STRIDER NZAus

Protocol

STRIDER (NZAus): A Randomised Controlled Trial of **S**ildenafil **T**her**r**apy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction (New Zealand and Australia).

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List of abbreviations

AEDF	Absent Umbilical Arterial End Diastolic Flow
AC	Abdominal Circumference
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BP	Blood Pressure
BPD	Biparietal Diameter
CNS	Central Nervous System
CRF	Case Report Form
CS	Caesarean Section
CTG	Cardiotocography
DSMB	Data and Safety Monitoring Board
DV	Ductus Venosus
EDD	Expected Delivery Date
EFW	Estimated Fetal Weight
EVT	Extravillous Trophoblast
FBC	Full Blood Count
FL	Femur Length
GA	Gestational Age
HC	Head Circumference
HIE	Hypoxic–Ischemic Encephalopathy
IPD	Individual Patient Data
IUGR	Intrauterine Growth Restriction
LFT	Liver Function Tests
LMP	Last Menstrual Period
MCA	Middle Cerebral Artery
MFM	Maternal Fetal Medicine
NEC	Necrotising Enterocolitis
NICU	Neonatal Intensive Care Unit
NO	Nitric Oxide
PI	Pulsatility Index
PPHN	Persistent Pulmonary Hypertension of The Newborn
PSV	Peak Systolic Velocity
RCT	Randomised Control Trial
REDF	Reversed Umbilical Arterial End Diastolic Flow
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SGA	Small for Gestational Age
SMD	Subject Medication Diary
SUSAR	Suspected Unexpected Serious Adverse Reaction
UA	Umbilical Artery
UV	Umbilical Vein

1. SUMMARY

Severe early onset intrauterine growth restriction (IUGR) is associated with high rates of death before birth, death in the neonatal period and long term handicap as a consequence of being born so early and so small. We currently have no treatment for this disease other than close monitoring and (if the baby is mature enough and grown sufficiently to have a chance of survival) delivery when monitoring suggests the situation is 'in extremis'.

The majority of these cases are due to abnormal placental development and poor blood supply to the fetus. Sildenafil, as a vasodilator, has the potential to improve blood supply to the uteroplacental vessels and thus improve supply to the baby and possibly aid fetal growth. Data from a small case-control study suggest some potential benefits in fetal growth associated with sildenafil use in pregnancies with very early onset IUGR where the prognosis was otherwise extremely poor.

The purpose of this double blind randomised placebo controlled trial is to assess the effect of sildenafil on fetal growth in similar pregnancies with poor prognosis. The results will be combined with similar planned studies worldwide to assess its impact on the most important outcome of all, neonatal survival free of major handicap.

2. BACKGROUND

2.1 SGA and IUGR

Being born small for gestational age (SGA) is one of the three major complications of pregnancy and occurs in approximately 10% of pregnancies. Babies may be born SGA and with no complications (constitutionally small) or due to a failure to fulfil their full 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.

IUGR occurring early in pregnancy is rare, affecting 0.2% of pregnancies <28 weeks gestation. Due to the severity of disease and extreme prematurity the risks to the fetus and infant are very high. Babies may die in-utero before reaching viable gestations or weights and are susceptible to the effects of hypoxia which may result in poor health in the neonatal period, as children and through to adulthood. There is currently no therapy to improve outcome once growth restriction has occurred and therefore the only treatment clinicians are able to offer is timely delivery. Intense monitoring aims to predict when the fetus has maximised its time in-utero and the risk of hypoxia and death is so high that early delivery is indicated. However, this often results in extreme preterm birth and its inherent risks including death, severe neonatal morbidity and again potential life-long health consequences. Recent North American data suggests of

infants delivered at 24-28 weeks with birthweight <10th centile, only 25% survive free of major morbidity, however by 30-32 weeks more than three quarters (78%) survive free of major morbidity [1].

Along with very significant health risks for these IUGR preterm babies there is an enormous emotional and financial burden for individuals, families, health care providers and society. The direct costs of their care, including the increased cost of intensive antenatal surveillance (and likely period of hospitalization), Caesarean delivery, neonatal intensive care, paediatric follow-up including specialised neurodevelopmental assessments and interventions, as well as the indirect costs to families (lost wages, supportive services, and relationship stress), contribute to a vastly disproportionate level of investment in these pregnancies. Therapy allowing expectant management and safe pregnancy prolongation could be associated with significant societal and financial savings.

2.2 Pathophysiology

The process of human placentation is central to reproductive success but complex and poorly understood. In normal pregnancy the uteroplacental circuit undergoes significant changes with extravillous trophoblast remodelling the maternal spiral arteries converting a high resistance, low flow circulation to a low resistance, high flow circulation, resulting in efficient gaseous and nutrient exchange across the placenta. In the process of normal spiral artery remodelling there is 'boring out' of the smooth muscle of these medium sized resistance vessels with removal of the nitric oxide (NO)-producing endothelium, the internal elastic lamina and the NO-responsive muscularis layers. The resulting effect of this removal of these layers by extravillous trophoblast is a system of vessels unresponsive to normal regional vascular control. Blood flow becomes predominantly modulated by changes in mean arterial pressure and regional blood flow diversion (e.g. to the thighs and buttocks during exercise).

IUGR (and preeclampsia) occurs as a consequence of inadequate or abnormal placental invasion and spiral artery remodelling leading to abnormalities of the maternal and/or fetal vascular compartments. This is reflected in abnormal Doppler waveforms of both fetal and maternal uteroplacental vessels. In IUGR poor gaseous and nutrient exchange across the placenta occurs as a result 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 this hypertensive disease.

2.3 Potential of sIldenafil, a NO-donor

Incomplete remodelling of maternal spiral arteries in cases of abnormal placentation results in a uteroplacental circulation with high resistance and low flow. The vessels have intact or partially intact muscular layers and so potentially remain responsive to nitric oxide. Sildenafil is a nitric oxide donor causing vasodilatation and so has the

potential to increase uteroplacental circulation and perfusion thus improving gaseous and nutrient exchange and fetal growth.

Animal Studies

In a mouse model of IUGR (catechol-O-methyl transferase knockout mouse (COMT-/-)) measures of pup growth, including body weight, crown/rump length and abdominal circumference were reduced compared to control mice. Treatment with sildenafil from gestational day 12.5 to 18.5 demonstrated normalisation of all growth measures. Despite no significant increase in uterine artery flow measured by Doppler waveform studies, abnormal umbilical Doppler waveforms (including reversed arterial blood flow velocity) normalized following treatment with sildenafil – suggesting a beneficial effect on fetoplacental blood flow [2]. Increased growth parameters have also been demonstrated in rat and guinea pig models [3, 4].

Human studies

In humans, ex vivo myometrial small artery function is aberrant in IUGR and sildenafil appears to improve vasodilatation in IUGR pregnancies. This has been demonstrated using small arteries dissected from myometrial biopsies obtained at Caesarean section from 27 normal pregnant women and 12 women whose pregnancies were complicated by IUGR [5]. Arteries were mounted on wire myographs and vessels constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation with sildenafil. Sildenafil significantly reduced vasoconstriction and significantly improved relaxation of IUGR small arteries.

2.4 Sildenafil in Pregnancy

As a nitric oxide donor, sildenafil is used in the management of pulmonary arterial hypertension for vasodilatation of pulmonary vasculature. There are now many case reports of its use in pregnancy [6-8] with improved maternal cardiorespiratory performance and 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 occurs as a result of failure of the pulmonary vasculature to relax at birth and consequent lack of the normal neonatal cardiorespiratory adaptation leading to hypoxaemia. This condition is more common in preterm infants and the risk of mortality and morbidity is high. Sildenafil selectively reduces pulmonary vascular resistance and appears to be a useful adjunctive therapy to current care including inhaled nitric oxide (iNO) therapy, surfactant and high-frequency oscillatory ventilation [9].

Interest in the use of sildenafil for the treatment of other placental ischaemic conditions has led to a small placebo controlled randomised trial of its use in women with early onset preeclampsia (NCT 00141310) [10]. In this British study, 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.

2.5 Sildenafil and IUGR – Clinical experience

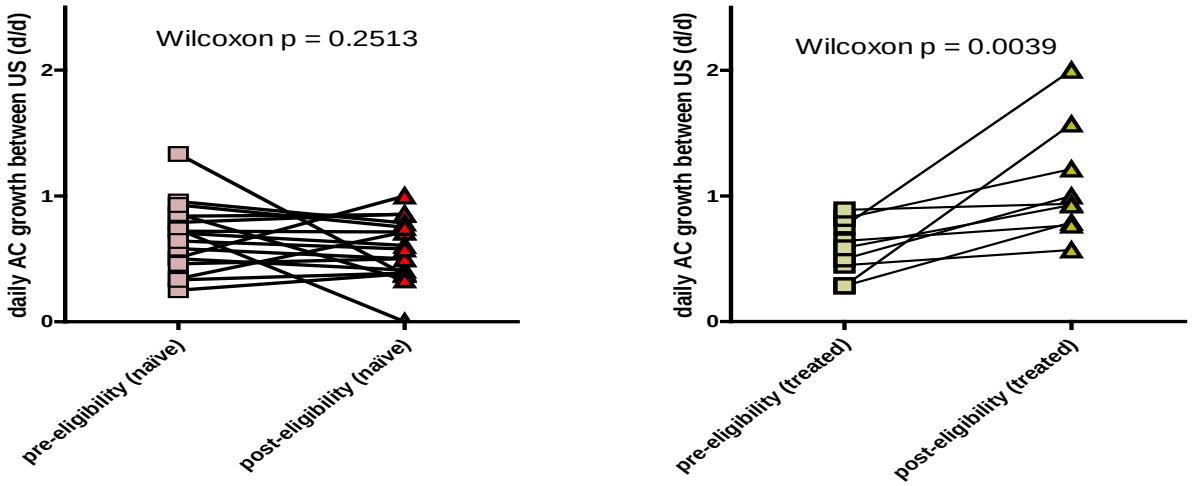
Whilst working in Canada, Professor Phil Baker has gained, and published his, experience of the use of sildenafil in women with severely growth restricted fetuses [11]. Within the British Columbia Provincial Health Services Authority there is a process for offering patients innovative therapy through formal information sharing and consenting process. Through this mechanism, patients facing dire prognoses can be offered innovative therapeutic interventions. Under this rubric, 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 demographics and outcomes are summarised in Table 1.

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 48h 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.

Table 1: Demographic & outcome data case-control study of sildenafil for severe early onset IUGR [11]. Expressed as median [interquartile range] or absolute number (%).

	Sildenafil-naïve (n=17)	Sildenafil-treated (n=10)	p value
Demographics			
Maternal age at EDD (years)	33 [28, 36.5]	34 [25, 40.5]	0.73
Nulliparous	8 (47%)	5 (50%)	1.00
GA at eligibility (days since LMP)	148 [137.5, 163]	158 [147.5, 164.5]	0.15
Uterine artery notching at eligibility	10 (59%)	8 (80%)	0.41
AC <1st percentile at eligibility	10 (59%)	6 (60%)	1.00
Umbilical artery Doppler positive EDF	13 (76%)	5 (50%)	0.22
Amniotic fluid index >50mm	15 (88%)	6 (60%)	0.15
Outcomes			
Secondary development of preeclampsia	5/9 (56%)	2/12 (17%)	0.16
Fetus with increased AC growth velocity post-eligibility/on Sildenafil	7 (41%)	9 (90%)	***0.02***
Eligibility-to-delivery interval (days)	42 [17, 55]	31.5 [9.5, 81]	0.87
GA at delivery (days since LMP)	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

Figure 1: Change in daily AC growth pre versus post-eligibility epochs.[11]



As yet there is no treatment for severe early onset IUGR other than delivery of the fetus with the inherent risks of extreme prematurity. This improvement in fetal growth after sildenafil treatment is exciting and if confirmed has potential for future therapy in these very high risk pregnancies. However, a great deal more evidence, both in terms of safety and outcome data, is required before it can be used in clinical practice.

STRIDER NZAus is a double blind randomised placebo controlled trial. It is designed with sufficient power to assess the effect of sildenafil on fetal growth velocity and further explore its safety profile in pregnancies complicated by severe early onset IUGR. STRIDER NZAus will be led by investigators at the University of Auckland and will recruit women from Maternal Fetal Medicine (MFM) centres across New Zealand and Australia.

The STRIDER IPD Collaboration is an international collaboration of individual patient data (IPD) analysis of several national (and bi-national) STRIDER RCTs. This prospectively planned IPD will have sufficient power to assess the effect of sildenafil on rates of survival without major morbidity in pregnancies complicated by severe early onset IUGR. Other STRIDER trials are planned in Ireland, Canada, United Kingdom and the Netherlands. The STRIDER IPD Collaboration will be led by Dr Peter von Dadelszen, University of British Columbia, Canada and Professor Philip Baker, University of Auckland, New Zealand.

3. TRIAL HYPOTHESIS & AIMS

3.1 Hypothesis

The primary hypothesis is: sildenafil therapy compared to placebo therapy will increase the likelihood of increased fetal growth velocity (measured by change in expected/observed increase in abdominal circumference per day) in pregnancies complicated by severe early onset IUGR.

This hypothesis has been set in line with the STRIDER IPD Collaboration.

3.2 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.

This aim has been selected in line with the STRIDER IPD Collaboration.

3.3 Secondary Aims

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 to EDD or hospital discharge (whichever comes later) 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.

3.4 Aim of STRIDER IPD Collaboration

To assess the effect of sildenafil compared to placebo therapy on the rates of infant survival without major morbidity (no evidence of CNS injury, bronchopulmonary dysplasia requiring home oxygen therapy, ≥grade 3 ROP or NEC) in pregnancies complicated by severe early onset IUGR. Outcome data relating to this outcome will be collected in STRIDER NZAus.

4. TRIAL & DRUG SAFETY

4.1 Potential Risks of IUGR to the Baby

There are significant risks for a fetus with severe early onset growth restriction. In-utero death may occur prior to reaching a viable gestational age or birthweight and, of infants born alive, 30% will die in the neonatal period and only 25% survive free of major morbidity [1].

4.2 Potential Risks of IUGR to the Mother

The main risk to the mother with severe early onset IUGR pregnancy is the development of secondary pre-eclampsia. 40% of cases of early onset IUGR are likely to develop co-existing preeclampsia. Close and systematic maternal assessment and surveillance is essential to monitor for preeclampsia. In addition if the fetus is considered viable and

delivery is required for severe early onset IUGR, operative caesarean section is almost always required to safely deliver the 'at risk' infant.

4.3 Potential Risks of Sildenafil Treatment

The most common sildenafil related side effects are headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision. (Sildenafil Citrate Data Sheet. Actavis. www.medsafe.govt.nz/profs/datasheet/s/silagratab.pdf). None of the women treated with sildenafil for severe early onset IUGR at British Columbia Women's Hospital complained of side effects [11] and sildenafil was similarly well tolerated in the UK RCT for pre-eclampsia [10]. Women will be asked to verbally report side effects and record these in their Subject Medication Diary (SMD) and this data will be collected in the CRF.

It is possible that sildenafil may improve fetal growth velocity to gain gestational age and maturity to a level that an infant that would have demised in-utero actually survives but due to the nature of extreme preterm birth and growth restriction has significant long term handicap. However if sildenafil does demonstrate an improvement in fetal growth velocity that results in improved survival, it is likely that it will also improve fetal growth in babies that would usually have survived with handicap to allow them to reach an age and size where handicap is less likely. One of the primary aims of this study is to assess this potential impact.

It is also possible that sildenafil has no effect or a negative effect on fetal growth velocity. In addition, vasodilatation in an already compromised fetus (with abnormal fetal Doppler waveforms) may lead to decompensation and earlier demise of a sick fetus. These possibilities can only be accurately assessed through an RCT of this nature.

5. STUDY DESIGN

STRIDER NZAus is a bi-national multicentre double blind randomised placebo controlled trial with intention-to-treat analysis.

5.1 Participating Centres:

Subjects will be recruited from Maternal Fetal Medicine centres across New Zealand and Australia. Each centre will nominate local investigators to oversee local recruitment.

The STRIDER NZAus trial will be coordinated by staff at The University of Auckland. Staff at the Auckland coordinating centre will include the STRIDER NZAus Principal Investigator and Lead Investigators, STRIDER NZAus Clinical Trial Manager, research midwives, research fellow (responsible for myometrial and placental studies) and any other staff required to support clinical trial activities or analysis.

5.2 STRIDER IPD Collaboration

Study design and outcome measures are aligned with other planned STRIDER trials in Ireland/United Kingdom, Canada and the Netherlands. Each trial will be funded and managed individually but results will be used in an international collaboration of IPD analysis (STRIDER IPD Collaboration). This prospectively planned IPD will have sufficient power to assess the effect of sildenafil on rates of survival without major morbidity in pregnancies complicated by severe early onset IUGR.

6. STUDY POPULATION – Inclusion & Exclusion Criteria

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

6.1 Inclusion Criteria:

1. Singleton pregnancy.

2a. $\geq 22^{0}$ weeks and $\leq 27^{6}$ weeks: AC measure ≤3rd percentile for gestational age; OR

2b. $\geq 28^{0}$ weeks and $\leq 29^{6}$ weeks: ultrasound estimate of fetal weight (EFW) <700g.

These criteria have been set in line with the STRIDER IPD Collaboration.

AC percentile must be calculated using ASUM Campbell Westerway chart [12]. EFW must be calculated using the Hadlock C formula [13].

6.2 Exclusion Criteria:

1. Known major fetal anomaly/syndrome/congenital infection that is deemed to be the likely cause for IUGR.
2. Known fetal aneuploidy (if untested for aneuploidy are eligible for the trial).
3. Already made plan for termination of pregnancy.
4. Maternal disease (e.g. preeclampsia) where it is expected that delivery is necessary within next 48 hours.
5. Any contraindication to sildenafil therapy.

These criteria have been set in line with the STRIDER IPD Collaboration.

6.3 Withdrawal of subjects

All study participants are free to discontinue the study drug and/or withdraw their consent at any point during treatment without prejudice. If a subject indicates that they wish to withdraw their consent for further participation data collected to the point of withdrawal will be retained and used as part of the intent to treat analysis. The Investigator is encouraged to ask a subject who is withdrawing which level of continued participation they agree to. Subjects who elect to discontinue the study drug early (subject initiated discontinuation prior to 32 weeks or delivery), may continue their participation in one of the following ways:

1. Early discontinuation of study drug but continue with all other trial involvement.
2. Early discontinuation of study drug, continued collection of data from clinical records and follow up contact to 6-12 weeks after delivery.
3. Early discontinuation of study drug, continued collection of data from clinical records only. No follow up contact.
4. Complete withdrawal of consent, i.e. early discontinuation of study drug, no further collection of data from clinical records and no follow up contact. If a subject specifically requests complete withdrawal of consent publically available information only such as from the Birth Register may still be accessed to collect survival status.

The level of continued follow up data collection a subject will permit must be recorded in the CRF. Wherever possible the reason for study treatment discontinuation or withdrawal of consent should be recorded in the CRF. All subjects will receive ongoing medical care according to clinical need.

7. STUDY NUMBERS & POWER CALCULATION

7.1 STRIDER NZAus study

Assuming 50% (placebo-treated) vs 80% (sildenafil-treated) 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**.

7.2 STRIDER IPD Collaboration

To be confirmed by STRIDER IPD Collaboration. Example: Assuming a 21% (placebo-treated) vs 35% rate of survival free of major handicap at the time of hospital discharge or EDD, whichever is later, (sildenafil-treated), with an α of 0.05, two sided, we will have 90% power to detect this difference if a total of 504 women are randomised at a ratio of 1:1 (229 in each treatment arm and 10% drop-out rate). STRIDER NZAus will contribute 122 cases to this IPD analysis.

7.3 Feasibility of recruitment

In a retrospective audit of deliveries 20^{+0} to 29^{+6} weeks at National Women's Hospital, Auckland 2006-2010 (inclusive), a total of 271 pregnancies were identified. However, only 53 cases met the study inclusion criteria and had the criteria identified before delivery. Allowing for some women who 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.

8. SUBJECT SELECTION & RECRUITMENT

Due to the very high risk nature of these pregnancies, women who are eligible for the STRIDER NZAus study are expected to be under the care of the Maternal Fetal Medicine high risk teams in each recruiting centre. Once women have been identified as eligible by meeting the inclusion criteria (and have no exclusion criteria) they will be provided with information regarding the trial. This will be done verbally and with a written information sheet and consent form provided by the study investigators.
All women will be given time for full consideration and consultation as required. Contact telephone numbers will be provided. Study investigators or the research midwife will then meet with the potential recruit again and if women wish to join the study the consent process, randomisation and first visit will be completed. Signed, written consent must be obtained by the subject in the presence of a Study Investigator.

For women who decline to take part in this drug trial antenatal care will continue to the same standard as for all women with this condition. Sildenafil will not be available as part of this standard of care.
Only after declining participation these women will be invited to contribute to the study by collection of data only. This should only be offered once women have had time to fully consider participation in the randomised trial and have formally declined. Signed consent for the collection of data only must be provided by the subject and Study Investigator (on the Declined Randomisation – Observational Group information sheet and consent form). Refer section 14 of the protocol for details of data collection for this group.

9. RANDOMISATION

This will be performed using a web-based randomisation service operating at British Columbia Women's Hospital (Vancouver, Canada). Randomisation will be stratified for;

1. Gestational age at recruitment (< or ≥ 24 weeks)
2. Present or absent/reversed end-diastolic flow in umbilical artery Doppler waveform.

Women will be randomised on a 1:1 ratio to sildenafil:placebo. The randomisation process will assign each subject with a unique study ID number. This study ID number will be required when allocating study drug containers and for recording data on the CRF. The randomisation service provides 24 hour access, 7 days per week.

If a woman is found not to be eligible for the trial when her details are entered into the randomisation program the program will return a screen failure notification. Potential subjects who have screen failed can be re-screened for eligibility and included in the trial at a later date if appropriate.

10. TREATMENT GROUPS & STUDY DRUG

10.1 Treatment groups

Women will be randomised to one of two groups:

1. *Sildenafil*
   Oral sildenafil citrate 25mg three times daily (tds).

OR

2. *Placebo*
   Matching placebo tablets containing no active ingredient three times daily (tds).

Participants, medical professionals caring for women and study investigators will remain blinded to treatment allocation until the study is completed and database lock has occurred.

These dosing regimens have been set in line with the STRIDER IPD Collaboration.

10.2 Drug Supply and Storage

Each study drug container will contain 30 tablets, equivalent to a 10 day supply. Both sildenafil and identical placebo tablets (containing no sildenafil citrate) will be sourced from a single supplier (Actavis). It will be packaged centrally (Anqual, School of Pharmacy, University of Auckland) and distributed to each study site according to requirement.

The Investigator at each site is responsible for study drug inventory and accountability throughout the trial. The study drug must be stored in a limited access area or locked cabinet. Storage should be in a temperature controlled area below 25^{o}C.

10.3 Drug Issue and assessment of Compliance

At the time of randomisation the study drug allocation program (web based) will assign the first study drug container. Study drug will be re-issued as required thereafter by the study investigators and/or delegated study staff such as a research midwife. Subjects will be asked to return used and unused medication containers for regular 'pill count' to assess compliance. Women will also be asked to record their study drug usage in a subject medication diary (SMD).

10.4 Emergency Unblinding

In the event that there is an immediate need for the treating doctor to know a subject's treatment allocation in order to ensure patient safety it will be possible to break the randomisation code. The facility to perform emergency unblinding will be available 24 hours per day. It is recommended that the Investigator contact the Auckland Principal Investigator to discuss the particular situation before breaking the subject's randomisation code, if possible.

11. TREATMENT DURATION/INDICATIONS TO STOP TREATMENT

11.1 Treatment duration

Study drug treatment will commence as soon as possible following randomisation and continue tds until delivery or 32^0 weeks gestation (or intrauterine demise). Due to the nature of this condition and the inclusion criteria set it is unlikely that pregnancies will proceed beyond 32^0 weeks i.e. fetal compromise will determine that earlier delivery is necessary. In the event that a woman remains pregnant at 32^0 weeks treatment will be stopped as neonatal outcomes beyond this gestation are generally very good and so it will no longer be appropriate to continue to use the study drug.

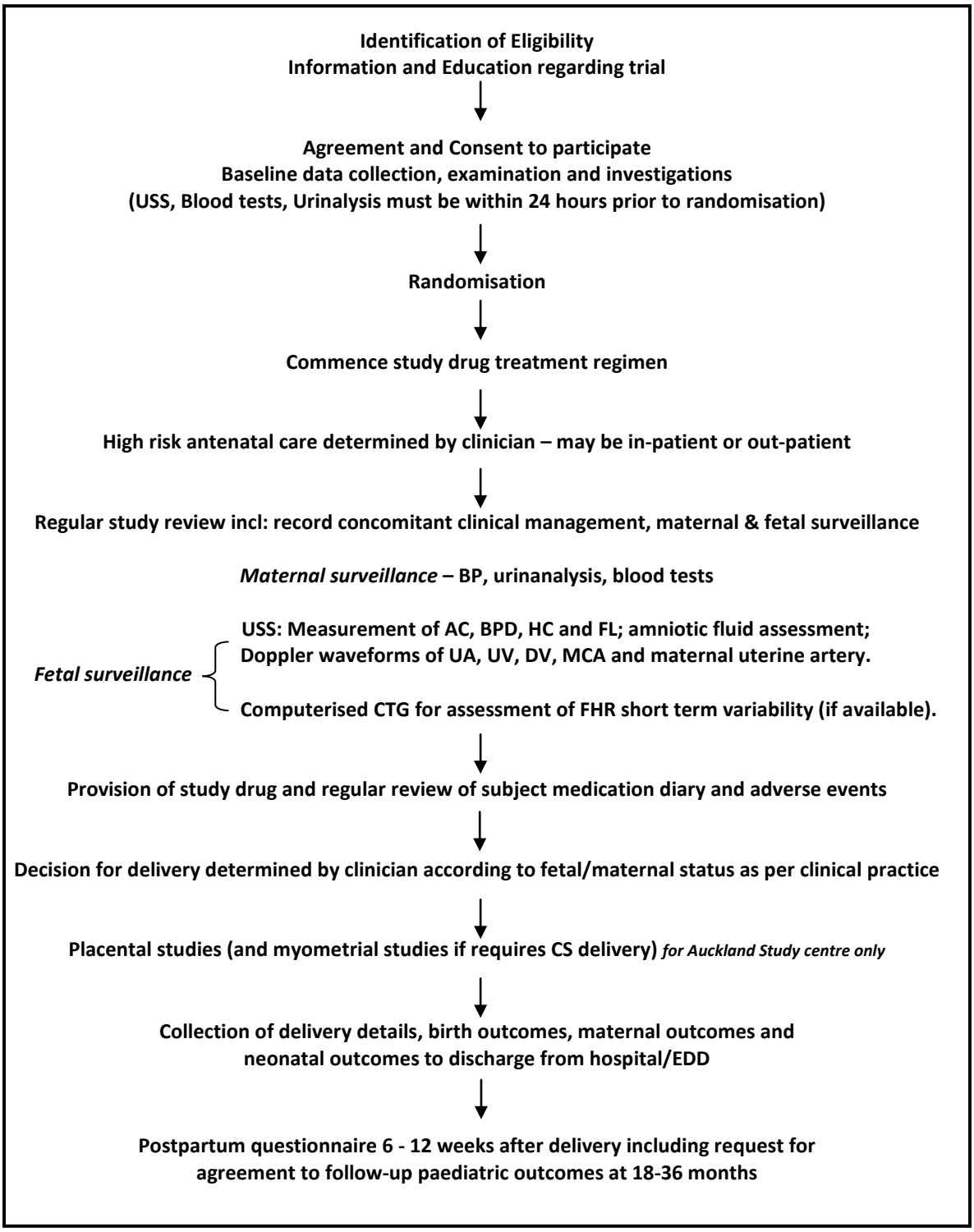
11.2 Additional indications to stop treatment

1. Severe maternal hypotension causing maternal and/or fetal compromise in the absence of other anti-hypertensive drug use (i.e. stop other antihypertensives first).
2. If the Investigator believes that it is in the best interests of the subject for safety or tolerability reasons (e.g. due an Adverse or Serious adverse event).
3. Subject request to discontinue study drug.

12. STUDY PROCEDURES & SUBJECT FLOW CHART

The study procedures are summarised in the flow chart below and in the schedule of assessments (Appendix 1).

Individual Subject Trial Flow Chart



12.1 Baseline data collection

Medical history and demographics: data will be collected on current and past medical history and demographics including date of birth, ethnicity, height and weight, past obstetric history, past medical history, medication use, details of aneuploidy screening and invasive tests and fetal infection screen.

Previous Ultrasound Scan (USS) data: the abdominal circumference (AC) measurement will be collected from the two most recent scans available (not including the randomisation scan). If multiple AC measurements are available one of the documented AC measurements should be from a scan > 12 days and as close to 14 days prior to randomisation.

Maternal assessments:

- Blood test results performed ≤24 hours prior to randomisation will be collected including: Full Blood Count (platelets), renal (creatinine, urea, urate) and liver function (AST, ALT, albumin).
- Urinalysis results performed ≤24 hours prior to randomisation will be collected.
- The highest blood pressure recording from the day of randomisation, prior to study drug treatment, will be collected.

Randomisation USS:

An USS must be performed ≤24 hours prior to randomisation and should include the following:

- Fetal growth measurements: abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL).
- Amniotic fluid measurement: single deepest vertical pocket.
- Doppler waveforms: umbilical artery (PI and presence/absence or reversed end diastolic flow) umbilical vein (pulsatile or non-pulsatile), ductus venosus (PI, presence of positive a wave), middle cerebral artery (MCA) (PI, PSV) and maternal uterine artery (PI, presence of notch).

Informed consent should be obtained before any study procedures which are not otherwise clinically indicated are performed or repeated for the purpose of meeting trial eligibility.

12.2 Study Drug Treatment Phase

Standard clinical management should be carried out at the discretion of the Investigator. It is anticipated that in many cases clinical assessments and scans will be required more frequently than the study protocol requires.

The study protocol time points are 48 hours, 5 days, 10 days, 14 days and weekly thereafter post-randomisation. With the exception of the first post-treatment study assessment which must be conducted as close as possible to 48 hours post-randomisation, routine clinical assessment and scan data can be used and the

assessment results closest to the protocol time points should be collected (recommended to be within +/- 2 days).

Maternal Assessment

The following assessments will be completed at 48 hours (BP only), days 5, 10, 14 and then weekly following randomisation:

- Blood pressure measurement.
- Dipstick urinalysis +/- Protein/Creatinine ratio or 24 hour urine collection.
- Blood tests including: Full blood count (platelets), renal (creatinine, urea, urate) and liver (AST, ALT, albumin) function.
- Concomitant medication review.
- Review of study drug compliance and SMD.
- Adverse Event/Serious Adverse Event assessment.
- Review of antenatal management.

Fetal Assessment

Ultrasound Scan

Following randomisation an USS should be performed at 48 hours, days 5, 10, 14 and then continued on a weekly basis and should include the following:

- Fetal growth measurements: AC, BPD, HC and FL.
- Amniotic fluid measurement: single deepest vertical pocket.
- Doppler waveforms: UA (PI and presence/absence or reversed end diastolic flow) UV (pulsatile or non-pulsatile), DV (PI, presence of positive a wave), MCA (PI, PSV) and maternal uterine artery (PI, presence of notch).

USS scans are performed in routine clinical practice in assessment of severe IUGR and will follow standard protocols (as described in the Ultrasound Imaging Manual).

Computerised CTG

Once the fetus has reached viability i.e. >24 weeks and EFW >500g, confirmed by medical team caring for each individual (with consideration for corticosteroids), a weekly computerised CTG will be performed to record short term variability, if available at the study site.

The above maternal and fetal assessments should continue until study drug treatment is discontinued or delivery occurs, whichever comes first. If study drug treatment is discontinued prior to delivery an additional post-treatment assessment should be carried out greater than 48 hours (but within 10 days) after the last dose of study drug.

12.3 Concomitant clinical management and co-interventions

Approximately 40% of women with severe early onset IUGR will develop or already have preeclampsia, this will require additional therapies, surveillance and possibly delivery indicated on maternal rather than fetal grounds.

All women with severe early onset IUGR, regardless of co-existing preeclampsia, will require intense fetal surveillance, possible in-patient stay and early delivery. Once the fetus has reached an appropriate gestational age and size (and is deemed viable) corticosteroids will be administered to improve fetal lung maturity and once delivery is planned magnesium sulphate therapy will be considered for perinatal neuroprotection. 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 by study investigators and will be recorded in the SMD.

Sildenafil is an antihypertensive agent and may be sufficient treatment for women with hypertension. In the event that further antihypertensive treatment is required, the recommended agents are; labetalol and methyldopa. Nifedipine and other calcium channel blockers are not recommended as first line treatment but may be considered if additional treatment is required. If women are already well controlled on an agent transfer to labetalol or methyldopa is not mandatory.

12.4 Placental tissue (for Auckland study recruits only)

A biopsy of placental tissue will be taken after delivery. This tissue will be analysed within the laboratory to compare the effect of sildenafil and placebo on chorionic plate and stem villous blood vessels within the placenta. See appendix for sample collection details.

This part of the study will be optional and women will have the opportunity to take part in the STRIDER NZAus study without consent for placental examination if they wish.

12.5 Myometrial biopsy: (for Auckland study recruits only)

The majority of women will require delivery by caesarean section (CS) due to the high risk nature of their pregnancy and risk to the fetus/neonate going through the stress of labour. In women undergoing CS, a small piece of muscle (approximately 0.5cm x 0.5 cm x 0.5cm) will be dissected from the uterine wall (at the site of the placental attachment) at the time of delivery in women undergoing caesarean section. The technique for sampling is safe and has been used for many years for research purposes; it will not affect the duration of the operation, cause any pain or discomfort to women and will not impair uterine healing following surgery. See appendix for sample collection details.

This part of the study will be optional and women will have the opportunity to take part in the STRIDER NZAus study without consent for myometrial examination if they wish.

12.6 Outcome data collection

Detailed data will be collected regarding delivery, maternal and fetal outcomes from the maternal and neonatal records. Maternal outcome data will be collected until the time of maternal hospital discharge. Neonatal outcome data will be collected to the time of hospital discharge or EDD, whichever is later. For neonates who are discharged from hospital prior to their EDD a phone call will be conducted by the Investigator or site

staff, i.e. research midwife, to collect any additional data/confirm no new diagnoses have been made up to the date of EDD.
A maternal and neonatal post-partum questionnaire will be carried out 6 – 12 weeks after delivery and will include request for agreement to follow up paediatric outcomes at 18-36 months (subject to additional funding being obtained).

13. SAFETY ASSESSMENT & MONITORING

13.1 Assessment of Adverse Events

Information will be collected regarding all adverse events (AE) that occur from the time of randomisation until maternal hospital discharge after delivery; fetal/neonatal death occurring prior to discharge or EDD; neonatal hospital discharge or EDD, whichever is later.

The general definition of an AE is any unfavourable and unintended change in structure, function, or chemistry of the body temporally associated with the study medication whether or not considered related to the use of the study medication. Worsening of pre-existing condition which is temporally associated with the use of the study medication may also be considered an AE.

In this high-risk population a large number of complications are anticipated in the absence of trial participation. Investigators should take the underlying condition into account in their assessment of potential adverse and serious adverse events. In general the following expected events do not need to be reported as AEs/SAEs unless the Investigator considers the event to be possibly, probably or definitely related to the study drug; these events will be documented in the CRF as part of maternal, delivery and neonatal outcomes:

- Gestational hypertension
- Preeclampsia
- Preterm delivery
- Hospitalisation due to preeclampsia
- Hospitalisation for fetal monitoring due to IUGR
- Hospitalisation for delivery
- Caesarean section
- Postpartum haemorrhage >500ml and <1000ml
- Admission to NICU
- Neonatal complications of prematurity

13.2 Serious Adverse Events

In this trial the following will be considered serious adverse events:

- Maternal death
- Fetal death
- Neonatal death

- Maternal life threatening event
- Maternal persistent or significant disability or incapacity
- Major antepartum or postpartum haemorrhage (>1000ml)
- Maternal hospitalisation/prolonged hospitalisation not related to preeclampsia, IUGR or standard postnatal recovery
- Unexpected congenital anomaly/birth defect
- Other medically important event considered to be an SAE by Investigator

Important medical events that may not result in death, threat to life, or not require hospitalisation may be also considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. The term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe.

13.3 Investigator review of AEs/SAEs:

The maximum intensity of adverse and serious adverse events must be assessed by an Investigator. The following are the minimum parameters to be collected for each event:

- Maximum intensity:

  Mild is awareness of sign or symptom, but easily tolerated
  Moderate is discomfort enough to interfere with usual activity
  Severe is incapacitating with inability to work or do usual activity
  Death

- Duration. The start and stop dates will be identified and recorded.

- Action taken in regards to the study drug. Does the event cause the study medication to be temporarily or permanently discontinued?

- Relationship to study medication. The investigator will determine if the study medication contributed to the AE/SAE. Factors to consider:

  Exposure: Was subject exposed to the study drug?

  Likely cause: Is the event reasonably explained by aetiology such as underlying disease or other environmental factors?

  Re-challenge: Was the subject re-exposed to the study drug? If yes, did the event recur or worsen?

Consistency with the study medication: Is the clinical/pathology presentation of the event consistent with previous knowledge regarding the study medication?

- Details of any treatment given.

Expectedness of SAEs

SAEs must also be assessed for expectedness in this clinical setting. The Investigator is responsible for determining whether an SAE is expected or not based on the underlying severe IUGR and the published reference safety information for sildenafil (this can include a sildenafil Investigator's Brochure, MedSafe/TGA product Data Sheets and this protocol). An unexpected adverse event/reaction is one that is not reported in the reference safety information, is more severe than previously reported or is not reasonably explained by the underlying condition.

Review of all of the known information about the SAE should conclude one of the following:

Expected Events:

- Expected Unrelated Event: the SAE is expected based on the known information about the study drug or the underlying condition and is not considered to be related to the study drug. This is referred to as an Expected SAE.
- Expected Related Event: an SAE which the Investigator considers possibly, probably or definitely related to the study drug. This is referred to as a SAR – Serious Adverse Reaction.

Unexpected Events:

- Unexpected Unrelated Event: the SAE is unexpected based on the known information about the drug or the underlying condition and is not considered related to the study drug. This is referred to as an Unexpected SAE.
- Unexpected Related Event: the SAE is unexpected based on the known information about the drug or the underlying condition and is considered possibly, probably or definitely related to the study drug. This is referred to as a SUSAR – Suspected Unexpected Serious Adverse Reaction.

In this cohort of early-onset severe IUGR and with the lack of an alternative therapy, fetal or neonatal death due to complications of severe IUGR or prematurity and prolonged stay in the neonatal unit and may occur and in this setting and so may be Expected Events (Expected SAEs). These fetal or neonatal deaths in the study reporting period will be recorded as SAEs on the CRF but do not require immediate reporting unless the Investigator has specific concerns about these events or believes they are likely to be causally related to the study drug i.e. considered as a SAR or SUSAR.

Maternal death and maternal life-threatening complications should always be considered unexpected events in this population and require immediate reporting.

13.4 Procedure for AE and SAE Reporting

All AEs and SAEs must be documented in the subject's CRF. SAEs may also require immediate reporting by the site, as below:

Actions for SAEs:

1. Report immediately, within 24 hours of becoming aware of the event:
- SAR – suspected adverse reaction.
- Unexpected SAE.
- SUSAR – Suspected Unexpected Serious Adverse Reaction.

2. Documented in the CRF only (do not require immediate reporting):
- Expected SAE.

Unexpected SAEs, SUSARs and SARs will be reported to the STRIDER DSMB, regulatory authorities and ethics committees, as required.

13.5 Data Safety Monitoring Board (DSMB)

The STRIDER NZAus has established a local DSMB chaired by Professor Caroline Crowther, Professor of Maternal and Perinatal Health, Liggins Institute, University of Auckland. The STRIDER NZAus DSMB will report to the Lead Investigator team. If required they will also liaise with the STRIDER IPD DSMB.

The DMSB established by the STRIDER IPD Collaboration includes experts in the field of obstetrics, MFM, neonatology, clinical pharmacology and epidemiology. The chair of the IPD DSMB is Dr Gideon Koren, Professor of Paediatrics and Clinical Pharmacology, University of Toronto.

14. DATA COLLECTION FOR THE OBSERVATIONAL GROUP

Women may agree to allow collection of their data only as part of the "Declined Randomisation – Observational Group". This should only be offered once women have had time to fully consider participation in the randomised trial and have formally declined. Women must provide signed, written consent to this level of participation. After consent has been obtained for a participant in this group they will be registered and will be provided with a unique study ID number which will be used when recording data on the CRF.

Care for these women will be as per standard clinical practice. Data will be collected from the subject's medical record and may include details of clinical indicated ultrasound scans, maternal assessments, details of pregnancy care and maternal and fetal/neonatal outcomes.

Data from this group of subjects will be used to help determine if the randomised study population is reflective of the general population at similar risk. It may also be included in the trial analysis as an additional comparator group. Subjects registered to the Observational group will have the same rights to study withdrawal and confidentiality as randomised trial subjects.

15. CONFIDENTIALITY & DATA COLLECTION

Data will be collected on CRFs using the subject's study ID number to ensure confidentiality for each woman and neonate. Data will be entered onto hard copy CRFs and into an electronic eCRF database. Completed hard copy CRFs will be submitted to the Auckland coordinating centre.
A copy of the signed consent form and contact details, including identifying information, for each randomised subject will be securely transmitted to the Auckland coordinating centre for the purpose of follow up. This data along with hard copy CRFs will be stored in the Department of Obstetrics and Gynaecology, University of Auckland for a minimum of 10 years. The Principal Investigator will remain responsible for data stored. Authorised staff at the Auckland coordinator centre will be the only individuals with access to this data.
The STRIDER NZAus Principal Investigator will release data for STRIDER IPD Collaboration. All data will be transferred under study ID only and will remain de-identified.

All investigators and subjects will remain blinded to treatment allocations until the study is complete and database lock has occurred. If a subject is un-blinded due to an urgent clinical need to reveal the study allocation the Investigator is advised to limit the distribution of this information to other site staff or study personnel.

16. OUTCOME MEASURES

16.1 Primary Outcome

The primary outcome is increase in fetal growth velocity.

Fetal growth velocity will be determined by AC growth velocity. Mean daily increase in AC (calculated as a proportion to that expected if AC were on 50th centile for gestational age) pre and post treatment will be compared.
Pre-treatment growth velocity epoch will be calculated from: most recent AC measurement >12 days and recruitment AC measure. Where there is no previous scan with recorded AC, the AC will have been assumed to lie on 50th centile at 8 weeks gestation.

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).
The proportions with increased AC growth velocity in the sildenafil group and placebo group will be compared.

This primary outcome has been selected in line with the STRIDER IPD Collaboration.

16.2 Secondary outcomes

Secondary outcomes include:

- Additional measures of fetal growth and wellbeing: mean absolute change in abdominal circumference (mm) per day, mean birthweight and mean birthweight centile, amniotic fluid index, deepest vertical amniotic fluid pocket and short term variability (STV) measured by computerised cardiotocography (CTG).
- Changes in uteroplacental, umbilical and fetal Doppler waveform studies.
- Maternal symptomatic hypotension, headaches, flushing and pre-eclampsia
- Randomisation-to-delivery interval, gestational age at delivery, mode of delivery and postpartum haemorrhage requiring transfusion.
- Measures of neonatal outcome; rates of intrauterine death, live-births, survival to hospital discharge, major morbidity including chronic lung disease requiring ambulatory oxygen therapy on hospital discharge, intraventricular haemorrhage grade 3-4, ≥grade 3 retinopathy of prematurity, necrotising enterocolitis, number of doses of surfactant, ventilator days, supplemental oxygen days and number of days to full feeds.
- Any adverse or serious adverse events.

For Auckland Study Centre

The effect of sildenafil compared to placebo will be assessed by vascular physiological studies:

Of myometrial vascular endothelial and vascular smooth muscle cells
Of placental chorionic plate and stem villous blood vessels.

16.3 Primary outcome of STRIDER IPD Collaboration.

The rate of infant survival without major morbidity (no evidence of CNS injury, bronchopulmonary dysplasia requiring home oxygen therapy, ≥grade 3 ROP or NEC).

17. STATISTICAL ANALYSES

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

Demographic and other baseline data will be summarised by study treatment groups. For continuous outcomes, t-test, linear regression and mixed model for repeated measures method will be used where appropriate. For categorical outcomes, Fisher's exact test, logistic regression and generalised linear mixed effects model will be used where appropriate. 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.

Details of statistical analysis method are described in the Statistical Analysis Plan.

18. MONITORING OF STUDY PROGRESS

Progress reports will be circulated to all local investigators on a monthly basis by the Auckland coordinating centre. Reports will include information such as number of women recruited, number of women completing the study and any adverse events or SAEs. Local Investigators may be requested to provide updates on study activity at their centres throughout the trial.

19. STUDY TIMELINE

2012 & 2013

Protocol preparation, NZ Ethics application, Auckland locality approval and grant applications.

Preparation of case report forms, randomisation program.

Manufacture and packaging of drug and placebo.

June 2013 - June 2014

Locality assessment applications for Wellington and Christchurch centres.

Ethics applications for Australia and formal recruitment of Australian MFM centres.

January 2014

Commence recruitment over 2 years (or reached total recruitment required).

January 2016

Estimated End recruitment.

June 2016

Completion of data collection & data analysis.
Publication preparation.

January 2016 - January 2018

Follow-up of surviving children between 18 – 36 months (will include questionnaire and possible neurodevelopmental assessment – pending funding) (will require additional ethics and grant applications).

20. ETHICS & REGULATORY

The study will be conducted in line with the Principles of the Declaration of Helsinki (1996) and the Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) issued by the European Medicines Agency (EMEA), which is based on the International Committee for Harmonisation (ICH) document E6, as well as any other good clinical practice standard which applies in the country or state where the trial is being carried out.

All centres must have received Ethics approval by an Institutional Review Board (IRB) or Ethics Committee (EC) and regulatory approval (if applicable) before commencing recruitment.

Ethics approval for NZ centres has been granted by the NZ HDEC, Ref: CEN/12/06/028.

21. FUNDING

Funding has been granted by The Health Research Council of New Zealand (13-242) to cover all costs of the trial (start date 1st September 2013).

22. REFERENCES

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Appendix 1 - Schedule of assessments and procedures for randomised subjects.

Study assessment/procedure	**Screening & Randomisation** CRF 1,2,3	**Double-Blind Treatment Period**				**48 hours post-treatment**** (if not delivered) CRF 5	**Delivery** CRF 7,8	**Postnatal (discharge /neonatal EDD)** CRF 8,9	**Follow Up 6-12 weeks postpartum** CRF11
		48 hours post-randomisation CRF 4	**Day 5*** CRF 5	**Day 10*** CRF 5	**Day 14* & weekly* to delivery** CRF 5				
Review of Eligibility	X								
Informed Consent	X								
Demographics	X								
Medical/Obstetric History	X								
Current Pregnancy Characteristics	X								
USS[1]	X	X	X	X	X	X			
Blood Pressure	X	X	X	X	X	X			
Urinalysis[2]	X		X	X	X	X			
FBC, Renal function, LFTs[3]	X		X	X	X	X			
Concomitant Medication review	X		X	X	X	X			
Randomisation	X								
Issue of Study Drug[4]	X		←	X	→				
Review of Study Drug compliance & SMD			X	X	X	*x*	*x*		
Adverse Event/Serious Adverse Event Assessment[5]		X	X	X	X	X	X		
Review of Antenatal Management			X	X	X	X	X		
Computerised CTG short term variability[6]			*x*	*x*	*x*	*x*			
Placental & Myometrial biopsy (Auckland centre only)[7]							*x*		
Labour and Delivery details							X		
Maternal & Neonatal outcomes to hospital discharge/EDD							X	X	
Postpartum Questionnaire									X

1. Screening ultrasound must be performed <24 hours prior to randomisation. AC measurement will also be collected from previous scans, if available. Detail on scanning parameters is located in the Ultrasound Imaging Manual.
2. Screening Urinalysis to be performed <24 hours prior to randomisation: dipstick protein analysis (required); Protein/Creatinine ratio and/or 24 hour urinary protein (if performed).
3. Screening Blood tests to be performed <24 hours prior to randomisation: Platelets, Creatinine, Urea, Urate, AST, ALT, Albumin.
4. Study drug to commence as soon as possible after randomisation and to continue until physician decision for delivery, Intrauterine death, participant request for withdrawal, physician decision to stop study drug or 32^0 weeks gestation. Study drug should be re-issued as required.
5. AE/SAEs to be collected from the time of randomisation through to maternal hospital discharge after delivery; fetal/neonatal death occurring prior to discharge or EDD; neonatal hospital discharge or EDD, whichever is later.
6. Computerised CTG to be performed weekly once the fetus has been determined as viable by the participant's medical team, if available.
7. Auckland Centre only: Placental and/or Myometrial biopsy will be obtained from participants who have given consent for these optional procedures.

* Day 5 onwards the assessments as close as possible to each time point will be collected for study purposes. These may be on the same day or on different days. (Note: the date of assessment will be recorded as the date of USS scan).

** If the study drug is discontinued prior to delivery an additional post-treatment assessment should be carried out greater than 48 hours (but within 10 days) after the last dose of study drug.