks gestation.

All participants receive two doses of betamethasone at the time of admission, 24 hours apart, to reduce the risks of neonatal respiratory distress syndrome, intracranial haemorrhage and necrotising enterocolitis. A single dose may be repeated 1 week later as per hospital protocol.[16] Most participants will be on antihypertensive treatment, and the dose and number of antihypertensives will be recorded.

Sample collection

Blood samples are collected routinely twice a week for measurements of the haemoglobin, the platelet count, urea and creatinine levels. These are used by clinicians to determine disease progression and severity and it may trigger a decision to deliver the pregnancy. Plasma samples will be collected at each routine blood draw and stored in an ultra-low temperature freezer for analysis after the trial is completed. They will be analysed for biomarkers known to be associated with pre-eclampsia.

Outcomes

The primary outcome is prolongation of pregnancy, measured from the time of enrolment to the time of delivery, in hours and days. The primary endpoint will be considered as right censored if delivery is induced at 34 weeks of gestation with no other fetal or maternal indications of delivery.

There are two secondary outcomes. The first secondary outcome will be to determine if metformin XR can reduce the time from birth to neonatal discharge from hospital. For neonates that are not admitted for neonatal care, the length of stay in neonatal care will be zero. Neonatal death or stillbirth will be considered a competing event. With this method, stillborn babies and babies that die during neonatal care will remain in the risk set also after death and hence contribute to a longer length of neonatal stay. Length of stay in neonatal care will be considered a confirmatory finding if both prolongation of pregnancy and time to neonatal discharge to home are statistically significant. The other secondary outcome will be birth weight. We aim to determine whether metformin can increase birth weight of babies born to women with preterm pre-eclampsia. This will also be considered a confirmatory finding if both the primary and both secondary outcomes are statistically significant.

All other outcomes, including a composite maternal and a composite perinatal outcome will be classified as exploratory outcomes (table 1). We will monitor for known side effects of metformin including nausea, vomiting and diarrhoea. The pre-eclampsia research endpoints were chosen using a consensus core outcome set.[17]

Statistical methodology

Numerical variables will be summarised with mean and SD, median and IQR and range (minimum and maximum value). Categorical variables will be summarised as number and percent. All randomised subjects will be included in

Table 1 Outcomes

Primary outcome	**Prolongation of gestation measured from the time of enrolment to the time of delivery, in hours and days**	
Secondary outcomes	1. Length of neonatal hospital admission, measured from date of birth until final discharge home 2. Neonatal birth weight	
Exploratory outcomes	Composite maternal adverse outcome	Including any of the following: ▶ Maternal death ▶ Eclampsia ▶ Pulmonary oedema ▶ Renal dialysis ▶ Cerebral vascular event ▶ Liver haematoma or rupture ▶ Placental abruption ▶ Admission to a high care or intensive care unit ▶ Posterior reversible encephalopathy syndrome ▶ Serum creatinine≥125 µmol/L ▶ Disseminated intravascular coagulation ▶ Platelet count less≤50×10^9 ▶ HELLP syndrome
	Composite perinatal adverse outcome	Including any of the following: ▶ Intrauterine fetal demise ▶ Neonatal death (within 6 weeks of the due date) ▶ Invasive ventilation (intubation and mechanical ventilation) ▶ Grade III/IV hyaline membrane disease ▶ Grade III/IV intraventricular haemorrhage diagnosed on ultrasound ▶ Neonates with necrotising enterocolitis requiring surgery ▶ Retinopathy of prematurity ▶ Neonatal sepsis defined as a confirmed laboratory bloodstream infection treated with a course of antibiotics ▶ Neonatal lactic acidosis
	Individual maternal outcomes	▶ Maternal death ▶ Eclampsia ▶ Pulmonary oedema ▶ Renal dialysis ▶ Cerebral vascular event ▶ Liver haematoma or rupture ▶ Placental abruption ▶ Admission to a high care or intensive care unit ▶ Posterior reversible encephalopathy syndrome ▶ Serum creatinine≥125 µmol/L ▶ Hypertension requiring intravenous treatment to control the blood pressure ▶ Disseminated intravascular coagulation ▶ Platelet count≤50×10^9 ▶ HELLP syndrome ▶ Liver transaminases>500 IU/L ▶ Mode of birth ▶ Use of antihypertensive agents (number of agents and daily dose at delivery) ▶ Major postpartum haemorrhage ▶ Thromboembolic disease ▶ Moderate or severe ascites noted on ultrasound, or at delivery ▶ Lactic acidosis
	Perinatal outcomes	▶ Significant changes in heart rate patterns on the non-stress test or cardiotocograph, as defined by the attending clinician, that necessitated delivery ▶ Intrauterine fetal demise ▶ Growth restriction at birth defined as a birth weight less than the third centile on the WHO fetal growth chart, the Gestational Related Optimal Weight software (GROW) fetal growth chart and/ or the Intergrowth birth weight charts. ▶ APGAR score of less than 7 at 5 min ▶ Invasive ventilation (intubation and mechanical ventilation) ▶ Non-invasive ventilation (continuous positive airway pressure (CPAP) support or high-flow nasal oxygen) ▶ Grade III/IV hyaline membrane disease ▶ Surfactant use ▶ Grade three or four intraventricular haemorrhage diagnosed on ultrasound ▶ Neonates with necrotising enterocolitis requiring surgery ▶ Length of hospital stay at Tygerberg hospital (days) ▶ Retinopathy of prematurity ▶ Neonatal sepsis defined as a confirmed laboratory bloodstream infection treated with a course of antibiotics ▶ Neonatal lactic acidosis ▶ Neonatal death (within 6 weeks of the due date)

Continued

Table 1 Continued

Primary outcome	Prolongation of gestation measured from the time of enrolment to the time of delivery, in hours and days	
	Tolerability of medication	► Nausea ► Vomiting ► Diarrhoea ► Headaches ► Compliance (took full treatment dose, decreased treatment dose but did not stop, stopped treatment, never started treatment)

HELLP, Haemolysis, elevated liver enzymes and low platelets.

the efficacy analyses according to the intention-to-treat principle.

Primary and secondary effectiveness analyses

An appropriate analysis of the difference between treatments with regard to non-normally distributed primary outcome, prolongation of gestation, and secondary outcome, neonatal birth weight, will be performed using linear regression on log-transformed data. Due to the presence of zeroes and competing events, length of neonatal stay will be analysed using competing risk analysis with neonatal death or stillbirth as competing events. Censoring will be accounted for, as appropriate. Covariate adjustment for gestational age strata, fetal growth restriction and 24-hour proteinuria collection will be performed to account for the study design and potential predictors for the outcomes. The treatment effect will be given as fold-change between metformin and placebo arms.

Exploratory effectiveness analyses

Exploratory outcomes will be analysed using linear regression, possibly after application of appropriate transformations (eg, log-transformation for positive, skewed variables). Questionnaire scales and ordinal variables will be treated as continuous variables in this regard. For binary and other non-normally distributed variables, robust SEs (HC3 method) will be employed to account for deviations against distributional assumptions. For binary variables, relative risks estimated using Poisson regression with robust SEs will also be presented.

Sensitivity analyses

Sensitivity analyses of the primary and secondary endpoints will be performed by restricting the efficacy analyses to the following groups of patients: subjects who took a first dose of the trial medication, subjects who always continued the treatment with full dose, and subjects who always continued with the medication at any dose. Additional sensitivity analyses will be performed by removing babies born with congenital abnormalities and lethal genetic conditions, limiting the maximum prolongation to 34 weeks and excluding women who were discharged home.

Multiple testing framework

The type I error rate of the primary and secondary outcomes will be maintained using a hierarchical testing procedure. In case of a successful test for the primary outcome, the entire probability mass α=0.05 will be transferred to the secondary outcomes, one by one, in the order listed above. Statistical significance will be declared for all outcomes with a significant result until the first encounter of a non-significant test. All these significant tests will be confirmatory findings. Estimates and CIs of remaining outcomes will be presented descriptively but not considered as confirmatory findings. Exploratory outcomes will be presented with point estimates and 95% confidence limits only.

Study populations, software and statistical analysis plan

All randomised subjects will be included in the intention-to-treat population and all randomised subjects with no major protocol violations will be included in the per-protocol-population. Final decisions regarding the per-protocol-population will be taken before the database is locked and unblinded. All enrolled participants who receive at least one dose of the trial medication will be included in the safety population. No interim analysis will be performed. Statistical analyses will be performed by using SAS/STAT software, V.9.4, of the SAS System for Windows (SAS Institute, Cary, NC). Further details can be found in the statistical analysis plan in the (Online supplemental file 1).

Sample size

The target sample size was set to 500 women to fulfil the following:

- 90% power to detect a 50% prolongation of gestation (mean log difference=0.405) with metformin XR compared with placebo (primary outcome). This corresponds to a 5 day prolongation from 10 to 15 days and hence comparable to the results of the PI 2 trial.[10] Assumptions were a coefficient of variation=2.04 (log SD=1.28 in both groups), log-normal distribution, two-sample t-test on log-transformed data, significance level alpha=0.05, two-sided test. This requires a total sample size of n=422 women.
- 90% power to detect median difference of 9 days in length of neonatal stay with metformin XR compared with placebo (main secondary outcome). This is 3 days less than that found in post-hoc PI2 analysis.[10] Assumptions included a median length of neonatal stay of 30 days in the placebo group, subdistribution HR=0.70 with metformin XR compared with placebo and 20% censoring (withdrawal) or competing events

Table 2 Serious and adverse outcomes

Serious adverse outcomes	► Maternal death. ► Fetal loss or neonatal death. ► Event that results in a longer postnatal hospital stay. ► Event that results in a persistent or significant disability in the mother or baby. ► Congenital or birth defect in the baby that is detected in the postnatal period and was not detected on ultrasound.
Adverse events	► Any unintentional, unfavourable clinical signs or symptoms. This includes complications of pre-eclampsia. ► Any new illness or disease or complications of existing disease or illness.
The following are not considered to be adverse events	► A pre-existing condition (unless it worsens significantly in pregnancy over and above what may be expected with the concurrent diagnosis of pre-eclampsia). ► Diagnostic or therapeutic procedures such as surgery.

(stillbirths or neonatal deaths). This requires a total sample size of n=422 women.

- Sample size uplift by 18% to account for participants stopping trial medication, resulting in a total sample size of n=500 women. With this sample size, we also have 80% to detect a 10% increase in neonatal birth weight (minor secondary outcome), assuming a coefficient of variation=0.37, which is similar to that found in post-hoc PI 2 analysis.[10]

Serious adverse events

Reporting and handling of serious adverse events will be in accordance with good clinical practice guidelines. Serious adverse events will be reported to the principal investigator by the research midwife. Within 24 hours of reporting, the Data Safety and Monitoring Committee, the Ethics Committee and the South African Health Products Regulatory Authority will be notified. Table 2 lists potential adverse and serious adverse events.

Protocol violations and deviations

All protocol violations and deviations will also be reported to the clinical trial monitor and Data Safety and Monitoring Committee, the Ethics Committee and the South African Health Products Regulatory Authority. All violations and deviations will be reported in the final publication.

Unblinding

If unblinding is required, the principal investigator will be contacted (CAC). She will contact the randomisation centre. Ideally, the principal investigator will remain blinded, and a member of the randomisation team will contact the clinical team directly. If there is a clinical need to unblind the principal investigator, this will be approved by the Data Monitoring Safety Committee.

Early termination of the trial

Any decision for early termination of the trial can be made by the Data Safety and Monitoring Committee and trial sponsor.

Patient and public involvement

We have run a study assessing women's perspectives on types of therapeutics and what they view as important outcomes. In small group interactions, women have expressed that the most important outcome is the health of their baby (unpublished data). We have therefore added neonatal outcomes as secondary outcomes. Our research group is facilitating the development of a South African patient organisation for pre-eclampsia. The results of the PI 3 trial will be made publicly available on our website (www.preeclampsiaresearch.org).

ETHICS AND DISSEMINATION

PI 3 has ethical approval (Health Research Ethics Committee 2, Stellenbosch University, Protocol number M21/03/007, Project ID 21639, Federal Wide Assurance Number 00001372, Institutional Review Board Number IRB0005239) is registered with the Pan African Clinical Trial Registry (PACTR202104532026017) and the South African Health Products Regulatory Authority (20211211). Data will be presented at international conferences and published in peer-reviewed journals.

DISCUSSION

In this trial, we should be able to confirm or refute whether metformin XR can prolong gestation in women diagnosed with preterm pre-eclampsia. We propose recruiting 500 women with preterm pre-eclampsia. This is ambitious but feasible. Our trial team is the only group that has run consecutive randomised controlled treatment trials for preterm pre-eclampsia.[7 10] While running these trials, we developed the infrastructure for an enduring pre-eclampsia clinical trials unit. Our trial site at Tygerberg Hospital is a referral hospital for more than half of the women in the Cape Town metropole accessing public healthcare. These women are all managed by the Obstetric Special Care Unit in this referral centre, which adheres to a strict protocol to expectantly manage preterm pre-eclampsia. This ensures that all women who are included receives a similar approach to care.[16] The size of the trial also means we are powered both to assess prolongation of pregnancy and also important neonatal health outcomes: birth weight and length of neonatal hospital admission.

A possible limitation of the trial is that we are conducting it at only one referral hospital. To counter this, we are working with international collaborators.

Members of our team together with Swedish investigators plan to recruit 294 women diagnosed with pre-eclampsia diagnosed between 22+0 and 33+6 weeks in the Pre-eclampsia Intervention 4 (PI 4) trial (NCT06033131). PI 4 is a double-blind randomised placebo controlled clinical trial that will be run across seven sites in Sweden and will randomise women diagnosed with preterm pre-eclampsia to either metformin XR or an identical placebo until delivery. Dutch collaborators are planning a similar multicentre trial which will include sites throughout the Netherlands. They will assess whether metformin, rather than metformin XR, can prolong gestation in women diagnosed with preterm pre-eclampsia.[16] Importantly, we have collaborated to ensure that these trial protocols are harmonised. Hence, we are using similar clinical definitions, similar inclusion criteria and similar outcomes. This will enable us to perform an individual patient meta-analysis once all trials are completed.

In summary, metformin is commonly used in pregnancy, it is temperature stable, inexpensive and readily available. If shown to prolong gestation in preterm pre-eclampsia, it could be widely and easily adopted around the world, particularly in settings with limited neonatal care options.

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Contributors CAC, SPW and ST developed and designed the trial CAC, SPW, LB and ST obtained funding for the trial. CAC, SPW and ST wrote the first draft of this manuscript. BWM, AB, LB, AG, FB, TJK-L and DH assisted with the study design. HI designed the statistical aspects of this protocol. All were involved in revision of the manuscript. All authors approved the final version to be submitted.

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REFERENCES

1 Chappell LC, Cluver CA, Kingdom J, *et al*. Pre-Eclampsia. *Lancet* 2021;398:341–54.
2 Abalos E, Cuesta C, Grosso AL, *et al*. Global and regional estimates of Preeclampsia and Eclampsia: A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013;170:1–7.
3 Moodley J. Maternal deaths due to hypertensive disorders of pregnancy: data from the 2014-2016 saving mothers' report. *Obstet Gynaecol Forum* 2018;28:28–32. Available: https://journals.co.za/doi/abs/10.10520/EJC-11ea64a35b
4 Suppo de Souza Rugolo L, Bentlin M, Petean Trindade CE. Preeclampsia: early and late neonatal outcomes. *Neoreviews* 2012;13:e532–41.
5 Fanaroff AA, Stoll BJ, Wright LL, *et al*. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007;196:147.
6 Paidas MJ, Tita ATN, Macones GA, *et al*. Prospective randomized double-blind, placebo controlled evaluation of the pharmacokinetics, safety and efficacy of recombinant antithrombin versus placebo in Preterm Preeclampsia (PRESERVE-1). *Am J Obstet Gynecol* 2020;223:739.
7 Cluver CA, Hannan NJ, van Papendorp E, *et al*. Esomeprazole to treat women with Preterm Preeclampsia: a randomised placebo controlled trial. *Am J Obstet Gynecol* 2018;219:388.
8 Vigil-De Gracia P, Ludmir J. Perinatal and hemodynamic evaluation of Sildenafil citrate for Preeclampsia treatment. *Obstet Gynecol* 2016;128:1181–2.
9 Groom KM, Ganzevoort W, Alfirevic Z, *et al*. Clinicians should stop prescribing Sildenafil for fetal growth restriction (FGR): comment from the STRIDER consortium. *Ultrasound Obstet Gynecol* 2018;52:295–6.
10 Cluver CA, Hiscock R, Decloedt EH, *et al*. Use of metformin to prolong gestation in Preterm pre-Eclampsia: randomised, double blind, placebo controlled trial. *BMJ* 2021;374:2103.
11 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (Redcap)-A Metadata-driven methodology and Workflow process for providing Translational research Informatics support. *J Biomed Inform* 2009;42:377–81.
12 Magee LA, Brown MA, Hall DR, *et al*. The 2021 International society for the study of hypertension in pregnancy classification, diagnosis & management recommendations for International practice. *Pregnancy Hypertens* 2022;27:148–69.

13 Cluver C, Walker SP, Mol BW, *et al*. A double blind, randomised, placebo-controlled trial to evaluate the efficacy of metformin to treat Preterm pre-Eclampsia (Pi2 trial): study protocol. *BMJ Open* 2019;9:e025809.
14 Song IH, Zong J, Borland J, *et al*. The effect of Dolutegravir on the pharmacokinetics of metformin in healthy subjects. *J Acquir Immune Defic Syndr* 2016;72:400–7.
15 te Brake LHM, Yunivita V, Livia R, *et al*. Rifampicin alters metformin plasma exposure but not blood glucose levels in diabetic tuberculosis patients. *Clin Pharma and Therapeutics* 2019;105:730–7.
16 Hall DR. Understanding expectant management of pre-Eclampsia. *Obstet Gynaecol Forum* 2016;26:22–7.
17 Duffy J, Cairns A, Richards-Doran D, *et al*. A core outcome set for pre-Eclampsia research: an international consensus development study. *BJOG* 2020;127:1516–26.