BMJ Open

The iSEARCH randomised controlled trial protocol: a pragmatic Australian phase III clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia

Sailesh Kumar ,[1] William Tarnow-Mordi,[2] Ben W Mol ,[3] Vicki Flenady,[4] Helen Liley ,[5,6] Nadia Badawi,[7] Susan P Walker ,[8,9] Jonathan Hyett,[10] Lene Seidler,[2] Emily Callander,[11] R O'Connell[2]

To cite: Kumar S, Tarnow-Mordi W, Mol BW, *et al*. The iSEARCH randomised controlled trial protocol: a pragmatic Australian phase III clinical trial of intrapartum sildenafil citrate to improve outcomes potentially related to intrapartum hypoxia. *BMJ Open* 2024;**14**:e082943. doi:10.1136/bmjopen-2023-082943

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-082943).

SK and WT-M contributed equally.

Received 07 December 2023
Accepted 15 May 2024

Linked

► http://dx.doi.org/10.1136/bmjopen-2023-082945

Check for updates

For numbered affiliations see end of article.

Correspondence to
Professor Sailesh Kumar; sailesh.kumar@mater.uq.edu.au

ABSTRACT

Introduction We showed in a phase II randomised controlled trial (RCT) that oral sildenafil citrate in term labour halved operative birth for fetal distress. We outline the protocol for a phase III RCT (can *i*ntrapartum *Sild*E*n*afil safely *A*vert the *R*isks of *C*ontraction-induced *H*ypoxia? (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 end point of 10 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 number ACTRN12621000231842.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ iSEARCH (can *i*ntrapartum *Sild*E*n*afil safely *A*vert the *R*isks of *C*ontraction-induced *H*ypoxia?) is a phase III randomised controlled trial (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 of similar trials.

⇒ The sample of 3200 women only has ~80% power to show a 35% reduction in the relative risk of the primary end point rather than a more moderate and realistic, yet still clinically relevant 20% risk reduction, which would require >10 000 women.

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.[7–9] Intrapartum hypoxia-ischaemia is associated with one in three cases of neonatal encephalopathy in high-income countries with low perinatal mortality rates (PMRs) and almost 60% of cases in low-income 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 1090 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 to 0.88).[15] This effect was driven by two trials,[16 17] which reported rates of operative birth for this indication.

Our phase II RCT[17] tested whether, compared with placebo, sildenafil citrate lowered rates of emergency operative birth for suspected fetal distress in 300 women in term labour. Sildenafil reduced (i) the RR of operative birth for fetal distress by 51% ((RR 0.49, 95% CI 0.33 to 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 to 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 6 September 2021. It is the world's first phase III RCT to repurpose sildenafil citrate by evaluating whether, compared with placebo, it improves perinatal outcome, by reducing the risk of intrapartum fetal compromise. Its primary end point is a composite of 10 adverse fetal or neonatal outcomes (table 1) very similar to that used in other large RCTs like the ARRIVE (A Randomized Trial of Induction Versus Expectant management) trial in term pregnancies.[20] Its target sample size of 3200 women yields >80% power to detect a reduction of 35% in the RR of its primary end point (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.

Table 1 Primary composite outcome

Components of composite primary end point	Rate (%)	Association with long-term adverse outcome
Intrapartum stillbirth[70]	0.1*	–
28-day neonatal mortality	0.24	–
Apgar score <4 at 5 min	0.5	↑ Risk of cerebral palsy[71]
Umbilical cord artery pH <7.0	2.2†	↑ Risk of Hypoxic Ischaemic Encephalopathy (HIE)[72]
Neonatal encephalopathy Sarnat grade 2 or 3[73]	0.5	↑ Risk of death or disability[74]
Neonatal seizures‡[73]	0.25	↑ Risk of death or disability[74]
Neonatal respiratory support for >4 hours	3.6	↑ Risk of cerebral palsy[75]
Neonatal unit admission for >48 hours	4.3	↑ Asthma after term respiratory morbidity[76]
Persistent pulmonary hypertension[73]	0.04	↑ Risk of death or disability[77]
Meconium aspiration[73]	0.75	↑ Risk of death or disability[78]
Total (corrected for overlap)	7.0	

*Based on data from Grobman *et al.*[20]
†Based on data from Yeh *et al.*[72]
‡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.

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-income countries and low-income 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 postpartum haemorrhage) and maternal death.

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 end point of 10 adverse neonatal outcomes? (table 1).

Secondary research questions

1. Does maternal oral sildenafil citrate in labour reduce the rate of the secondary outcomes of:
   - emergency operative birth for fetal distress;
   - intrapartum stillbirth;
   - death of baby before discharge from hospital;
   - Apgar score <4 at 5 min;
   - cord artery pH <7.0;
   - neonatal encephalopathy;
   - neonatal seizures;
   - neonatal respiratory support >4 hours;
   - neonatal unit (special care or intensive care) admission lasting >48 hours;
   - persistent pulmonary hypertension of the newborn;
   - meconium aspiration syndrome.
2. Is maternal oral sildenafil citrate in labour more cost-effective than placebo?

Study design

This is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind multicentre superiority trial of sildenafil citrate versus 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 three 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 RR of the composite perinatal end point by 35%, from 7% to 4.55%. The composite end point comprises the 10 components shown in table 1.

Secondary objectives

1. To evaluate whether sildenafil citrate results in a RR 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 RR of each individual component of the composite primary outcome, namely:
   - intrapartum stillbirth;
   - death of baby before hospital discharge;
   - Apgar score <4 at 5 min;
   - cord artery pH <7.0;
   - neonatal encephalopathy;
   - neonatal seizures;
   - neonatal respiratory support >4 hours;
   - neonatal unit (special care or intensive care) admission lasting >48 hours;
   - persistent pulmonary hypertension of the newborn;
   - meconium aspiration.
3. To evaluate whether sildenafil is more cost-effective than placebo.

Study period

Recruitment to iSEARCH began on 7 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.[25] 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 3200 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.[26]
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 using short-acting nitrate-containing medica-

tions 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), or other medications used to treat pulmonary arterial hypertension such as riociguat and other phosphodiesterase-5 inhibitors, are at risk of potentially life-threatening hypotension.[27]

5. Severe hepatic or renal impairment.[27]

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 Programme—Literacy and Numeracy[28] 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).[29]

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 50 mg 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, 20 mL of blood will be collected for assay of soluble Fms-like tyrosine kinase-1 (sFlt-1) and 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 hypoxaemia, generally 24–48 hours after birth but, if necessary, 4 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.[30] 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.[31–33]

Data analysis

We will adopt recommended approaches[34 35] to the analysis and reporting of composite end points, as in previous multicentre perinatal RCTs.[36–41] A detailed statistical analysis plan and health economic protocol will be published before unblinding and data analysis begin.[42] The Trial Management Committee (TMC) will base any modifications to the original objectives, such as a change in the components of the composite end point, 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.[43–46] 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 RR or mean difference, as appropriate, with 95% CIs. 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 the Consolidated Standards of Reporting Trials[47] and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis[48] guidelines.

There is only one primary outcome. Secondary outcomes include each of the 10 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 inter-related and potentially causally attributable to hypoxic birth injury, we will follow the advice outlined by Schulz and Grimes[49] 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 end point, 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 and Stone.[50 51]

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, dyspnoea, epistaxis, diarrhoea, tremor, headache, myalgia, paraesthesia, oedema, visual changes, vaginal itch, nausea and vomiting, intrapartum antiemetic use, postpartum haemorrhage of ≤1500 mL, anaemia, bronchitis, skin rash, intrapartum fever 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 to 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 to 0.88; p=0.01). The use of sildenafil in labour was not associated with increased risk of perinatal death (RR 0.89, 95% CI 0.56 to 1.43; p=0.64), nor with 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 (Sildenafil TheRapy in dismal prognosis early onset fetal growth restriction) trials,[52 53] or treatment of pre-eclampsia[16 54 55] was associated with a statistically significant increase in the risks of flushing (RR 6.83, 95% CI 1.49 to 31.23; p=0.01) and nasal bleeding (RR 10.53, 95% CI 1.36 to 81.3; p=0.02); an increase in risk of persistent pulmonary hypertension of the newborn (RR 2.52, 95% CI 1.00 to 6.32; p=0.05) and non-statistically significant increase in headaches (RR 1.41, 95% CI 0.97 to 2.05; p=0.08) and flushing (RR 2.59, 95% CI 0.69 to 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, that is, cumulative doses of up to 5250 mg.[52 53] 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.[56] 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 (RR 3.67, 95% CI 1.28 to 10.51; p=0.008). A subsequent meta-analysis of 329 participating women in all available trials showed no difference in neonatal deaths.[57] However, it is recommended that sildenafil citrate not be prescribed outside of clinical trials.[58] The indication and cumulative dosage of sildenafil citrate in the iSEARCH trial are markedly different from the STRIDER trials, as we will only administer a maximum 150 mg in women at term, which is about 35 times lower. Persistent pulmonary hypertension of the newborn will be monitored as one of 10 components of the primary composite end point by the independent data and safety monitoring board, as outlined below.

Safety of sildenafil during breast feeding

Limited data indicate that sildenafil citrate and its active metabolite in breast milk are poorly excreted into breast milk. 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.[59] Women taking sildenafil citrate for the treatment of pulmonary hypertension in the UK are advised to continue breast feeding because sildenafil citrate only passes into breast milk in tiny amounts, is unlikely to cause any side effects in the baby and breast feeding will benefit both mother and baby.[60] 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 (eg, 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 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 (eg, 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 Safety and 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 Haybittle,[61] Peto *et al*,[62] Geller and Pocock.[63] 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 end point, for example, employing a commonly used formal threshold of p<0.001 for nominal significance, as recommended by Geller and Pocock.[63]

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 SEs from the null, which is equivalent to p<0.0027,[61 62] which would be needed to justify recommending early stopping.

Limitations

The postulated 35% reduction in the RR of its primary composite end point is nearly twice as large as the 20% relative reduction in a 10-component composite outcome seen in the ARRIVE trial, which enrolled 6106 women.[20] This putative 35% RR reduction in iSEARCH may therefore reflect 'optimism bias'[64–66] and is an important limitation, dictated by financial constraints which precluded a larger study.

The 10 components of the primary composite end point (table 1) are all potentially related to intrapartum hypoxia.[20 67] However, a reduction in overall incidence of this end point could not be interpreted as indicating reductions in key individual components such as intrapartum stillbirth, neonatal mortality, Apgar score <4 at 5 min, 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 end point for which the chances of showing a reduction in incidence are greatest are (i) admission to neonatal unit for >48 hours, (ii) respiratory support for >4 hours 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 (although highly optimistic) reductions in RR of 50%–60%. However, unlike some of the other components of the composite outcome (eg, neonatal encephalopathy), these three components are significantly less likely to impact long-term health outcomes.

Regulatory compliance

Conduct of the *iSEARCH* trial will be informed by the International Conference on Harmonisation Guidelines for Good Clinical Practice[68 69] and WHO guidance.[29] 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.

ETHICS AND DISSEMINATION

The Australian iSEARCH RCT has been approved by Hunter New England Ethic Committee (ref no: 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.

Author affiliations
[1]Maternal & Fetal Medicine, Mater Medical Research Institute, South Brisbane, Queensland, Australia
[2]NHMRC Clinical Trials Centre, The University of Sydney, Sydney, New South Wales, Australia
[3]OB/GYN, Monash Medical School, Clayton, Victoria, Australia
[4]Mater Research Institute, The University of Queensland, Brisbane, Queensland, Australia
[5]Mater Research Institute, The University of Queensland, Saint Lucia, Queensland, Australia
[6]Neonatal Critical Care Unit, Brisbane, Queensland, Australia
[7]Neonatology, Children's Hospital at Westmead, Sydney, New South Wales, Australia
[8]Obstetrics and Gynaecology, University of Melbourne, Carlton, Victoria, Australia
[9]Obstetrics and Gynaecology, Mercy Hospital for Women, Heidelberg, Victoria, Australia
[10]Western Sydney University School of Medicine, Penrith South DC, New South Wales, Australia
[11]School of Public Health, University of Technology Sydney, Sydney, UK

X William Tarnow-Mordi @williamotm

Contributors SK wrote the first draft and made extensive revisions incorporating suggestions by the other authors. Other coauthors (WT-M, BWM, VF, HL, NB, SPW, JH, LS, EC, RO'C) collaboratively provided detailed comments regarding study design and choice of appropriate study outcomes. RO'C provided advice and suggestion for the proposed statistical analysis. SK and WT-M contributed equally to the manuscript. All authors and collaborators reviewed and approved the final version before submission.

Funding This work was supported by the Australian Medical Research Future Fund (grant number APP1199329).

Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement 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.

ORCID iDs
Sailesh Kumar http://orcid.org/0000-0003-0832-4811
Ben W Mol http://orcid.org/0000-0001-8337-550X
Helen Liley http://orcid.org/0000-0002-8249-9516
Susan P Walker http://orcid.org/0000-0001-9075-4655

REFERENCES

1 Ayres-de-Campos D, Arulkumaran S, Panel F. FIGO consensus guidelines on Intrapartum fetal monitoring: physiology of fetal oxygenation and the main goals of Intrapartum fetal monitoring. *Int J Gynaecol Obstet* 2015;131:5–8.
2 Turner JM, Mitchell MD, Kumar SS. The physiology of Intrapartum fetal compromise at term. *Am J Obstet Gynecol* 2020;222:17–26.
3 Maltepe E, Fisher SJ. Placenta: the forgotten organ. *Annu Rev Cell Dev Biol* 2015;31:523–52.
4 Janbu T, Nesheim BI. Uterine artery blood velocities during contractions in pregnancy and labour related to Intrauterine pressure. *Br J Obstet Gynaecol* 1987;94:1150–5.
5 Lear CA, Wassink G, Westgate JA, *et al*. The peripheral Chemoreflex: indefatigable Guardian of fetal physiological adaptation to labour. *J Physiol* 2018;596:5611–23.
6 Hilder L. *Australia's mothers and babies 2012. Perinatal statistics series No.30. Cat. No.PER 69*. Canberra: AIHW, 2014.
7 Badawi N, Keogh JM. Causal pathways in cerebral palsy. *J Paediatr Child Health* 2013;49:5–8.
8 Graham EM, Ruis KA, Hartman AL, *et al*. A systematic review of the role of Intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008;199:587–95.
9 Blencowe H, Cousens S, Jassir FB, *et al*. National, regional, and worldwide estimates of Stillbirth rates in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2016;4:e98–108.
10 Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2010;86:329–38.
11 Paauw ND, Terstappen F, Ganzevoort W, *et al*. Sildenafil during pregnancy: A Preclinical meta-analysis on fetal growth and maternal blood pressure. *Hypertension* 2017;70:998–1006.
12 Ramesar SV, Mackraj I, Gathiram P, *et al*. Sildenafil citrate decreases sFlt-1 and sEng in pregnant L-NAME treated Sprague-Dawley rats. *Eur J Obstet Gynecol Reprod Biol* 2011;157:136–40.
13 Wareing M, Myers JE, O'Hara M, *et al*. Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. *J Clin Endocrinol Metab* 2005;90:2550–5.
14 Maharaj CH, O'Toole D, Lynch T, *et al*. Effects and mechanisms of action of Sildenafil citrate in human chorionic arteries. *Reprod Biol Endocrinol* 2009;7:34.
15 Turner JM, Russo F, Deprest J, *et al*. Phosphodiesterase-5 inhibitors in pregnancy: systematic review and meta-analysis of maternal and perinatal safety and clinical outcomes. *BJOG* 2022;129:1817–31.
16 Trapani A, Gonçalves LF, Trapani TF, *et al*. Perinatal and hemodynamic evaluation of Sildenafil citrate for Preeclampsia treatment: A randomized controlled trial. *Obstet Gynecol* 2016;128:253–9.
17 Turner J, Dunn L, Tarnow-Mordi W, *et al*. Safety and efficacy of Sildenafil citrate to reduce operative birth for Intrapartum fetal compromise at term: A phase 2 randomized controlled trial. *Am J Obstet Gynecol* 2020;222:401–14.
18 Turner J, Dunn L, Kumar S. Oral Sildenafil citrate during labor mitigates the Intrapartum decline in Placental growth factor in term pregnancies. *Am J Obstet Gynecol* 2020;223:588–90.
19 Callander EJ, Tarnow-Mordi W, Morton R, *et al*. Intrapartum use of Sildenafil citrate to prevent fetal compromise and emergency operative birth in term pregnancies in the United Kingdom and Australia: A preliminary cost-effectiveness analysis. *Int J Gynaecol Obstet* 2024;164:1010–8.
20 Grobman WA, Rice MM, Reddy UM, *et al*. Labor induction versus expectant management in low-risk nulliparous women. *N Engl J Med* 2018;379:513–23.
21 Kumar S, Ghadge A. Can Intrapartum Sildenafil citrate safely avert the risks of contraction-induced hypoxia in labour? iSEARCH – a pragmatic Multicentre phase III randomised controlled trial. *Australian Clinical* 2021.
22 Kumar S, Tarnow-Mordi W, Mol B. The Isearch trials of oral Sildenafil in labour: protocol for a randomised trial in 3,200 Australian women and rationale for an individual participant data prospective meta-analysis of trials in 14,000 women in high-income countries and a mega-trial of 50,000 women in low or middle-income countries. *In Review* [Preprint].
23 Tarnow-Mordi WO, Robledo K, Marschner I, *et al*. To guide future practice, perinatal trials should be much larger, simpler and less fragile with close to 100% ascertainment of mortality and other key outcomes. *Semin Perinatol* 2023;47:S0146-0005(23)00092-7.
24 Smith V, Gallagher L, Carroll M, *et al*. Antenatal and Intrapartum interventions for reducing Caesarean section, promoting vaginal birth, and reducing fear of childbirth: an overview of systematic reviews. *PLoS ONE* 2019;14:e0224313.
25 Chow SSW, Creighton P, Chambers GM, *et al*. *Report of the Australian and New Zealand Neonatal Network* 2018. Sydney: ANZNN, 2020.
26 Peto R, Baigent C. Trials: the next 50 years. large scale randomised evidence of moderate benefits. *BMJ* 1998;317:1170–1.

27 von Dadelszen P, Dwinnell S, Magee L, *et al*. Sildenafil citrate therapy for severe Early-Onset Intrauterine growth restriction. *BJOG* 2011;118:624–8.
28 Australian Curriculum, Assessment and Reporting Authority 2022, NAPLAN National Report for 2022, ACARA, Sydney, Available: https://www.nap.edu.au/home
29 World Health Organisation, Geneva. WHO guidance for best practices for clinical trials. draft for public consultation. 2023. Available: https://cdn-auth-cms.who.int/media/docs/default-source/research-for-health/2023-07_who-guidance-for-best-practices-for-clinical-trials_draft-for-public-consultation.pdf?sfvrsn=7a5c9fa5_3
30 Mahle WT, Martin GR, Beekman RH, *et al*. Endorsement of health and human services recommendation for pulse Oximetry screening for critical congenital heart disease. *Pediatrics* 2012;129:190–2.
31 Yu L-M, Hey E, Doyle LW, *et al*. Evaluation of the ages and stages questionnaires in identifying children with Neurosensory disability in the magpie trial follow-up study. *Acta Paediatr* 2007;96:1803–8.
32 Kenyon S, Pike K, Jones D, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with Preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008;372:1310–8.
33 Kenyon S, Pike K, Jones D, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous Preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;372:1319–27.
34 Cordoba G, Schwartz L, Woloshin S, *et al*. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ* 2010;341:c3920.
35 Ferreira-González I, Permanyer-Miralda G, Busse JW, *et al*. Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *J Clin Epidemiol* 2007;60:651–7.
36 Morley CJ, Davis PG, Doyle LW, *et al*. Nasal CPAP or intubation at birth for very Preterm infants. *N Engl J Med* 2008;358:700–8.
37 Askie LM, Henderson-Smart DJ, Irwig L, *et al*. Oxygen-saturation targets and outcomes in extremely Preterm infants. *N Engl J Med* 2003;349:959–67.
38 INIS Collaborative Group, Brocklehurst P, Farrell B, *et al*. Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med* 2011;365:1201–11.
39 Kenyon SL, Taylor DJ, Tarnow-Mordi W, *et al*. Broad-spectrum antibiotics for Preterm, Prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001;357:979–88.
40 Tarnow-Mordi W, Morris J, Kirby A, *et al*. Delayed versus immediate cord clamping in Preterm infants. *N Engl J Med* 2017;377:2445–55.
41 Tita ATN, Carlo WA, McClure EM, *et al*. Azithromycin to prevent sepsis or death in women planning a vaginal birth. *N Engl J Med* 2023;388:1161–70.
42 Gamble C, Krishan A, Stocken D, *et al*. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA* 2017;318:2337–43.
43 Coskinas X, Simes J, Schou M, *et al*. Changes to aspects of ongoing randomised controlled trials with fixed designs. *Trials* 2020;21:457.
44 Coskinas X, Schou IM, Simes J, *et al*. Reacting to Prognostic Covariate imbalance in randomised controlled trials. *Contemp Clin Trials* 2021;110:S1551-7144(21)00280-9.
45 Coskinas X, Simes RJ, Martin AJ. Changes to design and analysis elements of research plans during randomised controlled trials in Australia. *Med J Aust* 2022;217:526–31.
46 Orkin AM, Gill PJ, Ghersi D, *et al*. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA* 2021;326:257–65.
47 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
48 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Circulation* 2015;131:211–9.
49 Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005;365:1591–5.
50 Pocock SJ, Stone GW. The primary outcome fails - what next *N Engl J Med* 2016;375:861–70.
51 Pocock SJ, Stone GW. The primary outcome is positive - is that good enough *N Engl J Med* 2016;375:971–9.
52 Groom KM, McCowan LM, Mackay LK, *et al*. STRIDER Nzaus: a Multicentre randomised controlled trial of Sildenafil therapy in early-onset fetal growth restriction. *BJOG* 2019;126:997–1006.
53 Sharp A, Cornforth C, Jackson R, *et al*. Maternal Sildenafil for severe fetal growth restriction (STRIDER): a Multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018;2:93–102.
54 Furuhashi F, Tanaka H, Maki S, *et al*. Tadalafil treatment for Preeclampsia (medication in Preeclampsia; MIE): a multicenter phase II clinical trial. *J Matern Fetal Neonatal Med* 2021;34:3709–15.
55 Samangaya RA, Mires G, Shennan A, *et al*. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor Sildenafil for the treatment of Preeclampsia. *Hypertens Pregnancy* 2009;28:369–82.
56 Pels A, Derks J, Elvan-Taspinar A, *et al*. Maternal Sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction: A randomized clinical trial. *JAMA Netw Open* 2020;3:e205323.
57 Sharp A, Cornforth C, Jackson R, *et al*. Mortality in the UK STRIDER trial of Sildenafil therapy for the treatment of severe early-onset fetal growth restriction. *Lancet Child Adolesc Health* 2019;3:e2–3.
58 Groom KM, Ganzevoort W, Alfirevic Z, *et al*. Clinicians should stop prescribing Sildenafil for fetal growth restriction (FGR): comment from the STRIDER consortium. *Ultrasound Obstet Gyne* 2018;52:295–6.
59 National Institute of Child Health and Human Development 2006 - Sildenafil. *Drugs and lactation database (LactMed)*. Bethesda (MD), 2006. Available: https://www.ncbi.nlm.nih.gov/books/NBK500617
60 National Health Service. Pregnancy, breastfeeding and fertility while taking sildenafil, Available: https://www.nhs.uk/medicines/sildenafil-viagra/pregnancy-breastfeeding-and-fertility-while-taking-sildenafil/
61 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *BJR* 1971;44:793–7.
62 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1976;34:585–612.
63 Geller NL, Pocock SJ. Interim analyses in randomized clinical trials: ramifications and guidelines for practitioners. *Biometrics* 1987;43:213–23.
64 Djulbegovic B, Kumar A, Magazin A, *et al*. Optimism bias leads to inconclusive results-an empirical study. *J Clin Epidemiol* 2011;64:583–93.
65 Zakeri K, Noticewala S, Vitzthum L, *et al*. Optimism bias' in contemporary national clinical trial network phase III trials: are we improving. *Ann Oncol* 2018;29:2135–9.
66 Chalmers I, Matthews R. What are the implications of optimism bias in clinical research *Lancet* 2006;367:449–50.
67 Webbe JWH, Duffy JMN, Afonso E, *et al*. Core outcomes in Neonatology: development of a core outcome set for neonatal research. *Arch Dis Child Fetal Neonatal Ed* 2020;105:425–31.
68 ICH-E6 Good clinical practice. *International council for harmonisation of technical requirements for pharmaceuticals for human use*. Geneva, 2016. Available: https://database.ich.org/sites/default/files/ICH_E6-R3_GCPPrinciples_Draft_2021_0419.pdf
69 ICH. General considerations for clinical studies E8(R1). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2021. Available: https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf
70 Flenady V, Wojcieszek AM, Middleton P, *et al*. Stillbirths: recall to action in high-income countries. *Lancet* 2016;387:691–702.
71 Persson M, Razaz N, Tedroff K, *et al*. Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden. *BMJ* 2018;360:k207.
72 Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. *BJOG* 2012;119:824–31.
73 Jacobs SJ, Berg M, Tarnow-Mordi W, *et al*. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane database syst Rev 2013(1):Cd003311. 2013.
74 Ronen GM, Buckley D, Penney S, *et al*. Long-term prognosis in children with neonatal seizures: a population-based study. *Neurology* 2007;69:1816–22.
75 Thygesen SK, Olsen M, Østergaard JR, *et al*. Respiratory distress syndrome in moderately late and late Preterm infants and risk of cerebral palsy: a population-based cohort study. *BMJ Open* 2016;6:e011643.
76 Smith GCS, Wood AM, White IR, *et al*. Neonatal respiratory morbidity at term and the risk of childhood asthma. *Arch Dis Child* 2004;89:956–60.
77 Lipkin PH, Davidson D, Spivak L, *et al*. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. *J Pediatr* 2002;140:306–10.
78 Beligere N, Rao R. Neurodevelopmental outcome of infants with Meconium aspiration syndrome: report of a study and literature review. *J Perinatol* 2008;28:S93–101.