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# RidStress 2 randomised controlled trial protocol: an Australian phase III clinical trial of intrapartum sildenafil citrate or placebo to reduce emergency caesarean birth for fetal distress in women with small or suboptimally grown infants at term (≥37 weeks)

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## ABSTRACT

**Introduction** Small for gestational age (SGA) infants are at increased risk of fetal distress in labour requiring emergency operative birth (by caesarean section (CS), vacuum or forceps). We have previously shown that maternal oral sildenafil citrate (SC) in labour halves the need for operative birth for suspected fetal distress in women with appropriately grown term infants.

**Methods and analysis** RidStress 2 is a phase III randomised, double-blinded, placebo-controlled trial of 660 women with an SGA or suboptimally grown fetus (estimated fetal weight or abdominal circumference<10th centile for gestational age) planning a vaginal birth at term. The trial will determine whether oral intrapartum SC (50 mg eight hourly) reduces the relative risk of emergency CS for fetal distress compared with placebo. The primary outcome is CS for fetal distress, and the secondary outcomes are any operative birth for fetal distress, cost-effectiveness of SC treatment and 2-year childhood neurodevelopmental outcomes. To detect a 33% reduction in the primary outcome from 30% to 20% for an alpha of 0.05 and power of 80% with 10% dropout, requires approximately 660 women (330 in each arm). This sample size will also yield >90% power to detect a similar reduction for the secondary outcome of any operative birth (CS or instrumental vaginal birth) for fetal distress.

**Ethics and dissemination** Ethics approval was granted by the Mater Misericordiae Limited Human Research Ethics Committee (EC00332) on 11 September 2020. We plan to disseminate the results of this randomised controlled trial through presentations at scientific meetings and peer-reviewed journals, adhering to all relevant reporting guidelines.

**Trial registration number** RidStress 2 is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000354886, 29/03/2021) and the Therapeutic Goods Association of Australia (date registered: 16 March 2021).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ RidStress 2 will prospectively determine if intrapartum maternal oral sildenafil citrate reduces the risk of emergency operative birth for fetal distress in small for gestational age infants.
⇒ By assessing neurodevelopmental outcomes at 2 years of age in offspring, longer-term benefits or harm can be ascertained.
⇒ For efficient recruitment, RidStress 2 recruitment will be limited to larger tertiary centres in Queensland. This may limit generalisability beyond the tertiary setting.

## BACKGROUND AND RATIONALE

Small for gestational age (SGA) infants (birthweight<10th centile for gestational age) and those with fetal growth restriction (FGR) are at greater risk of developing fetal distress in labour and requiring operative birth,[1–3] compared with their appropriately grown counterparts. Due to underlying placental dysfunction (which limits nutrient and oxygen transfer),[4 5] this cohort poorly tolerates the intermittent hypoxic episodes generated by uterine contractions during labour.[6] They are thus unable to substantially use anaerobic metabolism to generate energy because of reduced cardiac and hepatic glycogen stores.[7–10 10] The hypoxic challenge of labour rapidly diminishes these stores, leading to impaired myocardial function,[11] cerebral hypoperfusion[12] and consequent fetal distress[13] and acidosis,[12] necessitating

emergency caesarean section (CS) or instrumental vaginal birth (IVB).[2 14 15]

Intrapartum fetal distress is the primary indication for ~23% of CS births in Australia.[16] Both emergency CS and IVB are associated with significant maternal and neonatal morbidity[17–19] as well as implications for future pregnancies.[20–22] Effective strategies to reduce emergency CS and IVB rates related to intrapartum fetal distress are thus urgently needed and are important research priorities.[18 23]

Sildenafil citrate (SC) is a phosphodiesterase-5 inhibitor (PDE-5) and potent vasodilator, which prevents intracellular degradation of cyclic guanosine monophosphate and increases bioavailability of nitric oxide.[24 25] PDE-5 is present in smooth muscle of blood vessels, including those of the uterus and placenta.[24 26] SC has been shown to improve fetoplacental blood flow in pregnancies complicated by FGR[27–29] and has a favourable safety profile in pregnancy.[30 31]

Our earlier phase II randomised controlled trial (RCT) (RidStress)[30] demonstrated that compared with placebo, intrapartum oral SC reduced emergency operative birth for fetal distress by 51% (RR 0.49, 95% CI 0.33 to 0.73, p=0.0004) and halved rates of pathological fetal heart rate patterns (15% vs 32%; RR 0.48, 95% CI 0.31 to 0.75, p=0.0009) for women in term labour. A subgroup analysis of women with infants weighing <10th centile for the study cohort demonstrated a non-significant reduction in operative birth (CS and IVB) for fetal distress (11.8% vs 38.5%; RR 0.31, 95% CI 0.07 to 1.33) and double the spontaneous vaginal birth rate (82.4% vs 38.5%; RR 2.14, 95% CI 1.04 to 4.41, p=0.02). We also demonstrated that women in the SC arm had a lower intrapartum decline in placental growth factor (PlGF) levels in labour, and the possible protective effect of SC was greatest in those with pretreatment PlGF levels of 85–400 pg/mL (p=0.004).[32] PlGF is a marker of placental function and has an important role in promoting angiogenesis and endothelial cell proliferation.[33 34]

The aim of this phase III RCT is to investigate if, compared with placebo, SC safely reduces emergency operative birth for fetal distress in women with SGA or suboptimally grown infants planning a vaginal birth at term. RidStress 2 will also contribute to an individual participant data prospective meta-analysis with considerably greater power to detect moderate benefits and harms.

Safely reducing CS births is an international research priority,[20 23] particularly in low-income and middle-income countries (LMICs), which might experience even greater obstetric and perinatal benefits. Although LMICs have very high rates of SGA infants,[35] they often lack the facilities for intrapartum monitoring and emergency operative birth, resulting in avoidable intrapartum stillbirths or neonatal deaths after birth asphyxia. The vast majority of all stillbirths occur in LMIC, with half occurring in labour.[17 35] SC is now off-patent, inexpensive, stable, easily administered orally with a favourable safety profile in about 1000 women so far.[31] If routine intrapartum SC safely reduces adverse birth outcomes and/or emergency operative birth and their long-term sequelae, it could improve maternal and neonatal outcomes of clinical care across a diverse range of healthcare settings and provide an important option for women attempting vaginal birth worldwide.

We hypothesised that women with an SGA infant may derive greater benefit from intrapartum SC therapy, resulting in lower rates of intrapartum fetal compromise and emergency operative birth for fetal distress.

## AIMS AND OBJECTIVES

This study aims to test the hypotheses that up to three oral doses of 50 mg SC (vs placebo) is safe and will reduce the relative risk of emergency operative birth for fetal distress in women with an SGA or suboptimally grown fetus.

Our objective is to undertake a 4-year, phase III RCT (RidStress 2) of 660 women with suspected SGA or FGR planning a vaginal birth at term (*population*), to test if SC (*intervention*) safely reduces the relative risk of emergency CS for fetal distress by 33% (from 30% to 20%) (*primary outcome*) compared with placebo (*comparator*). An assessment of infant neurodevelopmental outcomes at 2 years will be undertaken, and a health economic analysis will be conducted.

### Primary objective

To evaluate whether, compared with placebo, SC achieves a 33% reduction (from 30% to 20%) in the relative risk of emergency CS for fetal distress (primary outcome).

### Secondary objectives

1. To evaluate whether, compared with placebo, SC reduces the relative risk of any operative birth (CS and IVB) for fetal distress by 33% (from 40% to 26%) and has similar perinatal and maternal outcomes.
2. To evaluate whether, compared with placebo, SC reduces rates of neurodevelopmental delay at 2 years of age.
3. To evaluate whether, compared with placebo, SC is cost-effective.
4. To evaluate whether prelabour maternal PlGF or soluble Fms-like tyrosine kinase-1 (sFlt-1), fetal biometry or fetoplacental Doppler assessment can stratify women who would benefit more from intrapartum SC therapy.

## METHODS AND ANALYSIS

### Trial design

RidStress 2 is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind, multicentre, superiority trial of intrapartum SC versus placebo in 660 women with a suspected SGA or suboptimally grown fetus at term ($\geq 37^{+0}$ weeks' gestation).

### Trial setting

RidStress 2 will be conducted at the Mater Mothers' Hospital, Royal Brisbane and Women's Hospital, Sunshine Coast University Hospital and Gold Coast University Hospital in Queensland, Australia. Recruitment to RidStress 2 began on 27 July 2021, and recruitment is planned to continue until 11 September 2025.

### Patient and public involvement statement

We involved clinician and consumer groups when designing this trial.

### Study population

Inclusion criteria:

1. Singleton pregnancy.
2. Planning a vaginal birth at term (>37 weeks' gestation).
3. Aged>18 years and able to give informed consent.
4. Pregnancy complicated by suspected SGA infant or late FGR.

SGA is defined as estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile for gestation based on ultrasound assessment.

FGR[36] is defined as EFW or AC <3rd centile or two out of three of the following:

1. EFW or AC <10$^{th}$ centile.
2. AC or EFW crossing centiles by>2 quartiles on growth charts (for the purposes of this trial, we defined this change over a minimum interval of 4 weeks).
3. Cerebroplacental ratio<5th centile or Umbilical Artery Pulsatility Index>95th centile for gestation.

Exclusion criteria:

1. Two or more previous CS births.
2. Previous classical CS.
3. Major fetal anomaly in this pregnancy.
4. Non-cephalic presentation.
5. Severe hepatic or renal impairment.
6. Participants who are taking any type of nitrate drug therapy or who use short-acting nitrate-containing medications during labour (such as sodium nitroprusside, bosentan, fosamprenavir and ritonavir combination, hepatic enzyme inhibitors CYP3A4 (including itraconazole, ketoconazole, ritonavir, cimetidine, erythromycin, saquinavir, darunavir), or hepatic enzyme substrates (CYP3A4), medications used to treat pulmonary arterial hypertension, and other phosphodiesterase type 5 inhibitors like riociguat), due to the risk of potentially life-threatening hypotension.

### Screening, registration and randomisation

This is summarised in figure 1. Women will be screened for eligibility and approached by obstetric caregivers or research midwives to participate in the trial from 32 weeks' gestation onwards. A confidential record of women who were screened for eligibility, approached and consented will be kept at each study site. For women who decline participation, a reason will be recorded where given. The rights of women to decline participation without providing a reason will be respected.

Signed consent to enter the study will only be obtained by members of the study team after full explanation and adequate time for consideration of information detailed in the patient information and consent form (online supplemental appendix 1). Consent may be obtained in-person, over the phone or by email. All participants will be free to withdraw from the trial at any time without reason or prejudice of their ongoing care. Women will receive no financial incentive to participate in this study. Their participation will be documented in their obstetric record and alerts placed on the relevant electronic patient administration systems. An email will be sent to women following their registration providing contact details for the trial staff and a copy of their signed patient information and consent form. All women will receive routine obstetric care until the onset of spontaneous labour or induction of labour (IOL).

Women will also be invited to consent to participate in childhood neurodevelopmental follow-up. If they consent, contact details will be recorded and follow-up assessment will be performed as described below. If consent is declined or withdrawn before follow-up takes place (2 years corrected age), no further contact will take place.

Prior to IOL or spontaneous labour, 20 mL of blood will be collected for assay of soluble sFlt-1 and PlGF levels. Excess serum and plasma will be aliquoted and stored for future related research at Mater Research Institute, University of Queensland, for which separate ethical approvals will be obtained. This is outlined in the patient information and consent form.

### Interventions

The study intervention is oral SC 50 mg, and the comparator will be an identical matching placebo. The trial medication will be given when participating women are admitted to the labour ward, either in spontaneous labour or for IOL (artificial rupture of membranes ± syntocinon infusion). Women will be given the study treatment by the attending midwife in the labour ward. Women will receive SC 50 mg or identical placebo orally every 8 hours until birth of the baby to a maximum of three doses. Participants who satisfy the below criteria will have their treatment ceased:

1. Acute severe maternal hypotension (<60/40 mm Hg × three episodes) sufficient to cause maternal and/or fetal compromise occurs.
2. The participant requests discontinuation from study.
3. The investigative team believes it is in the best interest of the participant on grounds of safety or side effect or tolerability that discontinuation takes place.

To monitor adherence to the trial intervention, the date and time of study drug administration will be recorded, unused investigational product will be returned to pharmacy, and accountability logs will be kept. An instruction sheet outlining trial processes will be provided to the attending midwife, and 24-hour phone support will be provided by the research team. Both the clinical and

| | Study period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | | Post-allocation | | | | | | | Close-out |
| **TIMEPOINT*** | ***>32 weeks gestation*** | ***>36 weeks gestation*** | ***Labour*** | ***Delivery of infant*** | ***7 day follow up*** | ***28 day follow up*** | ***6 month follow up*** | ***12 month follow up*** | ***18 month follow up*** | ***2 year follow up*** |
| **ENROLMENT:** | | | | | | | | | | |
| **Eligibility screen** | X | | | | | | | | | |
| **Informed consent** | X | | | | | | | | | |
| **Registration on Trial Database** | | X | | | | | | | | |
| **Allocation according to randomization schedule** | | X | | | | | | | | |
| **INTERVENTIONS:** | | | | | | | | | | |
| ***[Sildenafil 50mg capsule, orally, 8 hourly until delivery of infant or 3 doses]*** | | | X | | | | | | | |
| ***[Placebo]*** | | | X | | | | | | | |
| **ASSESSMENTS:** | | | | | | | | | | |
| ***Maternal baseline variables*** | | X | | | | | | | | |
| ***Collection of maternal blood samples*** | | X | | | | | | | | |
| ***Maternal Obstetric Outcome Variables*** | | | | X | X | | | | | |
| ***Neonatal Outcome Variables*** | | | | X | X | X | | | | |
| ***Collection of cord blood samples*** | | | | X | | | | | | |
| ***Placental histopathology*** | | | | X | | | | | | |
| ***Assessment of 28 day neonatal mortality*** | | | | | | X | | | | |
| ***Confirmation of Contact Details*** | | | | | | | X | X | X | |
| ***2 year neurodevelopmental assessment*** | | | | | | | | | | X |

**Figure 1** Schedule of enrolment, interventions and assessments for RidStress 2.

research teams will collaborate to monitor adherence to trial processes.

### Management of labour and puerperium

Management of labour will be in accordance with local protocols and guidelines. All women will have continuous electronic intrapartum fetal heart rate monitoring, with abnormalities classified according to Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines.[15] In the event of operative birth, the attending obstetrician will be asked to confirm the indication for operative birth and the role that fetal distress played in their decision-making.

Umbilical artery cord pH will be measured in all women after birth. Delayed cord clamping will always be facilitated. Where possible, 20 mL of cord blood will be collected for SC assays and storage for future research related to this study. The placenta will be sent for routine histopathological examination as per institutional guidelines. All biospecimens will be registered and stored at the Mater Research Institute in Brisbane, Australia.

All infants will also receive routine oxygen saturation screening 24–48 hours after birth (current standard practice in Australia). This test complements the newborn physical examination and is used to detect hypoxaemia in infants. Infants with oxygen saturation>95% are very unlikely to have major congenital heart or significant pulmonary disease (including persistent pulmonary hypertension of the newborn). Infants with oxygen saturations<95% will receive further assessment by the paediatric team and additional investigations will be performed as required.

### Trial outcomes

#### Primary outcome

Emergency CS for fetal distress (defined contemporaneously as an abnormality in fetal heart rate pattern, fetal scalp lactate or pH).

#### Secondary outcomes

Any operative birth (CS or IVB) for fetal distress, health economic costs, 2-year childhood neurodevelopmental outcomes and correlation between maternal placental biomarkers, prelabour ultrasound variables.

#### Obstetric and maternal outcomes

Other indications for operative birth, spontaneous vaginal birth, postpartum haemorrhage (blood loss>1.5 L), blood transfusion, peripartum hysterectomy, uterine rupture, third and fourth degree tears, length of stay in hospital, intensive care unit admission.

#### Perinatal outcomes

Intrapartum stillbirth or neonatal death<28 days, Apgar≤4 at 5 min, severe acidosis (cord artery pH<7.0 or base excess < −12 mmol/L), neonatal encephalopathy, seizures, respiratory support>4 hour, neonatal intensive care unit (NICU) admission>48 hours, persistent pulmonary hypertension of the newborn or meconium aspiration syndrome.

### Sample size

The incidence of the primary outcome is estimated at 30% based on data in a large recent RCT in term pregnancies[37] and local data from Mater Mother's Hospital. To detect a 33% reduction in the primary outcome from 30% to 20% for an alpha of 0.05 and 80% power with 10% dropout in each arm needs approximately 660 women (330 in each arm) (https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). This sample size will also yield>90% power to detect a similar reduction for the secondary outcome of any operative birth (CS or IVB) for fetal distress.

### Allocation and concealment of intervention

A computer-generated randomisation schedule with permuted block randomisation with randomly selected block sizes will be used. The block sizes and the randomisation schedule will be concealed to clinical staff, research staff and participants. Stratification will be performed by study site to ensure balance in treatment assignment across sites. The randomisation schedule was provided to the pharmaceutical manufacturer and identical trial medication kits containing either SC 50 mg or placebo were produced and numbered sequentially. Kits were then allocated sequentially to registered participants by the research staff.

### Blinding

Participants, research staff and healthcare providers will remain blinded to intervention allocation. Assessments of all outcomes and data analysis will be performed in a blinded manner. If emergency unblinding is deemed in the best interest of the participant or their infant, authority to do so will be obtained from the principal investigator, trial statistician and pharmacist. Unblinding will only occur if knowledge of the allocated treatment group is essential for ongoing management of the patient or their infant. The need for unblinding should be very uncommon, as the study intervention is rarely associated with severe side effects.[31]

### Data collection and management

All data collection will be recorded into electronic case report forms and stored in a secure online database (RedCap). Valid values, expected ranges and descriptions selected from a list will be specified in the electronic database to ensure data integrity. Baseline demographic and obstetric data will be entered into the RedCap database at the time of registration. Data for primary and secondary outcomes will be ascertained by reviewing the participants' medical records and cross-checked against details provided by the treating obstetrician. Adverse maternal and neonatal outcomes will be assessed by review of the participants' medical records at 7 days and at the 28-day follow-up. When the infant approaches 2 years, participants will be sent an electronic version of the Ages and Stages Questionnaire.[38] To promote retention

of trial participants until the time of neurodevelopmental follow-up, 6 monthly phone calls to participants will be made.

## Data analysis plan

Primary and secondary outcome analyses will adhere to an intention-to-treat basis, so all women randomised are analysed in their allocated group, using generalised linear models (binary or normal). Intervention effect will be presented as relative risk or mean difference as appropriate, with 95% CIs. Two-tailed p value<0.05 will be considered statistically significant. Primary analyses will be unadjusted. Number needed to screen and treat to prevent one adverse primary outcome will be calculated. Where there are differences in the baseline characteristics between the two treatment groups that might be associated with outcomes, secondary adjusted analysis of the primary outcome will be carried out using multiple (log-binomial) regression. No adjustment will be made for multiple comparisons. Reporting of findings will be done in accordance with Consolidated Standards of Reporting Trials[39] and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis[36] guidelines.

## Oversight and monitoring

### Trial Management Committee (TMC)

The TMC consists of all chief investigators for each participating site, and the coordinating centre is located at the Mater Mothers' Hospital and Mater Research—University of Queensland. Participating sites include the Mater Mother's Hospital, Royal Brisbane and Women's Hospital, Sunshine Coast University Hospital and Gold Coast University Hospital. The TMC will oversee and plan the conduct of the study at each site including aspects of monitoring, recruitment, progress, data management, modifications to the study protocol, adverse event reporting, Human Research Ethics Committee (HREC) and local governance approvals, consideration of relevant information from new research, and implementation of recommendations from external bodies and reviewing committees, including the Independent Data and Safety Monitoring Committee (IDSMC). Such recommendations may include modification of the study protocol, or stopping of the trial based on interim analysis, or other relevant information or advice. The TMC will be responsible for communicating any changes to the protocol or study conduct to participating sites, investigators, registries, journals or regulators.

### Independent Data and Safety Monitoring Committee (IDSMC)

A joint IDSMC who will oversee both RidStress 2 and iSEARCH (published in this *BMJ Open* issue and linked to this manuscript) has been established. The IDSMC will meet at least annually and comprises three perinatal care clinicians/researchers (one serving as Chair) and a biostatistician. All IDSMC members will be independent of sponsor, trial conduct and membership will be restricted to those that are free of significant conflicts of interest. The role of the IDSMC is to safeguard the interests of study participants by reviewing interim data on the primary outcome, adverse events and other outcome data after 50% recruitment or as appropriate (as per Peto *et al*, Haybittle, and Geller and Pocock).[37 40 41] There will be no adjustment to alpha for interim analyses. The IDSMC will provide the TMC a report outlining their recommendations.

### Interim analyses of the primary composite outcome

The IDSMC will advise the TMC if they consider there is proof beyond reasonable doubt of net benefit or harm for the primary outcome, employing a commonly used formal threshold of p<0.001 for nominal significance, as recommended by Geller and Pocock.[41]

### Interim analyses of mortality

The IDSMC will advise the TMC if they support the view that there is a difference in mortality due to intrapartum stillbirth and/or 28-day neonatal mortality identified as a deviation from the null indicated by a Haybittle-Peto boundary of 3 standard errors from the null, which is equivalent to p<0.0027,[37 40] which would be needed to justify recommending early stopping.

### Safety and adverse event reporting

We will adhere to National Health and Medical Research Council guidelines for safety monitoring and serious adverse event (SAE) reporting in clinical trials involving therapeutic goods.[42–44] All SAEs occurring from the time of administration of the trial medication until hospital discharge will be reported to the sponsor with oversight provided by the IDSMC. Adverse events will be assessed for causality, as 'expected' or 'unexpected' with consideration given to the temporal relationship between administration of the trial medication and SAE. Possible adverse drug reactions (summarised in online supplemental appendix 2)[45] will be recorded.

In addition, the following maternal and neonatal events will also be reported as SAEs for this study:

Maternal SAEs:

1. Maternal intensive care unit admission.
2. Maternal hypotension (<60/40 mm Hg × three episodes) requiring medical intervention.
3. Major postpartum haemorrhage>1500 mL.
4. Persistent visual changes requiring ophthalmic review.
5. Maternal death prior to discharge from hospital.

Neonatal SAEs:

1. Admission to NICU for >48 hours.
2. Cord arterial pH<7.0.
3. Hypoxic ischaemic encephalopathy.
4. Neonatal seizure.
5. Intrapartum stillbirth.
6. Neonatal death prior to discharge from hospital.

## Compliance and auditing

The trial will be conducted in compliance with full good clinical practice recommendations[46] and will be subject

to annual inspection and audit by Mater Misericordiae Limited under their remit as sponsor. The study will comply with all applicable laws and regulations and the principles laid down by the World Medical Association in the Declaration of Helsinki 2013. It is registered with the Australian and New Zealand Clinical Trial Registry. Trial results will be disseminated as soon as practical via presentations at clinical, academic and scientific meetings, peer-reviewed journals and general media. We will adhere to all relevant reporting guidelines.

## Ethics and dissemination

Ethics approval was granted by the Mater Misericordiae Limited Human Research Ethics Committee (EC00332) on 11 September 2020. We plan to disseminate the results of this RCT through presentations at scientific meetings and peer-reviewed journals, adhering to all relevant reporting guidelines.

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**Contributors** SK conceived the study and is the guarantor. All authors (TT, SK, HL, CL, RN, KK, NB, FdSC, KC and WTM) made substantial contributions to the study design. KC provided advice and guidance for the proposed statistical analysis. TT and SK contributed equally to the manuscript. All authors reviewed and approved the final version before submission and agreed to be accountable for all aspects of the work.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

**Patient consent for publication** Not applicable.

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**Appendix 1: RidStress2 Patient Information and Consent Form Version 3.0.**

## 1. Introduction

**We invite you to take part in the RidStress 2 Study**

- This randomised study tests if Sildenafil reduces the need for emergency caesarean section for fetal distress in labour in women with small or poorly grown babies. Small babies are at increased risk of fetal distress in labour.
- Please read this information sheet carefully.
- Please ask questions about anything you do not understand or that you want to know more about.
- Before deciding to take part, you may want to talk about it with a relative, friend or your local doctor.

**What is the purpose of this study?**

- The purpose of this study is to investigate if a drug (called Sildenafil) that relaxes blood vessels and improves blood flow and oxygen supply to the placenta and baby can lower the risk of fetal distress for small babies and reduce the need for an emergency caesarean section.
- The need to safely reduce avoidable caesarean births is now recognised as a major international research priority.

**What is fetal distress in labour?**

- Babies can become distressed when contractions during labour constrict (squeeze) placental blood vessels thus reducing oxygen supply.
- Without urgent delivery (by caesarean, vacuum or forceps birth) fetal distress may lead to stillbirth, loss of the baby after birth, or brain injury like cerebral palsy.

**What is Sildenafil (also known as Viagra®)?**

- Sildenafil is a medicine which dilates (opens up) blood vessels.
- It has been safely used for over twenty years to treat men with erection problems.
- It is also used to treat lung disease caused by narrow pulmonary arteries in pregnant women, other adults and babies.
- In pregnant women, Sildenafil works mainly on blood vessels in the pelvis to improve blood flow to the womb, placenta and your baby. If there is more blood flow and oxygen delivered to your baby, it may decrease the risk of fetal distress, the need for an emergency delivery and may improve the outcome for your baby.
- Side effects are uncommon and the majority of pregnant women who have taken Sildenafil report no symptoms.

**What did our first randomised study of Sildenafil in labour show?**

- We reported a study of 300 women with **normally grown babies** in the American Journal of Obstetrics and Gynaecology in January 2020 (https://pubmed.ncbi.nlm.nih.gov/31978434/).
- Half of the women took Sildenafil tablets and the other half took placebo tablets (containing no active medicine).
- We found that Sildenafil was safe for woman and their babies, AND
- Urgent delivery by vacuum, forceps or caesarean section was 50% less likely for women on Sildenafil.
- The results also strongly suggested that women with smaller babies may also benefit from this treatment. We now want to confirm if this is indeed the case and if women with small babies like you could also benefit from Sildenafil during labour.

**2. What does participation in this research involve?**

- Before labour, we will take a blood test from you (approx. 25ml) to measure a pregnancy related substance (hormone hormones called PlGF and sFlt) which reflect how well your placenta is functioning). A portion of this blood may also be used for future related research projects.
- During spontaneous labour or induction of labour half of the women in the study will be given tablets containing Sildenafil by their midwife.
- The other half of women will get tablets containing placebo.
- Nobody knows and no one can choose who will get Sildenafil or who will get placebo.
- Perform two ultrasound scans to look at blood flow in your baby.

**3. If you decide to take part, you will be asked to sign a consent form to confirm that you:**

- Understand what you have read in this document.
- Consent to taking part in the research. Remember, your participation is entirely voluntary (your choice).
- Consent to the tests and treatments as described in this document.
- Consent to the use of your personal and health information as described in this document.

**4. When you come to hospital to have your baby:**

- You will receive either Sildenafil or placebo.
- There is a 1 in 2 chance (or a 50:50 chance) of receiving Sildenafil.
- The Sildenafil tablet and the placebo tablet look identical. You, members of the research team, or the midwives and doctors caring for you in labour will not know which medication you are actually taking.
- Sildenafil is given as tablets of 50mg. Women will get one, every 8 hours – up to 3 doses. Placebo tablets look the same but have no active ingredient. Women will also get one, every 8 hours – up to 3 doses.
- After your baby is born and the umbilical cord cut, we will take a sample of blood and test its pH from the umbilical cord. You can still have delayed cord clamping if you wish.
- We will also take a small sample of your placenta for research related to this study.
- Taking part in this study does not prevent you breastfeeding your baby.

**5. If you take part in this study:**

- We will get all information needed for the study from your medical records. Your personal information will stay confidential and will only be used for the purposes of this study.
- The study takes place at the Mater Mother's Hospital in Brisbane. You will get the same quality of care as those not in the study. If emergency treatment is needed for you or your baby, this will happen without delay.
- We will contact you 1 month after your discharge to check if you and your baby are well.

**6. Follow up of your child:**

- If you are happy for follow up, a member of the research team will contact you every 6 months to check your contact details.
- When your child is about two years old, we will ask you specific questions about their thinking, speaking, movement, play and social development, using the Ages and Stages Questionnaire®.

**7. Do I have to take part in this research study?**

- No. Taking part in this study is voluntary. We encourage you to discuss your decision with your partner or support person and involve them in your decision making.
- If you decide to take part and later change your mind, you are free to withdraw at any stage.

- Your decision will not affect your routine care or relationship with those treating you or your baby.
- Participation in this study will not cost you anything. You will also not be paid to participate.
- No member of the study team gets any personal financial benefit from your involvement in this study.

## 8. What are the possible benefits of taking part?

- We cannot guarantee any benefits from taking part in this research.
- We will not know if Sildenafil has any benefit until this study is complete.
- If Sildenafil does reduce the risk of fetal distress and emergency delivery for small babies, it may help women and families worldwide.

## 9. What are the possible risks and disadvantages of taking part?

- In our previous study we found that up to 3 doses of 50 mg Sildenafil was safe, with no increase in complications for mothers or babies.
- Side effects of sildenafil are uncommon. Some women may experience dizziness or flushing.
- In a completely different study aimed to help women with fetuses with severe growth restriction in very early pregnancy (the STRIDER Trial) women took very large doses (up to 5,250 mg) of Sildenafil for over ten weeks during their pregnancy. This increased the number of babies with pulmonary hypertension (increased lung blood pressure) after birth, but did not increase any other complications. That study is very different from this study which uses a maximum of 150 mg of Sildenafil in women at term.

## 10. What if new information arises during this study?

- If this happens, your study doctor will tell you and discuss whether you should to continue in the study.

## 11. What if I withdraw from this study?

- If you withdraw, the study team will ask you to complete and sign a "Withdrawal of Consent" form.
- Data collected before you withdraw consent will form part of the study results.
- Whatever you decide, please be assured that it will not affect your routine care, or your relationship with the staff who are caring for you and your baby, or your relationship with your hospital.

## 12. What happens when the study ends?

- The results of the study will be published and/or presented at professional meetings. It will be impossible to identify you in any publications and/or presentations.
- Parts of this project will be used for Dr Tegan Triggs's research higher degree (PhD) through the University of Queensland. **No patient name or identifiable data will be published.**

## 13. What other information will be collected?

- By signing the Consent Form, you agree to let the study team obtain information for this study from your records at this hospital.
- The study also aims to find out if Sildenafil improves health service costs. We will collect data on any stays in hospital or visits to clinics, emergency departments or other health services or medical prescriptions for you and your child. We will ask you about some of this in a survey and collect the other information through your Medicare claims records from Services Australia, if you consent.
- We will ask you to fill out a consent form authorising access to your Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data as outlined on the back of this Consent Form.
- Medicare collects information on your medical visits and procedures, and the costs.
- PBS collects information on the prescription medications you fill at pharmacies. We need your separate consent to access this data from the Department of Human Services (DHS).
- By signing the Consent Form you allow the study team access to link with your health data in Admitted Patient Data Collection (APDC) and Emergency Department Data Collection (EDDC).

We will only collect reasons for, dates and length of hospital stay and emergency admissions related to your pregnancy.

- If you do not want to let us do this data linkage, please tick the box in the Consent Form for **opt-out**.

## 14. How will my personal information be accessed and what will happen to it?

- Your information will only be used for this study.
- Your study data will be held electronically at Mater Research for 33 years from the end of the study, after which it will be destroyed under security. Only authorised research staff will be able to access the data.
- The information collected in this study database will be identified by a unique research identification number.
- Your name, email address and contact number will be kept securely in the database, to allow us to communicate with you about the study as required. Only the study team will be able to view and use this information to communicate with you and keep you updated about the trial. We will communicate with you once a fortnight until you are admitted for the birth of your baby.
- Your health records and any information obtained in the study can be inspected to verify the procedures and data by representatives of Mater Research, the Therapeutic Goods Administration and relevant regulatory authorities, the approving Human Research Ethics Committee (HREC) or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the above study personnel and authorities.

## 15. Complaints and compensation

- If you suffer complications because of this study, you should contact the study team as soon as possible and you will be helped to arrange suitable medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication.
- You do not give up any legal right to take legal action for compensation for any injuries or complications resulting from the study. Compensation may be available if your complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of anyone involved in the study (for example, the researcher, the hospital, or the treating doctor).

## 16. Who is organising and funding the study?

- This study is sponsored by Mater Misericordiae Ltd.
- The study is funded by grants from the Royal Brisbane and Women's Hospital Foundation, WishList Sunshine Coast Health Foundation, Royal Australian and New Zealand College of Obstetrics and Gynaecology Women's Health Foundation/Norman Beischer Clinical Research Foundation, and The Research Foundation of The Cerebral Palsy Alliance.
- Participating organisations, the funding organisation and the study team have no conflicts of interest.

## 17. Who has reviewed the study?

- This study has been reviewed and approved by the Mater Misericordiae Ltd Human Research Ethics Committee (EC00332).
- Should you wish to discuss the study in relation to your rights as a participant, or should you wish to make an independent complaint, you may contact the HREC Liaison Officer or HREC Chairperson, Human Research Ethics Committee, Mater Misericordiae Ltd, Level 2, Aubigny Place, Raymond Terrace, South Brisbane, QLD 4101 or telephone: (07) 31631585 or email: research.ethics@mater.uq.edu.au.

## 18. Further information about this study and who to contact

- If you want to know more about this study you can contact the study team on RidStress2@mater.uq.edu.au.

- If you wish to complain or have any concerns about the way you have been treated during this study, contact the Principal Investigator, Professor Sailesh Kumar or Dr Tegan Triggs. The Mater Misericordiae Ltd complaints services are also available to you.

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**CONSENT FORM**

**Declaration by Participant**

□ I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

□ I understand the purposes, procedures and risks of the study described in the study.

□ I freely agree to take part in this study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

□ I have had an opportunity to ask questions and I am satisfied with the answers I have received.

□ I understand that, if I decide to discontinue the study, a member of the study team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

□ I understand that I will be given a signed copy of this document to keep.

**For the Follow-up assessment for neurodevelopmental outcomes at 2 years corrected age:**

□ **I give permission** for researchers to maintain contact and send me the Follow-up assessment at 2 years corrected age after birth.

□ I wish to opt out of the Follow-up assessment for neurodevelopmental outcomes at 2 years corrected age, as described above. I understand this opt out does not impact on my participation in the project.

**For the data linkage:**

□ **I give permission** for researchers to have access to my name and address, my hospital and emergency department records. I give permission for my information to be securely provided to approved third parties for purposes of this data linkage. I understand that such information will remain confidential.

□ I choose to opt out of the data linkage of my health information as described above. I understand this opt out does not impact on my participation in the project.

**For blood and placental samples:**

☐ **I consent to the storage and use of placental tissue** and/or blood samples taken from me or umbilical cord as described in the relevant section of the Participant Information Sheet and as approved by a Human Research Ethics Committee for:

- This specific study
- Other research that is closely related to this study
- Any future extended research that may include genetic testing for markers of hypoxia.

☐ No, I do not agree to allow blood and/or tissue samples to be collected and used for this study, or future/extended research, as described above. I understand this opt out does not impact on my participation in the project.

**For consent obtained over the telephone/telehealth:**

Consent was obtained by_____ (Name of Investigator), on _____ (DD/MM/YYYY).

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print)

_____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the study; its procedures and risks and I believe that the participant has understood that explanation.

**For consent obtained over the telephone/telehealth:**

Consent was obtained via telephone with _____ (Name of Participant) on _____ (DD/MM/YYYY).

Participant's signed consent for was received by the Investigator on _____ (DD/MM/YYYY).

Name of Study Doctor/

Senior Researcher† (please print) _____

Signature _____ Date _____

†A senior member of the research team must provide the explanation of, and information concerning, the study. Note: All parties signing the consent section must date their own signature.

**Appendix 2: Reported Adverse Drug Reactions – sildenafil citrate[50]**

| **More frequent** | **Less frequent** |
|---|---|
| Dizziness | Bronchitis |
| Flushing | Cellulitis/Skin rash |
| Gastro-oesophageal reflux/dyspepsia | Migraine-like headache |
| Headache requiring analgesia | Epistaxis |
| Myalgia/Limb pain | Hypo/paraesthesia |
| Vision changes (blurred, coloured, increased sensitivity) requiring ophthalmic review | |
| Vomiting | |