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The iSEARCH Randomised Controlled Trial Protocol – A pragmatic Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes related to birth asphyxia.

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The *iSEARCH* Randomised Controlled Trial Protocol – A pragmatic Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes related to birth asphyxia.

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ABSTRACT

Introduction

We showed in a Phase 2 RCT that oral sildenafil citrate in term labour halved operative birth for fetal distress. We outline the protocol for a Phase 3 RCT (iSEARCH) of 3200 women in Australia to assess if sildenafil citrate reduces adverse perinatal outcomes related to birth asphyxia.

Methods and analysis

iSEARCH will enrol 3200 Australian women in term labour to determine whether up to three 50 mg oral doses of sildenafil citrate versus placebo reduce the relative risk of a primary composite endpoint of ten perinatal outcomes reflecting birth asphyxia by 35% (from 7% to 4.55%). Secondary aims are to evaluate reductions in the relative risk of emergency caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%) and in healthcare costs. To detect a 35% reduction in the primary outcome for an alpha of 0.05 and power of 80% with 10% dropout in each arm requires 3200 women (1600 in each arm). This sample size will also yield >90% power to detect a 25% reduction for the secondary outcome of any operative birth (caesarean section or instrumental vaginal birth) for fetal distress.

Ethics and dissemination

Ethical approval for the iSEARCH RCT was granted by the Hunter New England Human Research Ethics Committee (Ref No: 2020/ETH02791). Results will be disseminated through websites, peer-reviewed publications, scientific meetings and social media, news outlets, television and radio.

Trial Registration

iSEARCH is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000231842) and the Therapeutics Goods Administration of Australia (registered 27 August 2021) and the first participant was randomised on 6 September 2021.

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ARTICLE SUMMARY *(198 WORDS)*

Strengths and limitations of this project

► iSEARCH is an AU$3.42 million, Phase 3 RCT of 3200 women in term labour, funded by the Australian Medical Research Future Fund to determine if intrapartum sildenafil citrate reduces a ten-component primary composite endpoint reflective of birth asphyxia. In secondary analyses, this sample could demonstrate a 25% reduction in emergency operative birth for fetal distress with 90% power.

► Childhood neurodevelopmental outcomes at 2 years will be assessed and health economic analysis will be undertaken to determine cost effectiveness to the healthcare system.

► The sample of 3,200 women only has ~80% power to show a 35% reduction in the relative risk of the ten-component primary composite endpoint. This putative 35% relative risk reduction may reflect optimism bias and is an important limitation, dictated by financial constraints. A sample with over 90% power to show a more moderate and realistic 20% reduction in relative risk of this outcome would require over 12,000 women. To detect a similar reduction in perinatal death, defined as intrapartum stillbirth and/or 7-day neonatal mortality, will require tens of thousands of women.

► iSEARCH and the RidStress 2 RCT (whose protocol is published in this issue of BMJ Open) will contribute to aggregate meta-analyses and individual participant data prospective meta-analyses (IPD PMA) of highly streamlined RCTs worldwide, powered to show moderate, clinically relevant effects on adverse perinatal outcome.

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INTRODUCTION

Fetal distress in labour usually reflects pre-existing placental impairment[1 2] which reduces the capacity of the fetus to cope with the stress of uterine contractions.[3] In many term pregnancies, uterine blood flow falls by 60% during contractions,[4] provoking fetal distress. Fetal decompensation occurs[5] if there is insufficient time for placental reperfusion between contractions.[1]

Suspected fetal distress due to hypoxia in labour is a key factor in up to 23% of emergency caesarean births in Australia.[6] Hypoxic fetal injury can lead to intrapartum stillbirth and severe neonatal morbidity including neonatal encephalopathy and cerebral palsy.[7 8 9] Intrapartum hypoxia-ischemia causes 1 in 3 cases of neonatal encephalopathy in high-income countries with low perinatal mortality rates (PMRs) and almost 60% of cases in low-or middle-income countries with moderate or high PMRs.[10] Other than emergency operative birth [caesarean section or instrumental (forceps or vacuum) vaginal birth], options are limited.

Sildenafil Citrate is a phosphodiesterase-5 inhibitor that enhances the bioavailability of Nitric Oxide by inhibiting cyclic guanosine monophosphate degradation. Increased tissue Nitric Oxide levels improve vasodilatation and reduce vascular dysfunction secondary to vasoconstrictors and antiangiogenic factors.[11 12] Sildenafil citrate preferentially dilates pelvic blood vessels and increases utero-placental blood flow.[13 14] Our systematic review of 10 obstetric randomised controlled trials (RCTs) of 1,090 women found that phosphodiesterase-5 inhibitor use in pregnancy was associated with a 42% relative reduction of operative birth for intrapartum fetal distress [Relative Risk (RR) 0.58, 95% CI 0.38-0.88] in two trials in a total of 400 women.[15]

Our Phase 2 RCT[16] tested whether, compared to placebo, sildenafil citrate lowered rates of emergency operative birth for fetal distress in 300 women in term labour. Sildenafil reduced (i) the relative risk (RR) of operative birth for fetal distress by 51% [(RR 0.49, 95% CI 0.33 – 0.73), p=0.0004; Number Needed to Treat for Benefit = 5 (3-11)] and (ii) rates of pathological fetal heart rate (FHR) patterns (15% vs. 32%; RR 0.48, 95% CI 0.31 – 0.75, p=0.0009) by 52%. This trial, however, lacked power to

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show a statistically significant improvement in neonatal outcomes to support the rationale for sildenafil citrate treatment in labour. A subsequent cost effectiveness analysis concluded that oral intrapartum sildenafil citrate may be cost effective compared with standard care, but that its effects on neonatal outcomes should be evaluated in large RCTs.[17]

The Australian iSEARCH (can **i**ntrapartum **S**ild**E**nafil safely **A**vert the **R**isks of **C**ontraction-induced **H**ypoxia in labour?) trial began on 6th September 2021. It is the world's first Phase 3 RCT to re-purpose sildenafil citrate by evaluating whether, compared to placebo, it improves perinatal outcome, by reducing the risk of intrapartum fetal compromise. Its primary endpoint is a composite of ten adverse fetal or neonatal outcomes (Table 1) very similar to that used in other large RCTs like the ARRIVE trial in term pregnancies.[18] Its target sample size of 3,200 women yields >80% power to detect a reduction of 35% in the relative risk of its primary endpoint (from 7% to 4.55%, equivalent to a pooled event rate of 5.78%). It also has 90% power to detect a 25% reduction in the secondary outcome of emergency operative birth for fetal distress, from 20% to 15%. It is funded by the Australian Medical Research Future Fund and will run until August 2024.

Together with RidStress 2 (protocol published in this issue of BMJ Open), iSEARCH will contribute to an individual participant data prospective meta-analysis (IPD PMA) of similar trials in high- and low- and middle-income countries which may provide evidence for a smaller but still clinically meaningful reduction in adverse perinatal outcomes.[19] [20] This global evidence, in turn, may support the introduction of sildenafil citrate as an option for routine intrapartum care for women planning a vaginal birth at term.

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METHODS AND ANALYSIS:

Primary Research Question

Does maternal oral sildenafil citrate in labour, compared with placebo, reduce the primary composite endpoint of ten adverse neonatal outcomes? (Table 1)

Secondary Research Questions

(a) Does maternal oral sildenafil citrate in labour reduce the rate of the secondary outcomes of:

a. Emergency operative birth for fetal distress
b. Intrapartum stillbirth
c. Death of baby before discharge from hospital
d. Apgar score <4 at 5 minutes
e. Cord artery pH <7.0
f. Neonatal encephalopathy
g. Neonatal seizures
h. Neonatal respiratory support >4h
i. Neonatal unit (Special Care or Intensive Care) admission lasting >48 h
j. Persistent pulmonary hypertension of the newborn
k. Meconium aspiration syndrome

(b) Is maternal oral sildenafil citrate in labour more cost effective than placebo?

Table 1: Primary composite outcome

Components of composite primary endpoint	Rate	Association with long term adverse outcome
Intrapartum stillbirth [21]	0.1%*	-
28-day neonatal mortality	0.24%	-
Apgar score <4 at 5 minutes	0.5%	↑ risk of cerebral palsy[22]
Umbilical Cord artery pH <7.0	2.2%¥	↑ risk of HIE[23]
Neonatal encephalopathy, Sarnat Grade 2 or 3	0.5%	↑ risk of death or disability[24]
Neonatal seizures§	0.25%	↑ risk of death or disability[24]
Neonatal respiratory support for >4 h	3.6%	↑ risk of cerebral palsy[25]
Neonatal unit admission for >48 h	4.3%	↑ asthma after term respiratory morbidity[26]
Persistent pulmonary hypertension	0.04%	↑ risk of death or disability[27]
Meconium aspiration	0.75%	↑ risk of death or disability[28]
Total (corrected for overlap)	7.0%	

**based on data from Grobman et al [18]; ¥based on data from Yeh et al [23]*

§although seizures include non-encephalopathic causes like stroke or metabolic disorders, in a randomised trial, those causes not influenced by Sildenafil will tend to be evenly balanced between study arms and therefore tend not to bias the comparison. In this pragmatic trial, seizures, persistent pulmonary hypertension and meconium aspiration are all defined using local protocols.

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Study design: This is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind multicentre superiority trial of sildenafil citrate vs. placebo for women in labour at term ($\geq 37^{+0}$ weeks).

Patient and public involvement: We involved clinician and consumer groups when designing this trial through the use of electronic media and face to face interviews. Of >400 women and clinicians in 68 sites in Australia and overseas, >90% endorsed iSEARCH and, if its hypotheses were confirmed, >85% would want sildenafil citrate to become an option in routine care.

Aim: This study aims to test the hypothesis that up to 3 doses of oral 50 mg sildenafil citrate (vs. placebo) are safe and will improve perinatal and maternal outcomes related to intrapartum hypoxia.

Primary objective:

To evaluate whether, compared with placebo, sildenafil citrate reduces the relative risk of the composite perinatal endpoint by 35%, from 7% to 4.55%. The composite endpoint comprises the ten components shown in Table 1.

Secondary objectives:

1. To evaluate whether sildenafil citrate results in a relative risk reduction of Caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%).

2. To evaluate whether sildenafil citrate results in a reduction of the relative risk of each individual component of the composite primary outcome, namely:

    a. Intrapartum Stillbirth
    b. Death of baby before hospital discharge
    c. Apgar Score <4 at 5 minutes
    d. Cord Artery pH <7.0
    e. Neonatal Encephalopathy
    f. Neonatal seizures
    g. Neonatal respiratory support >4h
    h. Neonatal unit (Special Care or Intensive Care) admission lasting >48h
    i. Persistent pulmonary hypertension of the newborn
    j. Meconium aspiration

3. To evaluate whether Sildenafil is more cost-effective than placebo.

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Study Period: Recruitment to iSEARCH began on 7th September 2021 and is expected to end by 31 August 2024.

Sample Size: The incidence of the composite adverse outcome is estimated at 7% based on data from several of the participating hospitals, the ARRIVE RCT,[18] and the Australian and New Zealand Neonatal Network.[29] To detect a 35% reduction from 7% to 4.55% for an alpha of 0.05 and >80% power with 10% drop out in each arm, needs about 3,200 women. This sample size also yields >90% power to detect a 25% reduction for the secondary outcome of caesarean section or instrumental vaginal birth for fetal distress.

Study population

Inclusion criteria:

1. Women with singleton or dichorionic twin pregnancies, planning vaginal birth at term (≥37^{+0} weeks gestation).
2. Age ≥18 years.
3. Willing and able to comply with all study requirements.
4. Signed, written informed consent.

Exclusion criteria:

1. A woman should not be enrolled if the responsible clinician or the woman are, for any medical or non-medical reasons, reasonably certain that sildenafil citrate would be inappropriate for her in comparison with no treatment or some other treatment that could be offered outside the trial.[30]
2. Monochorionic twins, triplets or higher order multiple births, which are generally delivered electively before term.
3. Women who are taking any type of nitrate drug therapy or who utilize short-acting nitrate-containing medications during labour (such as sodium nitroprusside, bosentan, fosamprenavir and ritonavir combination, hepatic enzyme inhibitors CYP3A4 (including itraconazole,

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ketoconazole, ritonavir, cimetidine, erythromycin, saquinavir, darunavir), or hepatic enzyme substrates (CYP3A4), medications used to treat pulmonary arterial hypertension, and other phosphodiesterase type 5 inhibitors, due to the risk of potentially life-threatening hypotension.[31]

4. Severe hepatic or renal impairment.[31]

Screening, registration and randomisation: All women attending antenatal clinics in participating hospitals from $\geq 34^{+0}$ weeks will be screened for eligibility by study midwives. Women who consent to participate will be registered in an online trial registration database. Once registered, each woman is assigned a unique study number and receives routine care until spontaneous labour or induction of labour, when randomisation is undertaken. Individuals may only be registered and randomised once. Randomisation is undertaken after the responsible midwife or obstetrician has again confirmed that the woman is eligible. If an eligible woman presents for the first time in labour, screening, registration and randomisation are done together. Once registration and randomisation are completed, the participant is assigned a treatment arm. Randomisation is web-based, using a computer-generated concealed allocation sequence, stratified by study site.

At registration, each woman will be invited to consent to allow data linkage with her child or children's educational outcomes in the National Assessment Program – Literacy and Numeracy (NAPLAN);[32] for data to be extracted from Medicare Benefits Schedule and Pharmaceutical Benefits Schemes claims records for herself and her infant and from the Australian cerebral palsy register. Such consent may be withdrawn at any time and without a reason. Each woman will also be invited to give consent to participate in childhood neurodevelopmental follow-up at 2-3 years corrected age. If she consents to this, contact details will be recorded and follow-up assessment will be performed as described below. Any decline for follow-up will be properly explored to ensure that withdrawal is not automatically interpreted to mean complete removal from the study as this may have possible implications for the reliability of trial findings. It may also be disadvantageous to these women because they could miss

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out on some aspects of the RCT that may matter to them (such as being informed about progress and results of the study).[33]

Study Treatments: The study intervention is oral sildenafil citrate. The control intervention is placebo. Study treatment only begins after transfer to the labour ward either in spontaneous labour or for induction of labour (artificial rupture of membranes +/- oxytocin). Women are given the first dose by the attending midwife in the labour ward. Women receive sildenafil citrate 50mg or identical placebo orally every 8 hours to a maximum of three doses, from identical matched treatment packs supplied by the trial pharmacy.

Management of Labour and Puerperium: Intrapartum FHR monitoring will be performed in all women. Where possible, umbilical artery cord pH will be measured in all women after birth. Classification of FHR abnormalities is based on the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines.[46] In a subset of women, 20ml of blood will be collected for assay of soluble Fms-like tyrosine kinase-1 (sFlt-1) and Placental Growth Factor (PlGF) levels. Where possible, these women will also have an ultrasound scan performed to assess the fetoplacental circulation and liquor volume before and after treatment. The ultrasound data and maternal sFlt-1 and PlGF levels will allow post-hoc subgroup analysis to identify cohorts at risk of fetal distress that might derive greater benefit from sildenafil citrate treatment. Otherwise, intrapartum management will be in accordance with local hospital guidelines.

To detect possible persistent pulmonary hypertension of the newborn, all infants will also receive routine oxygen saturation screening to detect hypoxemia, generally 24-48 hours after birth but, if necessary, four hours after birth. Infants with oxygen saturations of >95% are very unlikely to have major congenital heart or significant pulmonary disease, including persistent pulmonary hypertension of the newborn.[34] Infants with oxygen saturations $\leq$95% will receive further assessment by the paediatric team which may include echocardiography.

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Trial Outcomes: In-hospital maternal and neonatal outcome events occurring from randomisation to discharge home will be collected from medical records into electronic Case Report Forms (eCRFs). Assessments of outcome will be blinded to treatment allocation. All primary outcome data will be routinely available before discharge and collected electronically. There are no formal study assessments visits. Research midwives will contact women 30 days after discharge to ascertain further relevant issues. Childhood follow up will be conducted by linkage with educational databases and cerebral palsy registers and using parent report questionnaires.[35-37]

Data Analysis: We will adopt recommended approaches[38 39] to the analysis and reporting of composite endpoints, as in previous multi-centre perinatal RCTs.[40-45] A detailed Statistical Analysis Plan and health economic protocol will be published before unblinding and data analysis begin.[46] The Trial Management Committee (TMC) will base any modifications to the original objectives, such as a change in the components of the composite endpoint, adjudication of events, or handling of missing data, on a review of the pooled event rate, pooled adherence rates and pooled missing data while remaining blinded to differences by allocated treatment and to the direction of any treatment effect.[47-50] Primary and secondary analyses will adhere to an intention-to-treat basis using generalised linear models (binary or normal). Intervention effect will be presented as relative risk or mean difference, as appropriate, with 95% confidence intervals. Primary analyses will be unadjusted. Numbers needed to treat to prevent one adverse outcome will be calculated. Where there are differences in baseline characteristics between the two treatment groups that might be associated with outcomes, secondary analyses of the primary outcome will be carried out using multiple (log-binomial) regression. Reporting will follow CONSORT[51] and TRIPOD[52] guidelines.

There is only one primary outcome. Secondary outcomes include each of the ten individual components of the primary composite outcome (Table 1). For the secondary outcomes, no formal adjustments for multiplicity are planned. Because the secondary outcomes are interrelated and causally attributable to birth asphyxia, we will follow the advice outlined by Schulz and Grimes[53] and

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interpret the pattern and consistency of findings across related outcomes, rather than focusing on any single, statistically significant result. Subgroup analyses will be performed by testing for interactions and findings will be reported as exploratory. Results of other endpoint, subgroup and sensitivity analyses will be interpreted in proper context and with due consideration of the risk of Type I error. Interpretation of statistical evidence will also consider the recommendations of Pocock *et al*.[54 55] We will undertake an aggregate meta-analysis of the effect of intrapartum sildenafil on Caesarean section or instrumental vaginal birth for fetal distress using pooled data from iSEARCH, RidStress and any other relevant published trials.

Safety of sildenafil citrate: In our systematic review[15] of the efficacy and safety of phosphodiesterase inhibitors (sildenafil citrate or tadalafil) in 10 RCTs in 1090 women in pregnancy, we found that use of phosphodiesterase inhibitors in term labour was not associated with an increase in maternal side effects, including dizziness, flushing, dyspepsia, gastritis, palpitations, arthralgia, dyspnea, epistaxis, diarrhoea, tremor, headache, myalgia, paraesthesia, oedema, visual changes, vaginal itch, nausea and vomiting, intrapartum antiemetic use, post-partum haemorrhage of ≤1500 mL, anemia, bronchitis, skin rash , intrapartum pyrexia, or placental abruption. Use of phosphodiesterase inhibitors in labour may have been associated with a small increase in vaginal birth (RR 1.24, 95% CI 1.00–1.55; p=0.05) and a statistically significant reduction in risk of operative birth for intrapartum fetal compromise (RR 0.58, 95% CI 0.38–0.88; p=0.01). Use of sildenafil in labour was not associated with increased risk of perinatal death (RR 0.89, 95% CI 0.56–1.43; p=0.64), nor of maternal admissions to intensive care and no maternal deaths were reported.

Chronic use of phosphodiesterase inhibitors for the treatment of severe fetal growth restriction, as in the STRIDER trials,[56 57] or treatment of pre-eclampsia[58-60] was associated with a statistically significant increase in the risks of flushing (RR 6.83, 95% CI 1.49–31.23; p=0.01) and nasal bleeding (RR 10.53, 95% CI 1.36–81.3; p=0.02); an increase in risk of persistent pulmonary hypertension of the newborn (RR 2.52, 95% CI 1.00–6.32; p=0.05) and non-statistically significant increase in headaches (RR 1.41, 95% CI 0.97–2.05; p = 0.08) and flushing (RR 2.59, 95% CI 0.69–9.90; p=0.16).[15]

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The international STRIDER RCTs used daily maternal Sildenafil doses of 75 mg in pregnant women with severe fetal growth restriction between 20 and 30 weeks gestation for up to 10 weeks, i.e. cumulative doses of up to 5,250 mg.[56 57] In 2019, the Dutch STRIDER trial was stopped on the advice of the Data Safety Monitoring Board due to an increase in persistent pulmonary hypertension of the newborn with a non-significant increase in neonatal deaths in the sildenafil citrate group.[61] Persistent pulmonary hypertension of the newborn occurred in 16 neonates (18.8%) in the sildenafil citrate group vs. 4 neonates (5.1%) in the placebo group (relative risk, 3.67; 95% CI, 1.28-10.51; P = 0.008). A subsequent meta-analysis of 329 participating women in all available trials showed no difference in neonatal deaths.[62] However it was recommended that sildenafil citrate not be prescribed outside of clinical trials.[63] The indication and cumulative dosage of sildenafil citrate in the iSEARCH trial are very different from the STRIDER trials as we will only use a maximum 150mg in women at term, which is about thirty five times lower. Persistent pulmonary hypertension of the newborn will be monitored as one of ten components of the primary composite endpoint by the independent data and safety monitoring board, as outlined below.

Safety of sildenafil during breastfeeding: Limited data indicate that sildenafil citrate and its active metabolite in breastmilk are poorly excreted into breastmilk. Amounts ingested by the infant are far below doses given to treat infants and would not be expected to cause any adverse effects in breastfed infants.[64] Women taking sildenafil citrate for the treatment of pulmonary hypertension in the UK are advised to continue breastfeeding because sildenafil citrate only passes into breast milk in tiny amounts, is unlikely to cause any side effects in the baby and breastfeeding will benefit both mother and baby.[65] We will monitor concentrations of sildenafil citrate in breast milk and any potentially related adverse events in a subset of women in the trial.

Role of study sponsor and funders: The University of Sydney, as sponsor of iSEARCH, and the Medical Research Future Fund as funder of iSEARCH have had no role in study design, collection or

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management of data. Both will also have no role in analysis or interpretation of data, writing of manuscripts or decisions to publish.

The iSEARCH Trial Management Committee: The TMC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g., Human Research Ethics committees). It will consider recommendations from the Independent Data Safety and Monitoring Committee (IDSMC) about whether to continue the study as planned, modify, or stop, based on interim analyses or other information. The TMC will consist of all Chief Investigators.

The iSEARCH Trial Coordinating Centre is the NHMRC Clinical Trials Centre (CTC). It will support the TMC in the day-to-day conduct of the trial, and study processes, including data management, ensuring compliance with regulatory requirements and confidentiality of data collection, liaising with ethics committees, biostatistical team, IDSMC, and answering queries from participating sites including the receipt and timely management of reports of Adverse Events. A list of participating sites is available in the trial registration entry at the Australian New Zealand Clinical Trials Registry (ACTRN12621000231842).

Compliance: Participant medication compliance will be monitored and documented in the medical records and electronic Case Record Forms (eCRFs), which will be held on a secure server, ensuring confidentiality. The iSEARCH trial may be subject to audit or inspection by representatives of the NHMRC CTC or representatives of independent regulatory bodies (e.g., the Therapeutic Goods Administration).

Unblinding: Unblinding is not generally necessary for the management of a patient with an adverse event and, as it may have an impact on the study's validity, is discouraged. The need for unblinding should be very uncommon as the study intervention is rarely associated with severe side effects and it will not delay or prevent standard management of the participant. However, if required, it should

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be done centrally after discussion with the Study Chair and NHMRC CTC representative using the emergency unblinding number in the Study Manual.

The Independent Data and Safety Monitoring Committee: The IDSMC will review interim data on the primary outcome, specified adverse events and other evidence after 50% of recruitment or whenever they deem appropriate, as recommended by Peto, Pocock and others.[66-68] There will be no adjustment to alpha for interim analyses.

Interim analyses of the primary composite outcome: The IDSMC will advise the TMC if in their view there is proof beyond reasonable doubt of net benefit or harm for the primary composite endpoint, for example employing a commonly used formal threshold of P<0.001 for nominal significance, as recommended by Geller and Pocock.[68]

Interim analyses of mortality: The IDSMC will advise the TMC if in their view 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,[66 67] which would be needed to justify recommending early stopping.

Ethics and regulatory compliance: Conduct of the iSEARCH RCT will be informed by the International Conference on Harmonization Guidelines for Good Clinical Practice[69 70] and World Health Organisation guidance.[33] It will comply with applicable laws and regulations and principles laid down by the World Medical Association in the Declaration of Helsinki 2013. It was registered with the Australian and New Zealand Clinical Trial Registry and ethical and regulatory approvals were obtained before it began. Changes and amendments to the protocol can only be made by the TMC. Approval by the Institutional Human Research Ethics Committee is required prior to the implementation of any amendments.

Discussion

iSEARCH is the world's first Phase 3 trial to re-purpose sildenafil citrate, a widely available, well characterised, affordable, off-patent vasodilator, by evaluating whether, compared to placebo, it

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improves perinatal and maternal outcomes by reducing operative birth for intrapartum fetal compromise. We will also seek consent for data linkage with national databases of educational outcomes and cerebral palsy registries and maintain contact with a subset of participating women to collect longer-term outcome data, in separately funded studies. This is a major area of unmet need,[71] [72] to which *iSEARCH* will make an important initial contribution. However, the postulated 35% reduction in the relative risk of its primary composite endpoint is nearly twice as large as the 20% relative reduction in a ten-component composite outcome seen in the ARRIVE trial, which enrolled 6,106 women.[18] The relative risk reduction in iSEARCH may therefore reflect 'optimism bias'[73-75] and is an important limitation, dictated by financial constraints which precluded a larger study.

The ten components of the primary composite endpoint (Table 1) are all related to intrapartum hypoxia.[18] [76] However, a reduction in overall incidence of this endpoint could not be interpreted as indicating reductions in key individual components such as intrapartum stillbirth, neonatal mortality, Apgar score <4 at 5 minutes, neonatal encephalopathy or seizures, because the rates of these events vary between 0.1% and 0.5%, at which iSEARCH is greatly underpowered to detect any differences. The three individual components of the composite endpoint for which the chances of showing a reduction in incidence are greatest are (i) admission to neonatal unit for >48 h, (ii) respiratory support for >4 h and (iii) cord pH <7. Their estimated event rates are 3.6%, 4.3% and 2.2% respectively, (Table 1) for which our sample of 3200 gives ~80% power to show (albeit highly optimistic) reductions in relative risk of 50-60%.

The next, critically important step will be to undertake a large-scale randomised placebo-controlled study of oral intrapartum sildenafil addressing the primary outcome of perinatal death, adequately powered in high, low-and middle-income countries. Secondary outcomes would include low Apgar score; emergency operative birth by Caesarean Section, vacuum or forceps; maternal infant separation due to neonatal unit admission; neonatal encephalopathy; severe maternal morbidity (including post-partum haemorrhage) and maternal death.

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Another equally important step in evaluating the impact of intrapartum sildenafil citrate will be to establish an IPD PMA of iSEARCH trials. It is essential that all trials contributing to an IPD PMA achieve close to 100% ascertainment of their primary outcome data, by streamlining data collection to minimise the rate of missing values.[77] This global collaborative approach will provide randomised evidence addressing realistically moderate, yet clinically important reductions in adverse perinatal outcome, and whether sildenafil citrate is similarly effective in subgroups of women in different healthcare settings. If routine intrapartum sildenafil citrate safely reduces adverse birth outcomes and/or emergency operative birth and their long-term sequelae,[78] it could provide an important option for women attempting vaginal birth worldwide[6] and potentially reduce the global health burden attributable to birth asphyxia.

Ethics and dissemination

The Australian iSEARCH RCT has been approved by Hunter New England Ethic Committee (Ref Number 2020/ETH02791). Each component trial within the iSEARCH Collaboration will be approved by relevant local, regional or national Human Research Ethics Committee. We plan to disseminate the results of this trial via presentations at clinical, academic and scientific meetings as well as peer reviewed journals. We will adhere to all relevant reporting guidelines.

Authors' contributions

SK wrote the first draft. SK and WTM contributed equally to the manuscript. All authors and collaborators reviewed and approved the final version before submission.

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Competing interest statement

None of the authors have any competing interests to declare.

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Data sharing:

Individual de-identified participant data for findings reported in the iSEARCH Trial will be available for 5 years after publication. Researchers wishing to gain access to data should provide a methodologically sound proposal to isearch.study@sydney.edu.au, which will be reviewed by the Trial Management Committee.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13, 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10, 11

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9, 10, 14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14, 15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9, 10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13, 15

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9, 10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The iSEARCH Randomised Controlled Trial Protocol – A pragmatic Australian Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia.

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The iSEARCH Randomised Controlled Trial Protocol – A pragmatic Australian Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia.

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ABSTRACT

Introduction

We showed in a Phase 2 RCT that oral sildenafil citrate in term labour halved operative birth for fetal distress. We outline the protocol for a Phase 3 RCT (iSEARCH) of 3200 women in Australia to assess if sildenafil citrate reduces adverse perinatal outcomes related to intrapartum hypoxia.

Methods and analysis

iSEARCH will enrol 3200 Australian women in term labour to determine whether up to three 50 mg oral doses of sildenafil citrate versus placebo reduce the relative risk of a primary composite endpoint of ten perinatal outcomes potentially related to intrapartum hypoxia by 35% (from 7% to 4.55%). Secondary aims are to evaluate reductions in the relative risk of emergency caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%) and in healthcare costs. To detect a 35% reduction in the primary outcome for an alpha of 0.05 and power of 80% with 10% dropout in each arm requires 3200 women (1600 in each arm). This sample size will also yield >90% power to detect a 25% reduction for the secondary outcome of any operative birth (caesarean section or instrumental vaginal birth) for fetal distress.

Ethics and dissemination

Ethical approval for the iSEARCH RCT was granted by the Hunter New England Human Research Ethics Committee (Ref No: 2020/ETH02791). Results will be disseminated through websites, peer-reviewed publications, scientific meetings and social media, news outlets, television and radio.

Trial Registration

iSEARCH is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000231842) (registered 4 March 2021) and the Therapeutics Goods Administration of Australia and the first participant was randomised on 6 September 2021.

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ARTICLE SUMMARY *(198 WORDS)*

Strengths and limitations of this project

- ► iSEARCH is a Phase 3 RCT of 3200 women in term labour to determine if maternal oral sildenafil citrate reduces adverse neonatal outcomes and operative birth rates potentially secondary to intrapartum hypoxia.

- ► Childhood neurodevelopmental outcomes at 2 years will be assessed and health economic analysis will be undertaken to determine cost effectiveness to the healthcare system.

- ► iSEARCH and other highly streamlined RCTs worldwide will contribute to individual participant data prospective meta-analyses (IPD PMA) powered to show moderate, clinically relevant effects on adverse perinatal outcome.

- ► The sample of 3,200 women only has ~80% power to show a 35% reduction in the relative risk of the primary endpoint rather than a more moderate and realistic, yet still clinically relevant 20% risk reduction, which would require more than 10,000 women.

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INTRODUCTION

Fetal distress in labour usually reflects pre-existing placental impairment[1, 2] which reduces the capacity of the fetus to cope with the stress of uterine contractions.[3] In many term pregnancies, uterine blood flow falls by 60% during contractions,[4] provoking fetal distress. Fetal decompensation occurs[5] if there is insufficient time for placental reperfusion between contractions.[1]

Suspected fetal distress due to hypoxia in labour is implicated in up to 23% of emergency caesarean births in Australia.[6] Hypoxic fetal injury can lead to intrapartum stillbirth and severe neonatal morbidity including neonatal encephalopathy and cerebral palsy.[7] [8] [9] Intrapartum hypoxia-ischemia is associated with 1 in 3 cases of neonatal encephalopathy in high-income countries with low perinatal mortality rates (PMRs) and almost 60% of cases in low-or middle-income countries with moderate or high PMRs.[10] Other than emergency operative birth [caesarean section or instrumental (forceps or vacuum) vaginal birth], options are limited.

Sildenafil Citrate is a phosphodiesterase-5 inhibitor that enhances the bioavailability of Nitric Oxide by inhibiting cyclic guanosine monophosphate degradation. Increased tissue Nitric Oxide levels improve vasodilatation and reduce vascular dysfunction secondary to vasoconstrictors and antiangiogenic factors.[11, 12] Sildenafil citrate preferentially dilates pelvic blood vessels and increases utero-placental blood flow.[13, 14] Our systematic review of 10 randomised controlled trials (RCTs) of 1,090 women found that phosphodiesterase-5 inhibitor use in pregnancy was associated with a 42% relative reduction of operative birth for intrapartum fetal distress [Relative Risk (RR) 0.58, 95% CI 0.38-0.88] .[15] This effect was driven by two trials[16], **[17]** which reported rates of operative birth for this indication.

Our Phase 2 RCT**[17]** tested whether, compared to placebo, sildenafil citrate lowered rates of emergency operative birth for suspected fetal distress in 300 women in term labour. Sildenafil reduced (i) the relative risk (RR) of operative birth for fetal distress by 51% [(RR 0.49, 95% CI 0.33 – 0.73), p=0.0004; Number Needed to Treat for Benefit = 5 (3-11)] and (ii) rates of pathological fetal heart rate

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(FHR) patterns (15% vs. 32%; RR 0.48, 95% CI 0.31 – 0.75, p=0.0009) by 52%. Concentrations of sildenafil citrate or its metabolite were only 3.6% of maternal levels, consistent with low rates of transplacental transfer to the fetus. Use of sildenafil citrate also attenuated the normal intrapartum decline in placental growth factor (PlGF) levels suggesting that it had a role in preserving placental function in labour.[18] This trial, however, lacked power to show a statistically significant improvement in neonatal outcomes to support the rationale for sildenafil citrate treatment in labour. A subsequent cost effectiveness analysis concluded that oral intrapartum sildenafil citrate may be cost effective compared with standard care, but that its effects on neonatal outcomes should be evaluated in large RCTs.[19]

The Australian iSEARCH (can **i**ntrapartum **S**ild**E**nafil safely **A**vert the **R**isks of **C**ontraction-induced **H**ypoxia in labour?) trial began on 6th September 2021. It is the world's first Phase 3 RCT to re-purpose sildenafil citrate by evaluating whether, compared to placebo, it improves perinatal outcome, by reducing the risk of intrapartum fetal compromise. Its primary endpoint is a composite of ten adverse fetal or neonatal outcomes (Table 1) very similar to that used in other large RCTs like the ARRIVE trial in term pregnancies.[20] Its target sample size of 3,200 women yields >80% power to detect a reduction of 35% in the relative risk of its primary endpoint (from 7% to 4.55%, equivalent to a pooled event rate of 5.78%). It also has 90% power to detect a 25% reduction in the secondary outcome of emergency operative birth for fetal distress, from 20% to 15%. It is funded by the Australian Medical Research Future Fund and will run until August 2024.

The next, critically important step will be to undertake large-scale randomised placebo-controlled studies of oral intrapartum sildenafil addressing the primary outcome of perinatal death, adequately powered in high, low-and middle-income countries. Secondary outcomes would include low Apgar score; emergency operative birth by Caesarean Section, vacuum or forceps; maternal infant separation due to nursery admission; neonatal encephalopathy; severe maternal morbidity (including post-partum haemorrhage) and maternal death.

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Another equally important step in evaluating the impact of intrapartum sildenafil citrate will be to establish an individual participant data prospective meta-analysis (IPD PMA) of iSEARCH trials which may provide evidence for a smaller but still clinically meaningful reduction in adverse perinatal outcomes.[21, 22] It is essential that all trials contributing to an IPD PMA achieve close to 100% ascertainment of their primary outcome data, by streamlining data collection to minimise the rate of missing values.[23] This global collaborative approach will provide randomised evidence addressing realistically moderate, yet clinically important reductions in adverse perinatal outcome, and whether sildenafil citrate is similarly effective in subgroups of women in different healthcare settings. If routine intrapartum sildenafil citrate safely reduces adverse birth outcomes and/or emergency operative birth and their long-term sequelae,[24] it could provide an important option for women attempting vaginal birth worldwide.[6]

METHODS AND ANALYSIS:

Primary Research Question

Does maternal oral sildenafil citrate in labour, compared with placebo, reduce the primary composite endpoint of ten adverse neonatal outcomes? (Table 1)

Secondary Research Questions

(a) Does maternal oral sildenafil citrate in labour reduce the rate of the secondary outcomes of:

a. Emergency operative birth for fetal distress
b. Intrapartum stillbirth
c. Death of baby before discharge from hospital
d. Apgar score <4 at 5 minutes
e. Cord artery pH <7.0
f. Neonatal encephalopathy
g. Neonatal seizures
h. Neonatal respiratory support >4h
i. Neonatal unit (Special Care or Intensive Care) admission lasting >48 h
j. Persistent pulmonary hypertension of the newborn
k. Meconium aspiration syndrome

(b) Is maternal oral sildenafil citrate in labour more cost effective than placebo?

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Table 1: Primary composite outcome

Components of composite primary endpoint	Rate	Association with long term adverse outcome
Intrapartum stillbirth [25]	0.1%*	-
28-day neonatal mortality	0.24%	-
Apgar score <4 at 5 minutes	0.5%	↑ risk of cerebral palsy[26]
Umbilical Cord artery pH <7.0	2.2%¥	↑ risk of HIE[27]
Neonatal encephalopathy Sarnat Grade 2 or 3[28]	0.5%	↑ risk of death or disability[29]
Neonatal seizures§[28]	0.25%	↑ risk of death or disability[29]
Neonatal respiratory support for >4 h	3.6%	↑ risk of cerebral palsy[30]
Neonatal unit admission for >48 h	4.3%	↑ asthma after term respiratory morbidity[31]
Persistent pulmonary hypertension[28]	0.04%	↑ risk of death or disability[32]
Meconium aspiration[28]	0.75%	↑ risk of death or disability[33]
Total (corrected for overlap)	7.0%	

**based on data from Grobman et al [20]; ¥based on data from Yeh et al [27]*

§although seizures include non-encephalopathic causes like stroke or metabolic disorders, in a randomised trial, those causes not influenced by Sildenafil will tend to be evenly balanced between study arms and therefore tend not to bias the comparison. In this pragmatic trial, seizures, persistent pulmonary hypertension and meconium aspiration are all defined using local protocols.

Study design: This is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind multicentre superiority trial of sildenafil citrate vs. placebo for women in labour at term (≥37^{+0} weeks).

Patient and public involvement: We involved clinician and consumer groups when designing this trial through the use of electronic media and face to face interviews. Of >400 women and clinicians in 68 sites in Australia and overseas, >90% endorsed iSEARCH and, if its hypotheses were confirmed, >85% would want sildenafil citrate to become an option in routine care.

Aim: This study aims to test the hypothesis that up to 3 doses of oral 50 mg sildenafil citrate (vs. placebo) are safe and will improve perinatal and maternal outcomes related to intrapartum hypoxia.

Primary objective:

To evaluate whether, compared with placebo, sildenafil citrate reduces the relative risk of the composite perinatal endpoint by 35%, from 7% to 4.55%. The composite endpoint comprises the ten components shown in Table 1.

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Secondary objectives:

1. To evaluate whether sildenafil citrate results in a relative risk reduction of Caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%).

2. To evaluate whether sildenafil citrate results in a reduction of the relative risk of each individual component of the composite primary outcome, namely:

    a. Intrapartum Stillbirth
    b. Death of baby before hospital discharge
    c. Apgar Score <4 at 5 minutes
    d. Cord Artery pH <7.0
    e. Neonatal Encephalopathy
    f. Neonatal seizures
    g. Neonatal respiratory support >4h
    h. Neonatal unit (Special Care or Intensive Care) admission lasting >48h
    i. Persistent pulmonary hypertension of the newborn
    j. Meconium aspiration

3. To evaluate whether Sildenafil is more cost-effective than placebo.

Study Period: Recruitment to iSEARCH began on 7th September 2021 and is expected to end by 31 August 2024.

Sample Size: The incidence of the composite adverse outcome is estimated at 7% based on data from several of the participating hospitals, the ARRIVE RCT [20] and the Australian and New Zealand Neonatal Network.[34] To detect a 35% reduction from 7% to 4.55% for an alpha of 0.05 and >80% power with 10% drop out in each arm, needs about 3,200 women. This sample size also yields >90% power to detect a 25% reduction for the secondary outcome of caesarean section or instrumental vaginal birth for fetal distress.

Study population

Inclusion criteria:

1. Women with singleton or dichorionic twin pregnancies, planning vaginal birth at term (≥37^{+0} weeks gestation).

2. Age ≥18 years.

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3. Willing and able to comply with all study requirements.
4. Signed, written informed consent.

Exclusion criteria:

1. A woman should not be enrolled if the responsible clinician or the woman are, for any medical or non-medical reasons, reasonably certain that sildenafil citrate would be inappropriate for her in comparison with no treatment or some other treatment that could be offered outside the trial.[35]
2. Monochorionic twins, triplets or higher order multiple births, which are generally delivered electively before term.
3. Women who are taking any type of nitrate drug therapy or who utilize 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, due to the risk of potentially life-threatening hypotension.[36]
4. Severe hepatic or renal impairment.[36]

Screening, registration and randomisation: All women attending antenatal clinics in participating hospitals from $\geq 34^{+0}$ weeks will be screened for eligibility by study midwives. Women who consent to participate will be registered in an online trial registration database. Once registered, each woman is assigned a unique study number and receives routine care until spontaneous labour or induction of labour, when randomisation is undertaken. Individuals may only be registered and randomised once. Randomisation is undertaken after the responsible midwife or obstetrician has again confirmed that the woman is eligible. If an eligible woman presents for the first time in labour, screening, registration and randomisation are done together. Once registration and randomisation are completed, the

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participant is assigned a treatment arm. Randomisation is web-based, using a computer-generated concealed allocation sequence, stratified by study site.

At registration, each woman will be invited to consent to allow data linkage with her child or children's educational outcomes in the National Assessment Program – Literacy and Numeracy (NAPLAN) [37] for data to be extracted from Medicare Benefits Schedule and Pharmaceutical Benefits Schemes claims records for herself and her infant and from the Australian cerebral palsy register. Such consent may be withdrawn at any time and without a reason. Each woman will also be invited to give consent to participate in childhood neurodevelopmental follow-up at 2-3 years corrected age. If she consents to this, contact details will be recorded and follow-up assessment will be performed as described below. Any decline for follow-up will be properly explored to ensure that withdrawal is not automatically interpreted to mean complete removal from the study as this may have possible implications for the reliability of trial findings. It may also be disadvantageous to these women because they could miss out on some aspects of the RCT that may matter to them (such as being informed about progress and results of the study).[38]

Study Treatments: The study intervention is oral sildenafil citrate. The control intervention is placebo. Study treatment only begins after transfer to the labour ward either in spontaneous labour or for induction of labour (artificial rupture of membranes +/- oxytocin). Women are given the first dose by the attending midwife in the labour ward. Women receive sildenafil citrate 50mg or identical placebo orally every 8 hours to a maximum of three doses, from identical matched treatment packs supplied by the trial pharmacy.

Management of Labour and Puerperium: Intrapartum FHR monitoring will be performed in all women. Where possible, umbilical artery cord pH will be measured in all women after birth. Classification of FHR abnormalities is based on the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines. In a subset of women, 20ml of blood will be collected for assay of soluble Fms-like tyrosine kinase-1 (sFlt-1) and Placental Growth Factor (PlGF) levels. Where

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possible, these women will also have an ultrasound scan performed to assess the fetoplacental circulation and liquor volume before and after treatment. The ultrasound data and maternal sFlt-1 and PlGF levels will allow post-hoc subgroup analysis to identify cohorts at risk of fetal distress that might derive greater benefit from sildenafil citrate treatment. Otherwise, intrapartum management will be in accordance with local hospital guidelines.

To detect possible persistent pulmonary hypertension of the newborn, all infants will also receive routine oxygen saturation screening to detect hypoxemia, generally 24-48 hours after birth but, if necessary, four hours after birth. Infants with oxygen saturations of >95% are very unlikely to have major congenital heart or significant pulmonary disease, including persistent pulmonary hypertension of the newborn.[39] Infants with oxygen saturations ≤95% will receive further assessment by the paediatric team which may include echocardiography.

Trial Outcomes: In-hospital maternal and neonatal outcome events occurring from randomisation to discharge home will be collected from medical records into electronic Case Report Forms (eCRFs). Assessments of outcome will be blinded to treatment allocation. All primary outcome data will be routinely available before discharge and collected electronically. There are no formal study assessments visits. Research midwives will contact women 30 days after discharge to ascertain further relevant issues. Childhood follow up will be conducted by linkage with educational databases and cerebral palsy registers and using parent report questionnaires.[40-42]

Data Analysis: We will adopt recommended approaches[43, 44] to the analysis and reporting of composite endpoints, as in previous multi-centre perinatal RCTs.[45-50] A detailed Statistical Analysis Plan and health economic protocol will be published before unblinding and data analysis begin.[51] The Trial Management Committee (TMC) will base any modifications to the original objectives, such as a change in the components of the composite endpoint, adjudication of events, or handling of missing data, on a review of the pooled event rate, pooled adherence rates and pooled missing data while remaining blinded to differences by allocated treatment and to the direction of any treatment

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effect.[52-55] Primary and secondary analyses will adhere to an intention-to-treat basis using generalised linear models (binary or normal). Intervention effect will be presented as relative risk or mean difference, as appropriate, with 95% confidence intervals. Primary analyses will be unadjusted. Numbers needed to treat to prevent one adverse outcome will be calculated. Where there are differences in baseline characteristics between the two treatment groups that might be associated with outcomes, secondary analyses of the primary outcome will be carried out using multiple (log-binomial) regression. Reporting will follow CONSORT[56] and TRIPOD[57] guidelines.

There is only one primary outcome. Secondary outcomes include each of the ten individual components of the primary composite outcome (Table 1). For the secondary outcomes, no formal adjustments for multiplicity are planned. Because the secondary outcomes are interrelated and potentially causally attributable to hypoxic birth injury, we will follow the advice outlined by Schulz and Grimes[58] and interpret the pattern and consistency of findings across related outcomes, rather than focusing on any single, statistically significant result. Subgroup analyses will be performed by testing for interactions and findings will be reported as exploratory. Results of other endpoint, subgroup and sensitivity analyses will be interpreted in proper context and with due consideration of the risk of Type I error. Interpretation of statistical evidence will also consider the recommendations of Pocock *et al*.[59, 60]

Safety of sildenafil citrate: In our systematic review[15] of the efficacy and safety of phosphodiesterase inhibitors (sildenafil citrate or tadalafil) in 10 RCTs in 1090 women in pregnancy, we found that use of phosphodiesterase inhibitors in term labour was not associated with an increase in maternal side effects, including dizziness, flushing, dyspepsia, gastritis, palpitations, arthralgia, dyspnea, epistaxis, diarrhoea, tremor, headache, myalgia, paraesthesia, oedema, visual changes, vaginal itch, nausea and vomiting, intrapartum antiemetic use, post-partum haemorrhage of ≤1500 mL, anaemia, bronchitis, skin rash , intrapartum pyrexia, or placental abruption. Use of phosphodiesterase inhibitors in labour may have been associated with a small increase in vaginal birth (RR 1.24, 95% CI 1.00–1.55; p=0.05) and a statistically significant reduction in risk of operative birth

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for intrapartum fetal compromise (RR 0.58, 95% CI 0.38–0.88; p=0.01). Use of sildenafil in labour was not associated with increased risk of perinatal death (RR 0.89, 95% CI 0.56–1.43; p=0.64), nor of maternal admissions to intensive care and no maternal deaths were reported.

Chronic use of phosphodiesterase inhibitors for the treatment of severe fetal growth restriction, as in the STRIDER trials,[61] [62] or treatment of pre-eclampsia[16, 63, 64] was associated with a statistically significant increase in the risks of flushing (RR 6.83, 95% CI 1.49–31.23; p=0.01) and nasal bleeding (RR 10.53, 95% CI 1.36–81.3; p=0.02); an increase in risk of persistent pulmonary hypertension of the newborn (RR 2.52, 95% CI 1.00–6.32; p=0.05) and non-statistically significant increase in headaches (RR 1.41, 95% CI 0.97–2.05; p = 0.08) and flushing (RR 2.59, 95% CI 0.69–9.90; p=0.16).[15]

The international STRIDER RCTs used daily maternal Sildenafil doses of 75 mg in pregnant women with severe fetal growth restriction between 20 and 30 weeks gestation for up to 10 weeks, i.e. cumulative doses of up to 5,250 mg.[61] [62] In 2019, the Dutch STRIDER trial was stopped on the advice of the Data Safety Monitoring Board due to an increase in persistent pulmonary hypertension of the newborn with a non-significant increase in neonatal deaths in the sildenafil citrate group.[65] Persistent pulmonary hypertension of the newborn occurred in 16 neonates (18.8%) in the sildenafil citrate group vs. 4 neonates (5.1%) in the placebo group (relative risk, 3.67; 95% CI, 1.28-10.51; P = 0.008). A subsequent meta-analysis of 329 participating women in all available trials showed no difference in neonatal deaths.[66] However it was recommended that sildenafil citrate not be prescribed outside of clinical trials.[67] The indication and cumulative dosage of sildenafil citrate in the iSEARCH trial are very different from the STRIDER trials as we will only use a maximum 150mg in women at term, which is about thirty five times lower. Persistent pulmonary hypertension of the newborn will be monitored as one of ten components of the primary composite endpoint by the independent data and safety monitoring board, as outlined below.

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Safety of sildenafil during breastfeeding: Limited data indicate that sildenafil citrate and its active metabolite in breastmilk are poorly excreted into breastmilk. Amounts ingested by the infant are far below doses given to treat infants and would not be expected to cause any adverse effects in breastfed infants.[68] Women taking sildenafil citrate for the treatment of pulmonary hypertension in the UK are advised to continue breastfeeding because sildenafil citrate only passes into breast milk in tiny amounts, is unlikely to cause any side effects in the baby and breastfeeding will benefit both mother and baby.[69] We will monitor concentrations of sildenafil citrate in breast milk and any potentially related adverse events in a subset of women in the trial.

Role of study sponsor and funders: The University of Sydney, as sponsor of iSEARCH, the University of Queensland as administering organisation and the Medical Research Future Fund as funder of iSEARCH have had no role in study design, collection or management of data. Both will also have no role in analysis or interpretation of data, writing of manuscripts or decisions to publish.

The iSEARCH Trial Management Committee: The TMC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g., Human Research Ethics committees). It will consider recommendations from the Independent Data Safety and Monitoring Committee (IDSMC) about whether to continue the study as planned, modify, or stop, based on interim analyses or other information. The TMC will consist of all Chief Investigators.

The iSEARCH Trial Coordinating Centre is the NHMRC Clinical Trials Centre (CTC). It will support the TMC in the day-to-day conduct of the trial, and study processes, including data management, ensuring compliance with regulatory requirements and confidentiality of data collection, liaising with ethics committees, biostatistical team, IDSMC, and answering queries from participating sites including the receipt and timely management of reports of Adverse Events. A list of participating sites is available in the trial registration entry at the Australian New Zealand Clinical Trials Registry (ACTRN12615000319572).

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Compliance: Participant medication compliance will be monitored and documented in the medical records and electronic Case Record Forms (eCRFs), which will be held on a secure server, ensuring confidentiality. The iSEARCH trial may be subject to audit or inspection by representatives of the NHMRC CTC or representatives of independent regulatory bodies (e.g., the Therapeutic Goods Administration).

Unblinding: Unblinding is not generally necessary for the management of a patient with an adverse event and, as it may have an impact on the study's validity, is discouraged. The need for unblinding should be very uncommon as the study intervention is rarely associated with severe side effects and it will not delay or prevent standard management of the participant. However, if required, it should be done centrally after discussion with the Study Chair and NHMRC CTC representative using the emergency unblinding number in the Study Manual.

The Independent Data and Safety Monitoring Committee: The IDSMC will review interim data on the primary outcome, specified adverse events and other evidence after 50% of recruitment or whenever they deem appropriate, as recommended by Peto, Pocock and others.[70-72] There will be no adjustment to alpha for interim analyses.

Interim analyses of the primary composite outcome: The IDSMC will advise the TMC if in their view there is proof beyond reasonable doubt of net benefit or harm for the primary composite endpoint, for example employing a commonly used formal threshold of P<0.001 for nominal significance, as recommended by Geller and Pocock.[72]

Interim analyses of mortality: The IDSMC will advise the TMC if in their view 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,[70, 71] which would be needed to justify recommending early stopping.

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Limitations: The postulated 35% reduction in the relative risk of its primary composite endpoint is nearly twice as large as the 20% relative reduction in a ten-component composite outcome seen in the ARRIVE trial, which enrolled 6,106 women.[20] This putative 35% relative risk reduction in iSEARCH may therefore reflect 'optimism bias'[73-75] and is an important limitation, dictated by financial constraints which precluded a larger study.

The ten components of the primary composite endpoint (Table 1) are all potentially related to intrapartum hypoxia.[20] [76] However, a reduction in overall incidence of this endpoint could not be interpreted as indicating reductions in key individual components such as intrapartum stillbirth, neonatal mortality, Apgar score <4 at 5 minutes, neonatal encephalopathy or seizures, because the rates of these events vary between 0.1% and 0.5%, at which iSEARCH is greatly underpowered to detect any differences. The three individual components of the composite endpoint for which the chances of showing a reduction in incidence are greatest are (i) admission to neonatal unit for >48 h, (ii) respiratory support for >4 h and (iii) cord pH <7. Their estimated event rates are 3.6%, 4.3% and 2.2% respectively, (Table 1) for which our sample of 3200 gives ~80% power to show (albeit highly optimistic) reductions in relative risk of 50-60%. However, unlike some of the other components of the composite outcome (e.g., neonatal encephalopathy), these three components are significantly less likely to impact longer term health outcomes.

Regulatory compliance: Conduct of the *iSEARCH* trial will be informed by the International Conference on Harmonization Guidelines for Good Clinical Practice[77, 78] and World Health Organisation guidance.[38] 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 was registered with the Australian and New Zealand Clinical Trial Registry and ethical and regulatory approvals were obtained before it began. Changes and amendments to the protocol can only be made by the TMC. Approval by the Institutional Human Research Ethics Committee is required prior to the implementation of any amendments.

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Ethics and dissemination

The Australian iSEARCH RCT has been approved by Hunter New England Ethic Committee (Ref Number 2020/ETH02791). Each component trial within the iSEARCH Collaboration will be approved by relevant local, regional or national Human Research Ethics Committee. We plan to disseminate the results of this trial via presentations at clinical, academic and scientific meetings as well as peer reviewed journals. We will adhere to all relevant reporting guidelines.

Authors' contributions

SK wrote the first draft and made extensive revisions incorporating suggestions by the other authors. Other co-authors (WTM, BWM, VF, HL, NB, SW, JH, ALS, EC, ROC) collaboratively provided detailed comments regarding study design and choice of appropriate study outcomes. ROC provided advice and suggestion for the proposed statistical analysis plan. SK and WTM contributed equally to the manuscript. All authors and collaborators reviewed and approved the final version before submission.

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Competing interest statement

None of the authors have any competing interests to declare.

Data sharing:

Individual de-identified participant data for findings reported in the iSEARCH Trial will be available for 5 years after publication. Researchers wishing to gain access to data should provide a methodologically sound proposal to isearch.study@sydney.edu.au, which will be reviewed by the Trial Management Committee.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13, 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10, 11

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9, 10, 14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14, 15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9, 10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13, 15

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9, 10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The iSEARCH Randomised Controlled Trial Protocol – A pragmatic Australian Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia.

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The iSEARCH Randomised Controlled Trial Protocol – A pragmatic Australian Phase 3 clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia.

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ABSTRACT

Introduction

We showed in a Phase 2 RCT that oral sildenafil citrate in term labour halved operative birth for fetal distress. We outline the protocol for a Phase 3 RCT (iSEARCH) of 3200 women in Australia to assess if sildenafil citrate reduces adverse perinatal outcomes related to intrapartum hypoxia.

Methods and analysis

iSEARCH will enrol 3200 Australian women in term labour to determine whether up to three 50 mg oral doses of sildenafil citrate versus placebo reduce the relative risk of a primary composite endpoint of ten perinatal outcomes potentially related to intrapartum hypoxia by 35% (from 7% to 4.55%). Secondary aims are to evaluate reductions in the relative risk of emergency caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%) and in healthcare costs. To detect a 35% reduction in the primary outcome for an alpha of 0.05 and power of 80% with 10% dropout in each arm requires 3200 women (1600 in each arm). This sample size will also yield >90% power to detect a 25% reduction for the secondary outcome of any operative birth (caesarean section or instrumental vaginal birth) for fetal distress.

Ethics and dissemination

Ethical approval for the iSEARCH RCT was granted by the Hunter New England Human Research Ethics Committee (Ref No: 2020/ETH02791). Results will be disseminated through websites, peer-reviewed publications, scientific meetings and social media, news outlets, television and radio.

Trial Registration

iSEARCH is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000231842) (registered 4 March 2021) and the Therapeutics Goods Administration of Australia and the first participant was randomised on 6 September 2021.

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ARTICLE SUMMARY *(198 WORDS)*

Strengths and limitations of this project

- ► iSEARCH is a Phase 3 RCT of 3200 women in term labour to determine if maternal oral sildenafil citrate reduces adverse neonatal outcomes and operative birth rates potentially secondary to intrapartum hypoxia.

- ► Childhood neurodevelopmental outcomes at 2 years will be assessed and health economic analysis will be undertaken to determine cost effectiveness to the healthcare system.

- ► iSEARCH and other highly streamlined RCTs worldwide will contribute to individual participant data prospective meta-analyses (IPD PMA) of similar trials.

- ► The sample of 3,200 women only has ~80% power to show a 35% reduction in the relative risk of the primary endpoint rather than a more moderate and realistic, yet still clinically relevant 20% risk reduction, which would require more than 10,000 women.

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INTRODUCTION

Fetal distress in labour usually reflects pre-existing placental impairment[1, 2] which reduces the capacity of the fetus to cope with the stress of uterine contractions.[3] In many term pregnancies, uterine blood flow falls by 60% during contractions,[4] provoking fetal distress. Fetal decompensation occurs[5] if there is insufficient time for placental reperfusion between contractions.[1]

Suspected fetal distress due to hypoxia in labour is implicated in up to 23% of emergency caesarean births in Australia.[6] Hypoxic fetal injury can lead to intrapartum stillbirth and severe neonatal morbidity including neonatal encephalopathy and cerebral palsy.[7] [8] [9] Intrapartum hypoxia-ischemia is associated with 1 in 3 cases of neonatal encephalopathy in high-income countries with low perinatal mortality rates (PMRs) and almost 60% of cases in low-or middle-income countries with moderate or high PMRs.[10] Other than emergency operative birth [caesarean section or instrumental (forceps or vacuum) vaginal birth], options are limited.

Sildenafil Citrate is a phosphodiesterase-5 inhibitor that enhances the bioavailability of Nitric Oxide by inhibiting cyclic guanosine monophosphate degradation. Increased tissue Nitric Oxide levels improve vasodilatation and reduce vascular dysfunction secondary to vasoconstrictors and antiangiogenic factors.[11, 12] Sildenafil citrate preferentially dilates pelvic blood vessels and increases utero-placental blood flow.[13, 14] Our systematic review of 10 randomised controlled trials (RCTs) of 1,090 women found that phosphodiesterase-5 inhibitor use in pregnancy was associated with a 42% relative reduction of operative birth for intrapartum fetal distress [Relative Risk (RR) 0.58, 95% CI 0.38-0.88] .[15] This effect was driven by two trials[16], **[17]** which reported rates of operative birth for this indication.

Our Phase 2 RCT**[17]** tested whether, compared to placebo, sildenafil citrate lowered rates of emergency operative birth for suspected fetal distress in 300 women in term labour. Sildenafil reduced (i) the relative risk (RR) of operative birth for fetal distress by 51% [(RR 0.49, 95% CI 0.33 – 0.73), p=0.0004; Number Needed to Treat for Benefit = 5 (3-11)] and (ii) rates of pathological fetal heart rate

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(FHR) patterns (15% vs. 32%; RR 0.48, 95% CI 0.31 – 0.75, p=0.0009) by 52%. Concentrations of sildenafil citrate or its metabolite were only 3.6% of maternal levels, consistent with low rates of transplacental transfer to the fetus. Use of sildenafil citrate also attenuated the normal intrapartum decline in placental growth factor (PlGF) levels suggesting that it had a role in preserving placental function in labour.[18] This trial, however, lacked power to show a statistically significant improvement in neonatal outcomes to support the rationale for sildenafil citrate treatment in labour. A subsequent cost effectiveness analysis concluded that oral intrapartum sildenafil citrate may be cost effective compared with standard care, but that its effects on neonatal outcomes should be evaluated in large RCTs.[19]

The Australian iSEARCH (can **i**ntrapartum **S**ild**E**nafil safely **A**vert the **R**isks of **C**ontraction-induced **H**ypoxia in labour?) trial began on 6th September 2021. It is the world's first Phase 3 RCT to re-purpose sildenafil citrate by evaluating whether, compared to placebo, it improves perinatal outcome, by reducing the risk of intrapartum fetal compromise. Its primary endpoint is a composite of ten adverse fetal or neonatal outcomes (Table 1) very similar to that used in other large RCTs like the ARRIVE trial in term pregnancies.[20] Its target sample size of 3,200 women yields >80% power to detect a reduction of 35% in the relative risk of its primary endpoint (from 7% to 4.55%, equivalent to a pooled event rate of 5.78%). It also has 90% power to detect a 25% reduction in the secondary outcome of emergency operative birth for fetal distress, from 20% to 15%. It is funded by the Australian Medical Research Future Fund and will run until August 2024.

The next, critically important step will be to undertake large-scale randomised placebo-controlled studies of oral intrapartum sildenafil addressing the primary outcome of perinatal death, adequately powered in high, low-and middle-income countries. Secondary outcomes would include low Apgar score; emergency operative birth by Caesarean Section, vacuum or forceps; maternal infant separation due to nursery admission; neonatal encephalopathy; severe maternal morbidity (including post-partum haemorrhage) and maternal death.

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Another equally important step in evaluating the impact of intrapartum sildenafil citrate will be to establish an individual participant data prospective meta-analysis (IPD PMA) of iSEARCH trials which may provide evidence for a smaller but still clinically meaningful reduction in adverse perinatal outcomes.[21, 22] It is essential that all trials contributing to an IPD PMA achieve close to 100% ascertainment of their primary outcome data, by streamlining data collection to minimise the rate of missing values.[23] This global collaborative approach will provide randomised evidence addressing realistically moderate, yet clinically important reductions in adverse perinatal outcome, and whether sildenafil citrate is similarly effective in subgroups of women in different healthcare settings. If routine intrapartum sildenafil citrate safely reduces adverse birth outcomes and/or emergency operative birth and their long-term sequelae,[24] it could provide an important option for women attempting vaginal birth worldwide.[6]

METHODS AND ANALYSIS:

Primary Research Question

Does maternal oral sildenafil citrate in labour, compared with placebo, reduce the primary composite endpoint of ten adverse neonatal outcomes? (Table 1)

Secondary Research Questions

(a) Does maternal oral sildenafil citrate in labour reduce the rate of the secondary outcomes of:

a. Emergency operative birth for fetal distress
b. Intrapartum stillbirth
c. Death of baby before discharge from hospital
d. Apgar score <4 at 5 minutes
e. Cord artery pH <7.0
f. Neonatal encephalopathy
g. Neonatal seizures
h. Neonatal respiratory support >4h
i. Neonatal unit (Special Care or Intensive Care) admission lasting >48 h
j. Persistent pulmonary hypertension of the newborn
k. Meconium aspiration syndrome

(b) Is maternal oral sildenafil citrate in labour more cost effective than placebo?

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Table 1: Primary composite outcome

Components of composite primary endpoint	Rate	Association with long term adverse outcome
Intrapartum stillbirth [25]	0.1%*	-
28-day neonatal mortality	0.24%	-
Apgar score <4 at 5 minutes	0.5%	↑ risk of cerebral palsy[26]
Umbilical Cord artery pH <7.0	2.2%¥	↑ risk of HIE[27]
Neonatal encephalopathy Sarnat Grade 2 or 3[28]	0.5%	↑ risk of death or disability[29]
Neonatal seizures§[28]	0.25%	↑ risk of death or disability[29]
Neonatal respiratory support for >4 h	3.6%	↑ risk of cerebral palsy[30]
Neonatal unit admission for >48 h	4.3%	↑ asthma after term respiratory morbidity[31]
Persistent pulmonary hypertension[28]	0.04%	↑ risk of death or disability[32]
Meconium aspiration[28]	0.75%	↑ risk of death or disability[33]
Total (corrected for overlap)	7.0%	

**based on data from Grobman et al [20]; ¥based on data from Yeh et al [27]*

§although seizures include non-encephalopathic causes like stroke or metabolic disorders, in a randomised trial, those causes not influenced by Sildenafil will tend to be evenly balanced between study arms and therefore tend not to bias the comparison. In this pragmatic trial, seizures, persistent pulmonary hypertension and meconium aspiration are all defined using local protocols.

Study design: This is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind multicentre superiority trial of sildenafil citrate vs. placebo for women in labour at term ($\geq 37^{+0}$ weeks).

Patient and public involvement: We involved clinician and consumer groups when designing this trial through the use of electronic media and face to face interviews. Of >400 women and clinicians in 68 sites in Australia and overseas, >90% endorsed iSEARCH and, if its hypotheses were confirmed, >85% would want sildenafil citrate to become an option in routine care.

Aim: This study aims to test the hypothesis that up to 3 doses of oral 50 mg sildenafil citrate (vs. placebo) are safe and will improve perinatal and maternal outcomes related to intrapartum hypoxia.

Primary objective:

To evaluate whether, compared with placebo, sildenafil citrate reduces the relative risk of the composite perinatal endpoint by 35%, from 7% to 4.55%. The composite endpoint comprises the ten components shown in Table 1.

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Secondary objectives:

1. To evaluate whether sildenafil citrate results in a relative risk reduction of Caesarean section or instrumental vaginal birth for fetal distress by 25% (from 20% to 15%).

2. To evaluate whether sildenafil citrate results in a reduction of the relative risk of each individual component of the composite primary outcome, namely:

    a. Intrapartum Stillbirth
    b. Death of baby before hospital discharge
    c. Apgar Score <4 at 5 minutes
    d. Cord Artery pH <7.0
    e. Neonatal Encephalopathy
    f. Neonatal seizures
    g. Neonatal respiratory support >4h
    h. Neonatal unit (Special Care or Intensive Care) admission lasting >48h
    i. Persistent pulmonary hypertension of the newborn
    j. Meconium aspiration

3. To evaluate whether Sildenafil is more cost-effective than placebo.

Study Period: Recruitment to iSEARCH began on 7th September 2021 and is expected to end by 31 August 2024.

Sample Size: The incidence of the composite adverse outcome is estimated at 7% based on data from several of the participating hospitals, the ARRIVE RCT [20] and the Australian and New Zealand Neonatal Network.[34] To detect a 35% reduction from 7% to 4.55% for an alpha of 0.05 and >80% power with 10% drop out in each arm, needs about 3,200 women. This sample size also yields >90% power to detect a 25% reduction for the secondary outcome of caesarean section or instrumental vaginal birth for fetal distress.

Study population

Inclusion criteria:

1. Women with singleton or dichorionic twin pregnancies, planning vaginal birth at term (≥37^{+0} weeks gestation).

2. Age ≥18 years.

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3. Willing and able to comply with all study requirements.
4. Signed, written informed consent.

Exclusion criteria:

1. A woman should not be enrolled if the responsible clinician or the woman are, for any medical or non-medical reasons, reasonably certain that sildenafil citrate would be inappropriate for her in comparison with no treatment or some other treatment that could be offered outside the trial.[35]
2. Triplets or higher order multiple births, which are generally delivered electively before term.
3. Contraindications to the investigational product (sildenafil citrate).
4. Women who are taking any type of nitrate drug therapy or who utilize 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), other medications used to treat pulmonary arterial hypertension such as riociguat, and other phosphodiesterase type 5 inhibitors, due to the risk of potentially life-threatening hypotension.[36]
5. Severe hepatic or renal impairment.[36]

Screening, registration and randomisation: All women attending antenatal clinics in participating hospitals from $\geq 34^{+0}$ weeks will be screened for eligibility by study midwives. Women who consent to participate will be registered in an online trial registration database. Once registered, each woman is assigned a unique study number and receives routine care until spontaneous labour or induction of labour, when randomisation is undertaken. Individuals may only be registered and randomised once. Randomisation is undertaken after the responsible midwife or obstetrician has again confirmed that the woman is eligible. If an eligible woman presents for the first time in labour, screening, registration and randomisation are done together. Once registration and randomisation are completed, the

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participant is assigned a treatment arm. Randomisation is web-based, using a computer-generated concealed allocation sequence, stratified by study site.

At registration, each woman will be invited to consent to allow data linkage with her child or children's educational outcomes in the National Assessment Program – Literacy and Numeracy (NAPLAN) [37] for data to be extracted from Medicare Benefits Schedule and Pharmaceutical Benefits Schemes claims records for herself and her infant and from the Australian cerebral palsy register. Such consent may be withdrawn at any time and without a reason. Each woman will also be invited to give consent to participate in childhood neurodevelopmental follow-up at 2-3 years corrected age. If she consents to this, contact details will be recorded and follow-up assessment will be performed as described below. Any decline for follow-up will be properly explored to ensure that withdrawal is not automatically interpreted to mean complete removal from the study as this may have possible implications for the reliability of trial findings. It may also be disadvantageous to these women because they could miss out on some aspects of the RCT that may matter to them (such as being informed about progress and results of the study).[38]

Study Treatments: The study intervention is oral sildenafil citrate. The control intervention is placebo. Study treatment only begins after transfer to the labour ward either in spontaneous labour or for induction of labour (artificial rupture of membranes +/- oxytocin). Women are given the first dose by the attending midwife in the labour ward. Women receive sildenafil citrate 50mg or identical placebo orally every 8 hours to a maximum of three doses, from identical matched treatment packs supplied by the trial pharmacy.

Management of Labour and Puerperium: Intrapartum FHR monitoring will be performed in all women. Where possible, umbilical artery cord pH will be measured in all women after birth. Classification of FHR abnormalities is based on the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines. In a subset of women, 20ml of blood will be collected for assay of soluble Fms-like tyrosine kinase-1 (sFlt-1) and Placental Growth Factor (PlGF) levels. Where

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possible, these women will also have an ultrasound scan performed to assess the fetoplacental circulation and liquor volume before and after treatment. The ultrasound data and maternal sFlt-1 and PlGF levels will allow post-hoc subgroup analysis to identify cohorts at risk of fetal distress that might derive greater benefit from sildenafil citrate treatment. Otherwise, intrapartum management will be in accordance with local hospital guidelines.

To detect possible persistent pulmonary hypertension of the newborn, all infants will also receive routine oxygen saturation screening to detect hypoxemia, generally 24-48 hours after birth but, if necessary, four hours after birth. Infants with oxygen saturations of >95% are very unlikely to have major congenital heart or significant pulmonary disease, including persistent pulmonary hypertension of the newborn.[39] Infants with oxygen saturations ≤95% will receive further assessment by the paediatric team which may include echocardiography.

Trial Outcomes: In-hospital maternal and neonatal outcome events occurring from randomisation to discharge home will be collected from medical records into electronic Case Report Forms (eCRFs). Assessments of outcome will be blinded to treatment allocation. All primary outcome data will be routinely available before discharge and collected electronically. There are no formal study assessments visits. Research midwives will contact women 30 days after discharge to ascertain further relevant issues. Childhood follow up will be conducted by linkage with educational databases and cerebral palsy registers and using parent report questionnaires.[40-42]

Data Analysis: We will adopt recommended approaches[43, 44] to the analysis and reporting of composite endpoints, as in previous multi-centre perinatal RCTs.[45-50] A detailed Statistical Analysis Plan and health economic protocol will be published before unblinding and data analysis begin.[51] The Trial Management Committee (TMC) will base any modifications to the original objectives, such as a change in the components of the composite endpoint, adjudication of events, or handling of missing data, on a review of the pooled event rate, pooled adherence rates and pooled missing data while remaining blinded to differences by allocated treatment and to the direction of any treatment

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effect.[52-55] Primary and secondary analyses will adhere to an intention-to-treat basis using generalised linear models (binary or normal). Intervention effect will be presented as relative risk or mean difference, as appropriate, with 95% confidence intervals. Primary analyses will be unadjusted. Numbers needed to treat to prevent one adverse outcome will be calculated. Where there are differences in baseline characteristics between the two treatment groups that might be associated with outcomes, secondary analyses of the primary outcome will be carried out using multiple (log-binomial) regression. Reporting will follow CONSORT[56] and TRIPOD[57] guidelines.

There is only one primary outcome. Secondary outcomes include each of the ten individual components of the primary composite outcome (Table 1). For the secondary outcomes, no formal adjustments for multiplicity are planned. Because the secondary outcomes are interrelated and potentially causally attributable to hypoxic birth injury, we will follow the advice outlined by Schulz and Grimes[58] and interpret the pattern and consistency of findings across related outcomes, rather than focusing on any single, statistically significant result. Subgroup analyses will be performed by testing for interactions and findings will be reported as exploratory. Results of other endpoint, subgroup and sensitivity analyses will be interpreted in proper context and with due consideration of the risk of Type I error. Interpretation of statistical evidence will also consider the recommendations of Pocock *et al*.[59, 60]

Safety of sildenafil citrate: In our systematic review[15] of the efficacy and safety of phosphodiesterase inhibitors (sildenafil citrate or tadalafil) in 10 RCTs in 1090 women in pregnancy, we found that use of phosphodiesterase inhibitors in term labour was not associated with an increase in maternal side effects, including dizziness, flushing, dyspepsia, gastritis, palpitations, arthralgia, dyspnea, epistaxis, diarrhoea, tremor, headache, myalgia, paraesthesia, oedema, visual changes, vaginal itch, nausea and vomiting, intrapartum antiemetic use, post-partum haemorrhage of ≤1500 mL, anaemia, bronchitis, skin rash , intrapartum pyrexia, or placental abruption. Use of phosphodiesterase inhibitors in labour may have been associated with a small increase in vaginal birth (RR 1.24, 95% CI 1.00–1.55; p=0.05) and a statistically significant reduction in risk of operative birth

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for intrapartum fetal compromise (RR 0.58, 95% CI 0.38–0.88; p=0.01). Use of sildenafil in labour was not associated with increased risk of perinatal death (RR 0.89, 95% CI 0.56–1.43; p=0.64), nor of maternal admissions to intensive care and no maternal deaths were reported.

Chronic use of phosphodiesterase inhibitors for the treatment of severe fetal growth restriction, as in the STRIDER trials,[61] [62] or treatment of pre-eclampsia[16, 63, 64] was associated with a statistically significant increase in the risks of flushing (RR 6.83, 95% CI 1.49–31.23; p=0.01) and nasal bleeding (RR 10.53, 95% CI 1.36–81.3; p=0.02); an increase in risk of persistent pulmonary hypertension of the newborn (RR 2.52, 95% CI 1.00–6.32; p=0.05) and non-statistically significant increase in headaches (RR 1.41, 95% CI 0.97–2.05; p = 0.08) and flushing (RR 2.59, 95% CI 0.69–9.90; p=0.16).[15]

The international STRIDER RCTs used daily maternal Sildenafil doses of 75 mg in pregnant women with severe fetal growth restriction between 20 and 30 weeks gestation for up to 10 weeks, i.e. cumulative doses of up to 5,250 mg.[61] [62] In 2019, the Dutch STRIDER trial was stopped on the advice of the Data Safety Monitoring Board due to an increase in persistent pulmonary hypertension of the newborn with a non-significant increase in neonatal deaths in the sildenafil citrate group.[65] Persistent pulmonary hypertension of the newborn occurred in 16 neonates (18.8%) in the sildenafil citrate group vs. 4 neonates (5.1%) in the placebo group (relative risk, 3.67; 95% CI, 1.28-10.51; P = 0.008). A subsequent meta-analysis of 329 participating women in all available trials showed no difference in neonatal deaths.[66] However it was recommended that sildenafil citrate not be prescribed outside of clinical trials.[67] The indication and cumulative dosage of sildenafil citrate in the iSEARCH trial are very different from the STRIDER trials as we will only use a maximum 150mg in women at term, which is about thirty five times lower. Persistent pulmonary hypertension of the newborn will be monitored as one of ten components of the primary composite endpoint by the independent data and safety monitoring board, as outlined below.

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Safety of sildenafil during breastfeeding: Limited data indicate that sildenafil citrate and its active metabolite in breastmilk are poorly excreted into breastmilk. Amounts ingested by the infant are far below doses given to treat infants and would not be expected to cause any adverse effects in breastfed infants.[68] Women taking sildenafil citrate for the treatment of pulmonary hypertension in the UK are advised to continue breastfeeding because sildenafil citrate only passes into breast milk in tiny amounts, is unlikely to cause any side effects in the baby and breastfeeding will benefit both mother and baby.[69] We will monitor concentrations of sildenafil citrate in breast milk and any potentially related adverse events in a subset of women in the trial.

Role of study sponsor and funders: The University of Sydney, as sponsor of iSEARCH, the University of Queensland as administering organisation and the Medical Research Future Fund as funder of iSEARCH have had no role in study design, collection or management of data. Both will also have no role in analysis or interpretation of data, writing of manuscripts or decisions to publish.

The iSEARCH Trial Management Committee: The TMC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g., Human Research Ethics committees). It will consider recommendations from the Independent Data Safety and Monitoring Committee (IDSMC) about whether to continue the study as planned, modify, or stop, based on interim analyses or other information. The TMC will consist of all Chief Investigators.

The iSEARCH Trial Coordinating Centre is the NHMRC Clinical Trials Centre (CTC). It will support the TMC in the day-to-day conduct of the trial, and study processes, including data management, ensuring compliance with regulatory requirements and confidentiality of data collection, liaising with ethics committees, biostatistical team, IDSMC, and answering queries from participating sites including the receipt and timely management of reports of Adverse Events. A list of participating sites is available in the trial registration entry at the Australian New Zealand Clinical Trials Registry (ACTRN12615000319572).

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Compliance: Participant medication compliance will be monitored and documented in the medical records and electronic Case Record Forms (eCRFs), which will be held on a secure server, ensuring confidentiality. The iSEARCH trial may be subject to audit or inspection by representatives of the NHMRC CTC or representatives of independent regulatory bodies (e.g., the Therapeutic Goods Administration).

Unblinding: Unblinding is not generally necessary for the management of a patient with an adverse event and, as it may have an impact on the study's validity, is discouraged. The need for unblinding should be very uncommon as the study intervention is rarely associated with severe side effects and it will not delay or prevent standard management of the participant. However, if required, it should be done centrally after discussion with the Study Chair and NHMRC CTC representative using the emergency unblinding number in the Study Manual.

The Independent Data and Safety Monitoring Committee: The IDSMC will review interim data on the primary outcome, specified adverse events and other evidence after 50% of recruitment or whenever they deem appropriate, as recommended by Peto, Pocock and others.[70-72] There will be no adjustment to alpha for interim analyses.

Interim analyses of the primary composite outcome: The IDSMC will advise the TMC if in their view there is proof beyond reasonable doubt of net benefit or harm for the primary composite endpoint, for example employing a commonly used formal threshold of P<0.001 for nominal significance, as recommended by Geller and Pocock.[72]

Interim analyses of mortality: The IDSMC will advise the TMC if in their view 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,[70, 71] which would be needed to justify recommending early stopping.

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Limitations: The postulated 35% reduction in the relative risk of its primary composite endpoint is nearly twice as large as the 20% relative reduction in a ten-component composite outcome seen in the ARRIVE trial, which enrolled 6,106 women.[20] This putative 35% relative risk reduction in iSEARCH may therefore reflect 'optimism bias'[73-75] and is an important limitation, dictated by financial constraints which precluded a larger study.

The ten components of the primary composite endpoint (Table 1) are all potentially related to intrapartum hypoxia.[20] [76] However, a reduction in overall incidence of this endpoint could not be interpreted as indicating reductions in key individual components such as intrapartum stillbirth, neonatal mortality, Apgar score <4 at 5 minutes, neonatal encephalopathy or seizures, because the rates of these events vary between 0.1% and 0.5%, at which iSEARCH is greatly underpowered to detect any differences. The three individual components of the composite endpoint for which the chances of showing a reduction in incidence are greatest are (i) admission to neonatal unit for >48 h, (ii) respiratory support for >4 h and (iii) cord pH <7. Their estimated event rates are 3.6%, 4.3% and 2.2% respectively, (Table 1) for which our sample of 3200 gives ~80% power to show (albeit highly optimistic) reductions in relative risk of 50-60%. However, unlike some of the other components of the composite outcome (e.g., neonatal encephalopathy), these three components are significantly less likely to impact longer term health outcomes.

Regulatory compliance: Conduct of the *iSEARCH* trial will be informed by the International Conference on Harmonization Guidelines for Good Clinical Practice[77, 78] and World Health Organisation guidance.[38] 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 was registered with the Australian and New Zealand Clinical Trial Registry and ethical and regulatory approvals were obtained before it began. Changes and amendments to the protocol can only be made by the TMC. Approval by the Institutional Human Research Ethics Committee is required prior to the implementation of any amendments.

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Ethics and dissemination

The Australian iSEARCH RCT has been approved by Hunter New England Ethic Committee (Ref Number 2020/ETH02791). Each component trial within the iSEARCH Collaboration will be approved by relevant local, regional or national Human Research Ethics Committee. We plan to disseminate the results of this trial via presentations at clinical, academic and scientific meetings as well as peer reviewed journals. We will adhere to all relevant reporting guidelines.

Authors' contributions

SK wrote the first draft and made extensive revisions incorporating suggestions by the other authors. Other co-authors (WTM, BWM, VF, HL, NB, SW, JH, ALS, EC, ROC) collaboratively provided detailed comments regarding study design and choice of appropriate study outcomes. ROC provided advice and suggestion for the proposed statistical analysis plan. SK and WTM contributed equally to the manuscript. All authors and collaborators reviewed and approved the final version before submission.

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Competing interest statement

None of the authors have any competing interests to declare.

Data sharing:

Individual de-identified participant data for findings reported in the iSEARCH Trial will be available for 5 years after publication. Researchers wishing to gain access to data should provide a methodologically sound proposal to isearch.study@sydney.edu.au, which will be reviewed by the Trial Management Committee.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13, 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10, 11

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9, 10, 14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14, 15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9, 10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13, 15

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9, 10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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