



**STRIDER NZAus: A Randomised Controlled Trial of Sildenafil Therapy
In Dismal Prognosis Early-Onset Intrauterine Growth Restriction
(New Zealand and Australia).**

Trial Summary

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Introduction

There is no current treatment available for intrauterine growth restriction (IUGR); the only management option obstetricians can offer is early birth. Sildenafil is a novel innovative therapy which may improve fetal growth and so delay delivery, potentially improving the chance of survival for babies and reducing prematurity related morbidity that contributes to long term handicap and disease. This will be the first randomised placebo controlled trial of sildenafil in pregnancies complicated by IUGR and will provide new knowledge in the management of IUGR, initially in those with severe early onset disease but if successful, it may be trialled in later onset disease.

IUGR. Birth of a small for gestational age (SGA) infant occurs in 10% of pregnancies. Babies may be born SGA with no complications (constitutionally small) or small due to a failure to fulfil their growth potential (IUGR). IUGR may occur for a number of reasons including abnormal fetal karyotype, fetal syndrome or anomaly and fetal infection. However the majority of cases of fetal growth restriction are due to abnormal placentation and are part of a spectrum of placental ischaemic conditions including preeclampsia and abruption. Poor placentation results in poor fetal growth and may lead to hypoxia and stillbirth. When IUGR is detected prior to birth, no treatment is available and so clinicians must instigate intensive monitoring and then balance risks of the hypoxic in-utero environment against risks of early birth. The greatest risk is for those babies with very early onset IUGR, who may require extreme preterm birth to avoid hypoxic injury or death.

IUGR early in pregnancy is rare, affecting approximately two per 1000 pregnancies at ≤ 28 weeks, however, due to the severity of disease and extreme prematurity, the risks to the fetus and infant are very high. Many babies will die in-utero before reaching viable gestations and/or birthweights. Of IUGR babies born alive between 24 and 28 weeks, 75% survive to be discharged from hospital but less than 25% are free of major morbidity (defined as intraventricular haemorrhage grade 3/4, periventricular leukomalacia, severe retinopathy, necrotising enterocolitis or chronic lung disease)⁴. Extreme preterm birth imposes significant risk of these short term morbidities which may result in long term handicap/cerebral palsy and potential life-long health consequences of metabolic syndrome conditions. Every year in New Zealand and worldwide babies are born IUGR ≤ 28 weeks resulting in these major health complications with an enormous emotional and financial burden for individuals, families, health care providers and society.

Life time risks of preterm IUGR include;¹⁻⁴

Neonatal: Death, respiratory distress syndrome, intraventricular haemorrhage, periventricular leukomalacia, retinopathy, chronic lung disease, sepsis, necrotising enterocolitis & jaundice.

Childhood: Cerebral palsy, developmental delay, cognitive impairment, blindness, hearing loss & short stature.

Adulthood: Hypertension, diabetes, dyslipidaemia & cardiovascular disease.

Pathophysiology. In normal pregnancy the uteroplacental circuit undergoes significant changes during the first and second trimesters to ensure efficient gaseous and nutrient exchange across the placenta from mother to fetus. Extravillous trophoblast remodels the maternal spiral arteries converting a high resistance, low flow circulation to a low resistance, high flow circulation. In the process of normal spiral artery remodelling there is 'boring out' of the smooth muscle of these maternal medium sized resistance vessels with diminution of the nitric oxide (NO) producing endothelium, the internal elastic lamina and the NO-responsive muscularis layers. The resulting effect of removal of these layers by extravillous trophoblast is a system of dilated vessels largely unresponsive to normal regional vascular control.

IUGR (and preeclampsia) occurs in association with inadequate/abnormal placental invasion and spiral artery remodelling evident as abnormal Doppler waveforms of the maternal compartment uteroplacental vessels (uterine arteries). In IUGR poor gaseous and nutrient exchange across the placenta occurs as a result of this inadequate/abnormal placental invasion leading to poor growth and ultimately hypoxia and death. In preeclampsia the abnormal placenta results in release of vasoactive substances into the maternal circulation and the clinical scenario of the disease. In early onset IUGR pregnancies, abnormalities of the fetal vascular compartment are common, evident as abnormal Doppler waveforms in the umbilical artery reflecting abnormal fetoplacental vascular development. Abnormalities in the fetal vascular compartment can coexist with abnormalities in the uteroplacental circulation or arise independently. Whilst the pathophysiology of these abnormal umbilical artery Doppler waveforms is as yet poorly understood they are a marker for fetuses at very high risk of perinatal morbidity and mortality⁸⁻¹⁰.

The potential of sildenafil. Sildenafil potentiates the effect of NO and thus may cause vasodilatation of vessels responsive to NO. This may include vessels within the fetal and/or maternal compartments of the uteroplacental circulation (incomplete remodelling of maternal spiral arteries results in vessels with intact or partially intact muscular layers). Sildenafil therefore has the potential to increase uteroplacental circulation and perfusion resulting in improved gaseous and nutrient exchange and improved fetal growth and well-being. Animal and in-vitro human studies support this concept.

In mouse models of IUGR measures of pup growth, including body weight, crown-rump length and abdominal circumference were reduced compared to control mice. Treatment with sildenafil at mid gestation demonstrated normalisation of all growth measures in the IUGR mice. Despite no significant increase in uterine artery flow measured by Doppler waveform studies, abnormal umbilical artery Doppler waveforms (including reversed arterial blood flow velocity) also normalised following treatment with sildenafil – suggesting a beneficial effect on fetoplacental blood flow in this model¹¹. Similar increased growth parameters have also been demonstrated with sildenafil in rat, guinea pig and sheep models¹²⁻¹⁴.

In a human ex vivo study, myometrial small arteries dissected from myometrial samples obtained at caesarean section from normal pregnancies were compared to small arteries from pregnancies complicated by IUGR¹⁵. Arteries were constricted and relaxed before and after incubation with sildenafil. Sildenafil significantly reduced vasoconstriction and significantly improved relaxation of small arteries from IUGR pregnancies.

Sildenafil in pregnancy. As sildenafil potentiates the action of NO it is used in the management of pulmonary arterial hypertension for selective vasodilatation of pulmonary vasculature. There are now several case reports of its use for this indication in pregnancy⁵⁻⁷ with improved maternal cardiorespiratory performance, improved echocardiographic status and delivery of healthy infants.

It is also increasingly used in the neonatal period in infants (including those born preterm) for the treatment of persistent pulmonary hypertension of the newborn (PPHN). PPHN is more common in preterm infants and the risk of mortality and morbidity is high. Sildenafil is increasingly used as an adjunctive therapy to current care of inhaled NO therapy, surfactant and high-frequency oscillatory ventilation¹⁶.

Interest in the use of sildenafil for the treatment of placental ischaemic conditions led to a small randomised placebo controlled trial in women with early onset preeclampsia¹⁷. In this UK study led by Professor Baker, 35 women with preeclampsia at gestational ages 24–34 weeks were recruited from nine hospitals and randomly assigned to sildenafil or placebo at gradually increasing daily doses. The primary endpoint was prolongation of pregnancy from randomisation to delivery. Details of all adverse events were collected. There was no difference in time from randomisation to delivery in the two treatment groups, with a median time of 4 days (range 1–15) in the sildenafil group and 4.5 days (range 1–30) in the placebo group. The median birthweights in the sildenafil and placebo treated groups were 1410g (range 553-2480) and 1043g (range 519-2510g) respectively, $p > 0.1$. At all doses, sildenafil was well tolerated with no increase in maternal or fetal morbidity or mortality. Plasma samples were taken to establish pharmacokinetic information. Sildenafil achieved maximum drug concentrations of 48ng/ml, 88ng/ml, and 271ng/ml after 3 days of 20mg, 40mg and 80mg tds respectively.

Sildenafil and IUGR. Our Canadian collaborators have gained and published experience of the use of sildenafil in women with severely growth restricted fetuses¹⁸. Within the British Columbia Provincial Health Services Authority there is a process for offering patients innovative therapy through formal information sharing and consenting process. Through this mechanism, patients facing dire prognoses can be offered innovative therapeutic interventions. Within this setting, sildenafil treatment was included in the management of a series of 10 women with severe early onset IUGR and, for analytical purposes, their outcomes were compared with a series of 17 women who fulfilled the treatment criteria but either declined or were not offered sildenafil. The baseline characteristics and outcomes are summarised in table 1.

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Table 1: Case-control study of sildenafil for severe early onset IUGR ¹⁸.

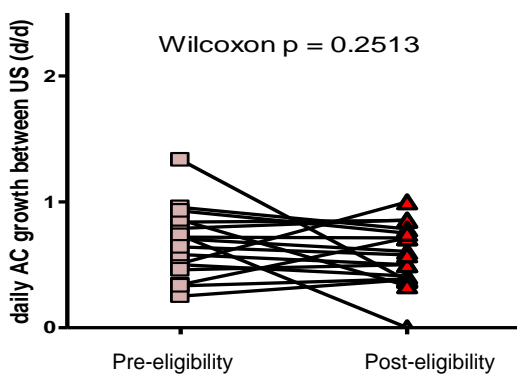
Expressed as median [interquartile range] or number (%). AC – abdominal circumference, EDF – end diastolic flow.

	Sildenafil-naïve (n=17)	Sildenafil-treated (n=10)	p value
Baseline characteristics			
Gestational age at eligibility (days)	148 [137.5, 163]	158 [147.5, 164.5]	0.15
AC <1st percentile at eligibility	10 (59%)	6 (60%)	1.00
Umbilical artery Doppler positive EDF	13 (76%)	5 (50%)	0.22
Outcomes			
Development of preeclampsia	5/9 (56%)	2/12 (17%)	0.16
Number with increased AC growth velocity post-eligibility	7 (41%)	9 (90%)	0.02
Eligibility-to-delivery interval (days)	42 [17, 55]	31.5 [9.5, 81]	0.87
Gestational age at delivery (days)	180.5 [165.5, 208]	189.5 [178.5, 229.5]	0.28
Live birth	6 (35%)	7 (70%)	0.12
Survival	6 (35%)	5 (50%)	0.69
Intact survival	5 (29%)	5 (50%)	0.42

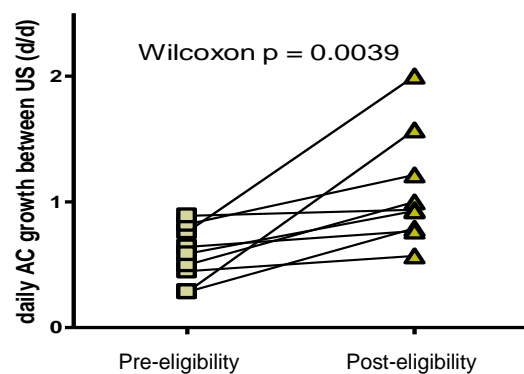
The women who received sildenafil treatment tended to have poorer indices of fetal well-being at baseline in terms of umbilical artery Doppler flow waveforms and amniotic fluid indices. Other than one woman who suffered a stillbirth within 48 hours of commencing sildenafil treatment, all sildenafil treated fetuses had increased fetal abdominal circumference growth velocity after treatment (odds ratio 12.9 [95% CI 1.3 - 126]) (figure 1). Sildenafil treated fetuses tended to be more frequently live born and to survive intact to primary hospital discharge (defined as no evidence of grade 3/4 intraventricular haemorrhage or periventricular leukomalacia).

Figure 1: Change in daily AC growth pre versus post-eligibility epochs ¹⁸.

Sildenafil naïve



Sildenafil treated



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The results from this small case-control study suggesting improvement in fetal growth after sildenafil treatment are exciting with potential for future therapy in these high risk pregnancies. Indeed we are aware some clinicians have considered its use outside of a clinical trial setting based simply on this small study. However, more evidence, both in terms of safety and outcome data, is essential before it can be introduced into clinical practice. It is possible and must be considered that there is potential for harm associated with sildenafil use. Although it is well tolerated in pregnancy for other indications⁵⁻⁷ it is possible that prolonged in-utero environment and/or relatively sudden vasodilatation, particularly in the fetal vascular compartment of an IUGR fetus that is already compromised may be harmful.

STRIDER NZAus is a randomised placebo controlled trial designed to answer the next step of our research question, **does sildenafil increase fetal growth velocity?** By collaboration with other studies planned worldwide we will also be able to use these data in further progressing our knowledge, **does sildenafil improve rates of survival free of major morbidity?** If sildenafil demonstrates a positive effect on growth and outcome in these cases of severe early onset IUGR, there is potential for its use at later gestations when outcomes may be less severe but still significant in effect on an individual's lifetime health. As the prevalence of later onset IUGR is higher it may potentially have an even greater impact on the population as a whole if used successfully at later gestations.

Additional studies within the clinical trial on uteroplacental Doppler waveforms and vascular physiology may provide further knowledge in the pathological basis of this disease and the potential effect of treatment.



Hypothesis and Aims

The primary hypothesis: Sildenafil compared to placebo therapy will increase the likelihood of increased fetal growth velocity in pregnancies complicated by severe early onset IUGR. By collaboration with an international consortium we will also examine the hypothesis that sildenafil therapy compared to placebo therapy will increase the rate of survival free of major handicap.

The primary aim: To assess the effect of sildenafil compared to placebo therapy on the proportion of pregnancies that have an increase in fetal growth velocity (measured by change in expected/observed increase in abdominal circumference per day) in pregnancies complicated by severe early onset IUGR.

The secondary aims include:

Effects on fetal growth and well-being:

1. To compare mean absolute change in abdominal circumference (mm) per day in fetuses treated with sildenafil and placebo.
2. To compare measures of uteroplacental, umbilical and fetal Doppler waveform studies in those treated with sildenafil and placebo.
3. To compare customised birthweight centiles in infants treated in-utero with sildenafil and placebo.

Effects on outcome:

1. To compare live-birth rates of infants treated in-utero with sildenafil and placebo.
2. To compare survival without major morbidity rates of infants treated in-utero with sildenafil and placebo.

To report frequency of adverse and serious adverse events associated with sildenafil use.

Myometrial and placental myography studies (Auckland Study Centre only):

1. To compare the effect of sildenafil and placebo on vascular endothelial and vascular smooth muscle cells in myometrium.
2. To compare the effect of sildenafil and placebo on chorionic plate and stem villous blood vessels within the placenta.



Design and Methods

Study design: STRIDER NZAus is a bi-national multicentre double blind randomised placebo controlled trial.

Recruiting centres will include Maternal-Fetal Medicine (MFM) units in New Zealand (Auckland, Wellington and Christchurch) and Australia. The Auckland study centre will lead and co-ordinate STRIDER NZAus. Staff at the Auckland study centre will include PI, STRIDER IPD Collaboration Co-PI, trial co-ordinator, local investigators, research midwives and research fellow (responsible for myometrial and placental studies).

Study population: Women with pregnancies affected by severe early onset IUGR will be identified from MFM clinics in each recruiting centre.

<u>Inclusion criteria</u>	<u>Exclusion criteria</u>
<ul style="list-style-type: none">• Singleton pregnancy• At $\leq 27^6$ weeks: AC $<3^{\text{rd}}$ percentile OR• At 28^0-30^0 weeks: EFW $<700\text{g}$	<ul style="list-style-type: none">• Known fetal aneuploidy, anomaly, syndrome or congenital infection• Plan made for termination

These criteria have been established in line with other studies in the STRIDER IPD Collaboration.

Power analysis: In the preliminary case control study in Canada use of sildenafil was associated with 90% of cases having an increased AC growth velocity compared with 41% in those untreated¹⁸. For this trial, assuming 50% placebo-treated vs 80% sildenafil-treated subjects will have increased post-randomisation AC growth velocity, with an α of 0.05, two sided, we will have 90% power to detect this difference if we randomise 58 women per group.

Allowing for a 5% drop-out rate, the **total sample size required is 122 women** for STRIDER NZAus.

Feasibility of recruitment: Severe early onset IUGR with delivery <28 weeks occurs in approximately 0.2% of the population. However, some cases will be associated with fetal abnormality and not all cases will be detected antenatally (and therefore not amenable to treatment/trial recruitment). When such early onset IUGR is identified prior to birth it is highly likely these women will be referred for MFM review and on-going care and therefore centres providing this tertiary level of care and facilities will be used as recruiting centres.

In a retrospective audit of deliveries of IUGR infants at 20^{+0} to 29^{+6} weeks at National Women's Health, Auckland 2006-2010 (inclusive), a total of 271 pregnancies were identified. However, only 53 cases met the study inclusion criteria and were also identified before delivery. Allowing for some women that would meet inclusion criteria but deliver after 30 weeks, it is likely that 10-15 eligible cases will be seen at National Women's Health per year. We plan to recruit 20 women from the Auckland site, a further 20 women from Christchurch and Wellington and the remainder from Australian centres.



Randomisation: This will be performed using a web-based randomisation service operating at British Columbia Women’s Hospital (Vancouver, Canada). Women will be randomised on a 1:1 ratio sildenafil:placebo. In stratification of our randomisation programme we will consider;

1. Gestational age at recruitment (<24⁰ and ≥24⁰ weeks)
2. Present or absent/reversed end-diastolic flow in umbilical artery Doppler waveform.

Treatment: Women will be randomised to one of two groups;

<u>Sildenafil group</u> Oral sildenafil citrate - 25mg tds	<u>Placebo group</u> Identical appearance inactive tablet - 1 tab tds
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Dosing regimens have been established in line with other studies in the STRIDER IPD Collaboration.

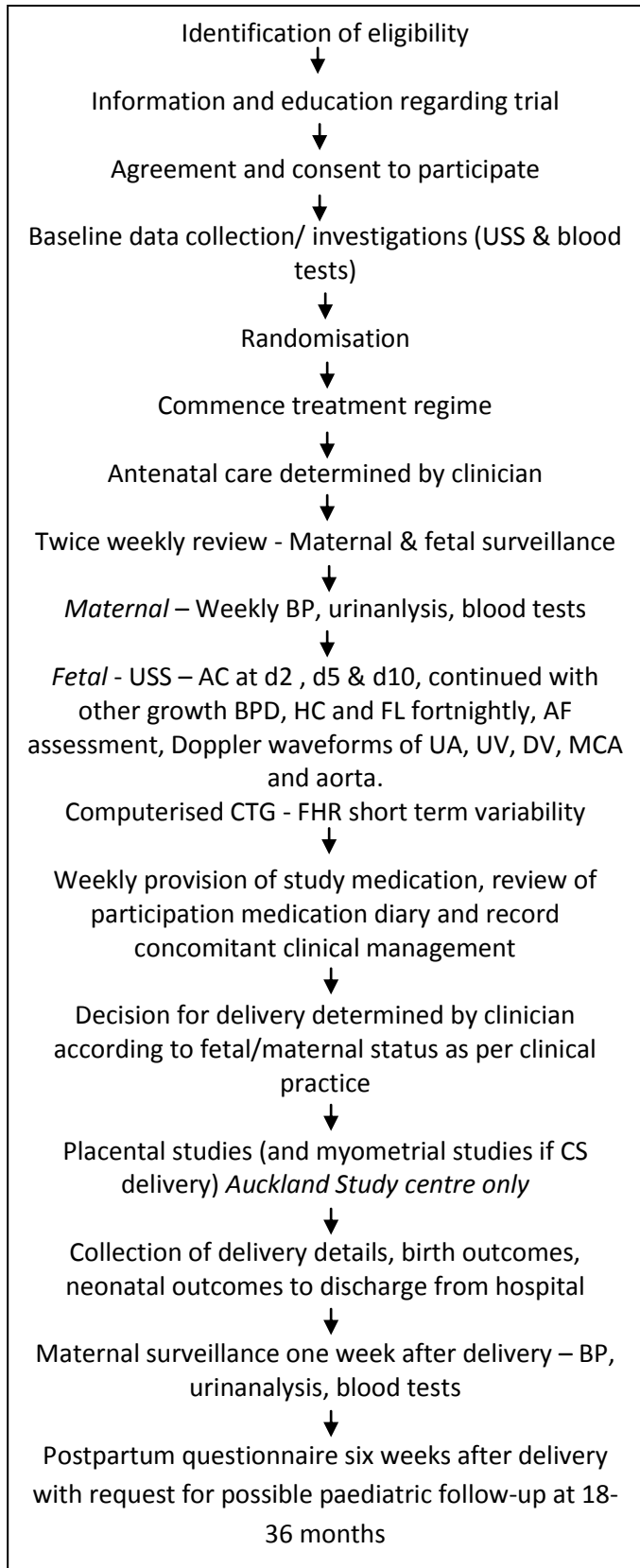
Sildenafil and placebo tablets identical in appearance will be supplied by Actavis and packaged appropriately by Anqual, School of Pharmacy, University of Auckland.

Drugs will be stored in each study centre under appropriate conditions and issued on a ten daily treatment pack basis to participants. Treatment will continue until delivery or 32 weeks (whichever occurs first). Participants, medical professionals and investigators will remain blinded to treatment allocation until the trial is completed.

Declined randomisation: For eligible women who decline randomisation in the trial we will request permission to collect outcome data. This will provide a third comparator group for pregnancy outcomes. Data from this group will be used in secondary analysis.

Data collection: All data will be collected on case record forms and entered onto a central internet based data collection system (REDCap) managed by British Columbia Women’s Hospital (Vancouver, Canada). Only STRIDER NZAus investigators will have access to this data but it will be formatted to be compatible with all trials within the STRIDER IPD Collaboration.

Individual patient trial schedule:



Baseline data collection: This will include maternal age, ethnicity, height and weight, obstetric history, medical history, medication use, aneuploidy screening/ testing and fetal infection screen. Previous scan data will include growth, liquor volume, fetal anatomy and uteroplacental/ fetal Doppler waveforms.

Antenatal care: Management will be determined by the individual clinician caring for each woman. In many cases this will be as an in-patient due to maternal condition (preeclampsia) or poor fetal condition requiring intensive monitoring or as an out-patient with close review.

Maternal surveillance: For trial purposes blood pressure measurement, urinalysis and pulse oximetry will be performed weekly.

Maternal blood tests: For trial purposes full blood count, renal (urea, electrolytes, creatinine, urate) and liver (AST, ALT, bilirubin, albumin) function will be tested prior to commencement of treatment, weekly once recruited and one week after delivery.

Ultrasound (USS): All measurements will be made on day of recruitment.

Fetal growth: abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL). AC will be measured on days 2, 5, 10 and 14 and then continued on a fortnightly basis with other growth parameters.

Amniotic fluid (AF) measurement: four quadrant amniotic fluid index (AFI) and single deepest vertical pocket will be performed twice weekly.

Doppler waveforms: Twice weekly umbilical artery (UA) (resistance index [RI], pulsatility index [PI] and presence/absence or reversed end diastolic flow) umbilical vein (UV) (pulsatile or non-pulsatile), ductus venosus (DV) (RI, PI, a wave), middle cerebral artery (MCA) (RI, PI, peak systolic velocity [PSV]), aortic isthmus (RI, PI, PSV) and maternal uterine artery (RI, PI, diastolic notch). Standardised protocols will be used. When decision for delivery is imminent scans may be performed more frequently on a clinical needs basis (these data will also be collected).

Computerised CTG: Once the fetus has reached viability i.e. >24 weeks and EFW >500g, confirmed by clinician caring for each individual, a weekly CTG will record short term heart rate variability.

Compliance: Participants will record medication use and side effects/adverse events in a participation medication diary. Participants will also be asked to return medication bottles to assess compliance.

Concomitant clinical management and co-interventions: 40% of women with severe early onset IUGR will have or develop preeclampsia, requiring additional therapies, surveillance and possibly delivery indicated on maternal rather than fetal grounds. All women with severe early onset IUGR, will require intense fetal surveillance, possible in-patient stay and early delivery. Prior to delivery corticosteroids will be administered to improve fetal lung maturity¹⁹ and magnesium sulphate therapy considered for perinatal neuroprotection²⁰. These additional therapies and management will be provided at the discretion of the clinician/study centre caring for each woman. Data regarding these co-interventions will be collected.

Long term follow-up: Participants will be sent a postpartum questionnaire six weeks after delivery. Further contact will be made at 18-36 months of infant age for assessment of paediatric outcomes (by questionnaire and/or examination). At this stage consent will be gained for contact at this time-point. Additional funding required for full two year study follow-up.

Patient safety: Indications to stop treatment;

1. Patient withdrawal. Participants are free to withdraw at any time (allowed for 5% drop-out).
2. Delivery or 32 weeks (whichever occurs first). Due to the severe nature of early onset IUGR the majority of participants will be delivered by 32 weeks (due to concerns for fetal and/or maternal well-being). If women remain undelivered at 32 weeks the drug will be stopped as prognosis is significantly improved by this gestation. Close observation including assessment of Doppler waveforms will be made in the first 24-48 hours after stopping treatment. If a positive treatment effect is seen within this RCT there may be a role for prolonged use (or at later gestations) but this would require additional investigation.



3. Severe maternal hypotension causing maternal and/or fetal compromise in the absence of other anti-hypertensive drug use.
4. Serious adverse event.

Adverse events will be reviewed by the Study Investigators using predefined parameters to assess each adverse event. The randomisation service provides 24 hour access to allow the randomisation code to be breached and reveal treatment group prior to the end of the study if required. A central data safety monitoring board (DSMB) has been established by the STRIDER IPD Collaboration. The DSMB will be used by all (bi-)national STRIDER trials. It includes experts in obstetrics, MFM, neonatology, clinical pharmacology and epidemiology. The chair is Professor Gideon Koren, Paediatrics and Clinical Pharmacology, University of Toronto, Canada.

Outcome Measures:

The primary outcome measure is;

- Fetal growth velocity determined by AC growth velocity.

Mean daily increase in AC (calculated as a proportion of that expected if AC were on 50th centile for gestational age) pre and post treatment will be calculated and proportions with increased AC growth velocity in the sildenafil group and placebo group will be compared. Pre-treatment growth velocity epoch will be calculated from the most recent AC measurement >12 days before recruitment and the recruitment AC measure. Post-treatment growth velocity epoch will be calculated from the recruitment AC measure and a 14 day AC measure, where delivery has occurred before 14 days the longest interval shall be used (10, 5 and finally 2 days).

This primary outcome has been established in line with other studies in the STRIDER IPD Collaboration.

Secondary outcomes will include;

- Fetal growth and wellbeing measures such as; mean absolute change in AC per day, mean birthweight and mean birthweight centile, amniotic fluid measures, changes in uteroplacental, umbilical and fetal Doppler waveform studies and fetal heart rate variability.
- Maternal parameters such as; symptomatic hypotension, headaches, flushing, preeclampsia and postpartum haemorrhage.
- Delivery outcomes such as; randomisation-to-delivery interval, gestational age at delivery, mode of delivery and number of days hospital in-patient stay.
- Neonatal outcomes such as; rates of intrauterine death and live-birth, survival to hospital discharge, several predefined major morbidities (including chronic lung disease requiring ambulatory oxygen therapy on hospital discharge, intraventricular haemorrhage grade 3-4, \geq grade 3 retinopathy of prematurity, necrotising enterocolitis, number of doses of surfactant, ventilator days, supplemental oxygen days and number of days to full feeds).



Statistical analyses: Data will be analysed on an intention-to-treat basis.

The primary outcome and categorical secondary outcomes will be compared between sildenafil-treated and placebo-treated groups by Fisher's exact test. For continuous secondary outcomes, t-test will be used to make comparison between the two groups. Mixed models repeated measure analysis will be conducted for repeatedly measured outcomes where appropriate. Further analysis adjusting for factors which may influence the outcome of interest, including but not limited to recruiting centre will be considered.

Descriptive summary statistics will be provided for continuous variables with mean, standard deviation, median, minimum and maximum. For categorical variables, frequency and percentage for each category will be presented. Two sided-p-values less than 0.05 will be used to determine statistical significance and all confidence intervals will be reported at a two sided 95% level.

Ethics: Approval has been granted by the New Zealand Multi Region Ethics Committee (with locality approval in Auckland) CEN/12/06/028. Appropriate approval is being sought for Australian centres.

Timeline: Recruitment will commence in the second half of 2013. We estimate it will take 2-3 years to complete recruitment. Ongoing data collection and checking will allow analysis as soon as recruitment and delivery/discharge of women and babies has occurred. We estimate publication of results of STRIDER NZAus early in 2017.

Vascular physiology studies: Participants recruited in Auckland will be invited to take part in a study involving placental and myometrial (if delivering by CS) biopsy. These samples will be used in a PhD project comparing the effect of sildenafil and placebo on dilatation and constriction of placental chorionic plate and stem villous blood vessels and myometrial small arteries.

STRIDER IPD Collaboration: STRIDER NZAus is powered to demonstrate a significant improvement in fetal growth velocity, however, if sildenafil is to be of clinical benefit it needs to improve neonatal survival and survival free of major morbidity. STRIDER NZAus is part of an international collaboration planning an individual patient data (IPD) analysis of several (bi-)national STRIDER trials. The IPD Collaboration has worked on study design, outcomes and data collection. All STRIDER trials will use very similar methodologies and outcomes to ensure they are comparable and compatible for future analysis. **This IPD will be powered to assess a primary outcome of survival free of major morbidity at time of hospital discharge.** For example, with an estimate of 21% (placebo) ⁴ vs 35% (sildenafil), α 0.05, two sided test and 90% power to detect difference, a total of 504 women need to be randomised (229 per group and 10% drop-out rate).

Other STRIDER trials are planned in UK/Ireland, the Netherlands, Canada and USA. The international collaboration is supported by the GoNet (Global Obstetrics Network) Initiative which aims to support and synergise global alignment, coordination and collaboration of perinatal research ²¹.

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