STRIDER: A Randomized Controlled Trial of **S**ildenafil **T**he**r**apy In**D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction

Version: 3.0
Date: 18/08/2014

STRIDER STUDY PROTOCOL

PROTOCOL DETAILS

Full study title: A Randomized Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction

Short study title: **STRIDER**

Liverpool Women's Ref: LWH 0980 **University of Liverpool Ref: UoL000984**

EudraCT Number: 2013-005398-32 **MHRA CTA Number: 04196/0032/001-0001**

REC reference: 14/NE/0011 **ISRCTN Number:** ISRCTN39133303

Co-Sponsors: University of Liverpool; Research Support Office, Waterhouse Building, 3 Brownlow Street, Liverpool, L69 3GL, UK and Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool L8 7SS.

This trial will be conducted in accordance with the UK Clinical Trial Regulations incorporating Statutory Instruments 2004 No. 1031: Medicines for Human Use (Clinical Trials) regulations and all subsequent amendments 2006. The study is designed to comply with the guidelines developed by the International Conference for Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in accordance with LCTU, UoL and LWFT Standard Operating Procedures (SOPs).

Development Safety Update Reports will be prepared and submitted to the MHRA and the REC and copied to the Sponsor(s) annually by:

Name: Professor Zarko Alfirevic

Signature: Zarko Alfirevic

Date: 5-10-2014

Current Protocol Version: **3.0**

Current Protocol Date: **18/08/2014**

INVESTIGATOR DECLARATIONS

'I confirm that I have read and approved this research protocol'

Investigator Signature: Zarko Alfirevic **Date:** 8-10-2014

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SPONSOR STUDY PROTOCOL APPROVAL

'I confirm on behalf of the co-sponsoring organisation that I have read and approved this research protocol'

On behalf of the University of Liverpool:

Signature: A Astor **Date:** 14/10/14

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TRIAL SUMMARY

FULL TITLE OF STUDY: **STRIDER**: A Randomized Controlled Trial of **S**ildenafil **T**he**r**apy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction

SHORT TITLE: STRIDER: Sildenafil for Early-Onset IUGR

TRIAL ACRONYM: STRIDER

PROTOCOL NUMBER: 3.0

EUDRACT NUMBER: 2013-005398-32 **ISRCTN Number:** ISRCTN391333031

BACKGROUND: Early onset intrauterine growth restriction (IUGR) most commonly occurs when the placental transfer of nutrients and oxygen is impaired due to an inadequate placental implantation. The resulting fetal malnutrition and hypoxia are considered untreatable in utero. The only current option is an elective preterm delivery in order to rescue the baby from an adverse intrauterine environment. IUGR and the associated indicated preterm birth expose the fetus and neonate to significant mortality and morbidity. This diagnosis causes an important management dilemma: early delivery causes extreme prematurity with all its sequelae while delivering baby too late risks intrauterine death or morbidity secondary to critical fetal hypoxia.

Sildenafil potentiates the effect of nitric oxide (NO) and thus may cause vasodilatation of vessels responsive to NO. The incomplete remodelling of maternal spiral arteries in IUGR results in vessels with intact or partially intact muscular layers, which remain responsive to regional vascular control. Sildenafil has the potential to increase uteroplacental circulation and perfusion resulting in improved gaseous and nutrient exchange and improved fetal growth and well-being.

Use of sildenafil in an obstetric population has been limited, but several case reports and small studies now exist. Sildenafil has been used in selected cases for the treatment of maternal pulmonary arterial hypertension where there is growing data on both its safety and efficacy to improve both maternal and fetal outcomes. There is also limited data suggesting that sildenafil has the potential to increase fetal weight.

AIM: The overarching aim of the STRIDER trial is to determine whether maternal treatment with oral sildenafil citrate improves perinatal outcomes in pregnancies complicated by severe early-onset IUGR without increasing risks to the mother.

Outcomes will be collected at discharge from hospital.

PRIMARY OUTCOME: Primary outcome is randomisation to birth interval. One week difference in the mean randomisation to birth interval is considered to be clinically important.

SECONDARY OUTCOMES:

Fetal outcomes include:

i) estimated fetal weight;

ii) abdominal circumference growth velocity;

iii) serial measurements of Doppler pulsatility index in the umbilical artery, middle cerebral artery and ductus venosus and uterine arteries;

iv) serial measurements of short term variability of the fetal heart rate recorded by transabdominal cardiotococography

Infant outcomes include:

i) gestational age at birth (days);

ii) survival to discharge,

iii) birth weight centile,

iv) length of admission on the Neonatal Intensive Care Unit,

v) Bronchopulmonary dysplasia requiring oxygen 36 weeks corrected age,

vi) necrotising enterocolitis (requiring surgery),

vii) retinopathy of prematurity (requiring treatment such as laser, grade 2/3 or more);

viii) severe central nervous system injury (detected by ultrasound and/or MRI) periventricular leucomalacia grade II or more, or intracerebral haemorrhage grade III or more or hydrocephalus;

ix) confirmed sepsis by positive blood culture

x) Patent ductus arteriosus needing medical or surgical treatment

xi) need for inotropes or vasopressors

xii) number of doses of surfactant;

xiii) ventilator days;

xiv) supplemental oxygen days;

xv) number of days to full feeds.

Maternal safety monitoring include:

i) mode of delivery,

ii) standardised blood pressure and pulse monitoring during treatment,

iii) pre-eclampsia;

iv) postpartum haemorrhage;

v) recording of the side effects e.g. headache, facial flushing;

vi) in-patient postnatal stay

TRIAL DESIGN: Randomised, double blind, placebo controlled trial of 112 women with a diagnosis of severe early-onset intrauterine growth restriction

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

All legally adult women with a diagnosis of a pregnancy affected by severe early-onset IUGR between 22^{+0} and 29^{+6} weeks of gestation will be considered for randomisation.

Inclusion criteria

- Singleton pregnancy with severe, early-onset IUGR between 22^{+0} and 29^{+6}**AND** a clinical decision to manage expectantly
    - IUGR is defined by the presence of two criteria:
        - **I. either an Estimated Fetal Weight<10th centile OR Abdominal Circumference <10th centile**
        - **II. AND absent or reversed end diastolic flow in the umbilical artery**
- Participants must be aged 16 years or older

Exclusion criteria

- Multiple pregnancy
- Known or suspected structural or chromosomal fetal abnormality
- Maternal illness (such as pre-eclampsia) which is expected to require delivery for maternal reasons within 72 hours
- Maternal wish not to have active management of the pregnancy, such as a decision to have termination of pregnancy
- Inability to give informed consent
- Cocaine use in this pregnancy
- Contraindication to sildenafil therapy,
    - known maternal cardiac disease
    - left ventricular outflow tract obstruction
    - concomitant treatment with nitrates, nitrate drugs for chest pains/heart problems including nitroglycerin (glyceryl trinitrate, GTN), Isosorbide dinitrate , isosorbide mononitrate.
    - Nitrates – some recreational drugs contain amyl nitrate (“poppers”)
    - Previous allergy to sildenafil, including hives, difficulty breathing, swelling of the face, lips tongue or face.

DECRIPTION OF IMP, DOSE AND MODE OF ADMINSTRATION: Sildenafil 25 mg 3 times per day or matching placebo to be administered orally until 31^{+6} or birth, whichever comes first.

SETTING: This trial will be coordinated from the University of Liverpool and conducted in hospitals in the UK. Recruitment of participants will be from tertiary level fetal medicine departments within

these hospitals.

DURATION OF TREATMENT AND PARTICIPATION: The first dose will be administered shortly after randomisation, between 22^{+0} and 29^{+6} weeks. The last treatment will be given at delivery or 31^{+6} weeks, whichever is sooner.

CRITERIA FOR EVALUATION: All patients randomly assigned to one of the treatments will be analysed together, regardless of whether or not they completed or received that treatment, on an intention to treat basis.

CLINICAL PHASE: 3

NUMBER OF PATIENTS : 112

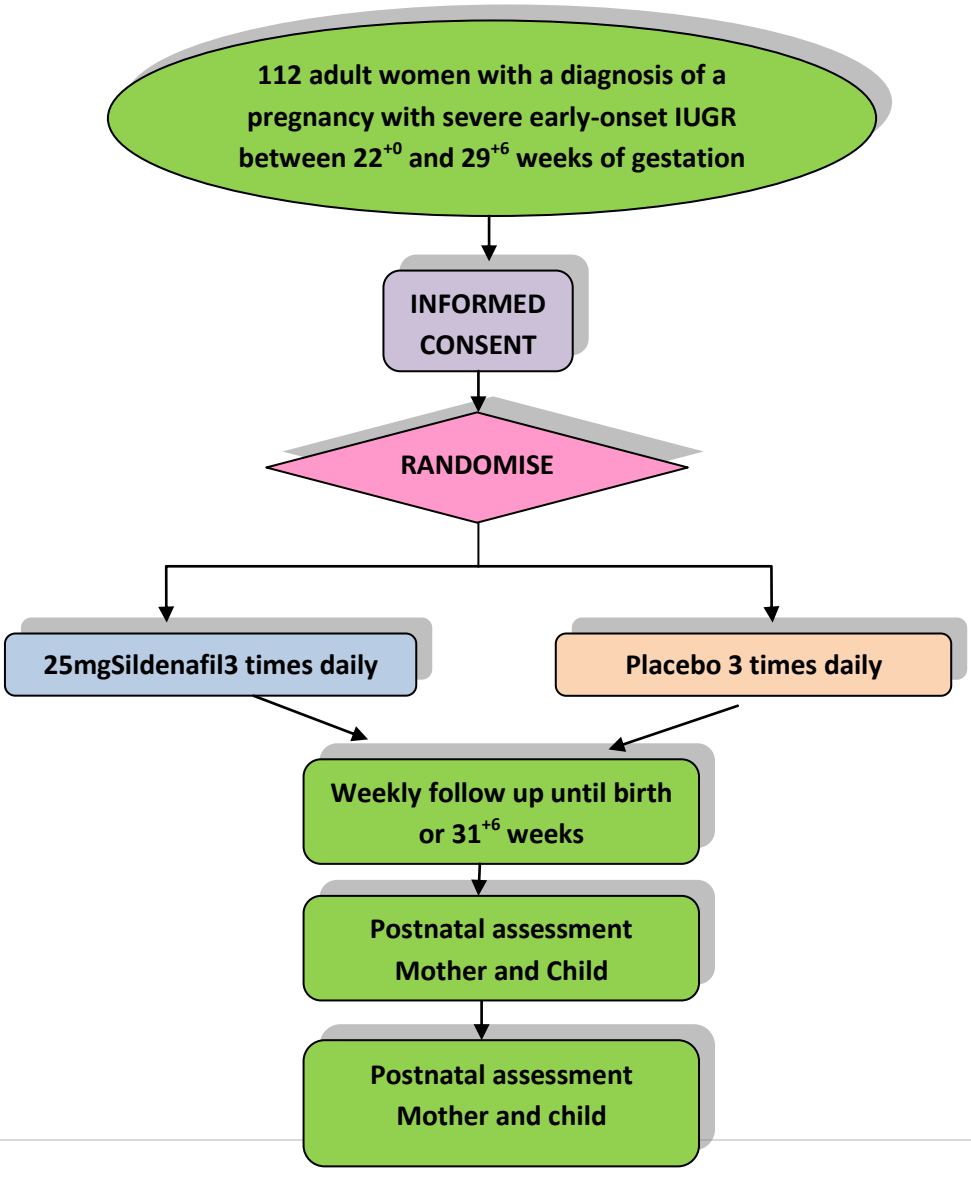
NUMBER OF CENTRES Max 25

PLANNED TRIAL START: March 2014

PLANNED DATE OF LAST PATIENT ENROLMENT: August 2016

PLANNED DATE OF LAST OUTCOME: January 2017

TRIAL SCHEMATIC:



ACCRONYMS & ABBREVIATIONS

ABPI – Association of the British Pharmaceutical Industry

AE – Adverse Event

AR – Adverse Reaction

CO – Cardiac Output

CRF – Case Record Form

CTU – Clinical Trials Unit

DIDB – Development International Birth Date

DMC – Data Monitoring Committee

DSUR – Development Safety Update Report

eCRF – electronic Case Record Form

EDC – Electronic Data Capture

EFW – Estimated fetal weight

EME – Efficacy and Mechanism Evaluation

EudraCT – European Clinical Trials Database

EVT – Extravilloustrophoblast

GCP – Good Clinical Practice

HTA – Health Technology Assessment

ICH – International Conference for Harmonisation

IMP - Investigational Medicinal Product

IMPD – Investigational Medicinal Product Dossier

IPD – Individual Patient Meta-analysis

ISF – Investigator Site File

IUGR – Intrauterine Growth Restriction

JRO – Joint Research Office

LCTU – Liverpool Cancer Trials Unit

LWFT – Liverpool Women's NHS Foundation Trust

MHRA – Medicines and Healthcare Products Regulatory Agency

MTA – Material Transfer Agreement

NIHR – National Institute for Health Research

NIMP – Non Investigational Medicinal Product

NO – Nitric Oxide

PSF – Product Specification File

PV - Pharmacovigilance

PWV – Pulse Wave Velocity

R&D – Research and Development

RCT – Randomised Control Trials

REC – Research Ethics Committee

RSI – Reference Safety Information

SAE – Serious Adverse Event

SAR – Serious Adverse Reaction

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

SUSAR – Suspected Unexpected Serious Adverse Reaction

SVR – Systematic Vascular Resistance

TCC – Trial Co-ordinating Centre

TMG – Trial Management Group

TSC – Trial Steering Committee

UoL – University of Liverpool

TDS – Three Times Daily

Contents

1. INTRODUCTION

1.1 Background

Early onset intrauterine growth restriction (IUGR) most commonly occurs when the placental transfer of nutrients and oxygen is impaired due to an inadequate placental implantation. The resulting fetal malnutrition and hypoxia are considered untreatable in utero. The only current option is an elective preterm delivery in order to rescue the baby from an adverse intrauterine environment. IUGR and the associated indicated preterm birth expose the fetus and neonate to significant mortality and morbidity. This diagnosis causes an important management dilemma: early delivery causes extreme prematurity with all its sequelae, whilst delivering the baby too late risks intrauterine death or morbidity secondary to critical fetal hypoxia. In addition, children born early after IUGR have increased risks of persistent short stature [1, 2] lower growth hormone secretion rates [3], increased risk of poor intellectual and psychological performance and neurodevelopment disabilities [4-6]. Finally, there is an association with morbidities later in life including delayed onset of puberty and an increased risk of developing cardiovascular complications in later life [7, 8]**.**

1.2 Existing Research

The process of human placentation is complex and poorly understood. Inadequate placental invasion into the uterine myometrium has been associated with IUGR, pre-eclampsia and recurrent pregnancy loss [9]. In normal pregnancy, the physiological process of spiral artery remodelling includes the removal of the nitric oxide (NO)-producing endothelium, the internal elastic lamina and the NO-responsive muscularis layers to the depth of the inner third of the myometrium. The removal of these layers by extravilloustrophoblast (EVT) converts the narrow bore, high resistance, low flow circulation to a wide bore, low resistance, high flow circulation, which is then unresponsive to normal regional vascular control.

In some pregnancies, the process of spiral artery remodelling is incomplete; the NO-modulating/modulated elements of endothelium and muscularis remain either partially intact, or fully intact. This absence of normal conversion of the spiral arteries means that the narrow bore, high resistance, low flow circulation is maintained. This is evident as abnormal Doppler waveforms of the maternal compartment uteroplacental vessels (uterine arteries) [10, 11]. Early-onset IUGR, in the absence of a fetal genetic abnormality or congenital infection, is usually the result of such abnormal placentation. 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.

1.3 Sildenafil and rationale for its use in IUGR

Sildenafil potentiates the effect of NO and thus may cause vasodilatation of vessels responsive to NO. Sildenafil has marketing authorisation in Europe and the UK and has been in clinical use for over 10 years and its safety profile in non-pregnant population is well established. For further details please refer to the SmPC.

In pregnancies complicated by IUGR, an incomplete remodelling of maternal spiral arteries results in vessels with intact or partially intact muscular layers, which remain responsive to regional vascular control. Sildenafil has the potential to increase uteroplacental circulation and perfusion resulting in improved gaseous and nutrient exchange and improved fetal growth and well-being. Our animal and in-vitro human studies support this concept [12-15].

Treatment with sildenafil at mid gestation demonstrated normalisation of all growth measures in IUGR mice [12]. Despite no significant increase in uterine artery flow measured by Doppler waveform studies, abnormal umbilical artery Doppler waveforms (including reversed arterial blood flow velocity) normalised following treatment with sildenafil – suggesting a beneficial effect on feto-placental blood flow in this model. Similar increased growth parameters have also been demonstrated with sildenafil in rat, guinea pig and sheep models [13-15].

In human ex-vivo studies, myometrial small arteries obtained at caesarean section from normal pregnancies were compared to small arteries from pregnancies complicated by IUGR [16]. Sildenafil significantly reduced vasoconstriction and significantly improved relaxation of small arteries from IUGR pregnancies, suggesting that perfusion of the placental bed would be improved by treatment with sildenafil.

1.4 Sildenafil in Pregnancy

As sildenafil potentiates the action of NO, it is used in the management of maternal pulmonary arterial hypertension for selective vasodilatation of the pulmonary vasculature. There are now several case reports of its use for this indication, suggesting improved maternal cardio-respiratory performance, improved echocardiographic status and delivery of healthy infants [17-19]. It is also used in the neonatal period in infants (including those born preterm) for the treatment of persistent pulmonary hypertension of the newborn. Sildenafil is increasingly used as an adjunctive therapy to current care of inhaled NO therapy, surfactant and high-frequency oscillatory ventilation [20].

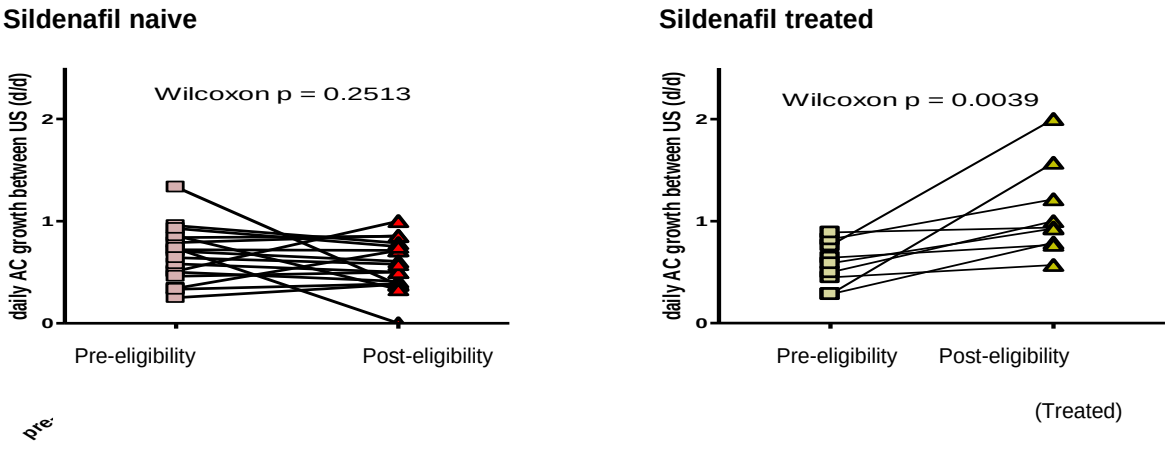
Interest in the use of sildenafil for the treatment of placental ischaemic conditions led to a small randomised placebo controlled trial in women with early onset preeclampsia [21]. In this UK study, 35 women with preeclampsia at gestational ages 24–34 weeks were recruited from nine hospitals and randomly assigned to sildenafil or placebo at gradually increasing daily doses. The primary endpoint was prolongation of pregnancy from randomisation to delivery. There was no difference in time from randomisation to delivery in the two treatment groups. The increase in the median birth weight in the sildenafil treated group compared to the placebo group (1410 g vs. 1043) was not statistically significant. 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.

1.5 Sildenafil in IUGR

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 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

intraventricularhaemorrhage or periventricular leukomalacia) [22]. Similar improvements in fetal blood flow have been observed in another small randomised controlled study of IUGR fetuses[23].

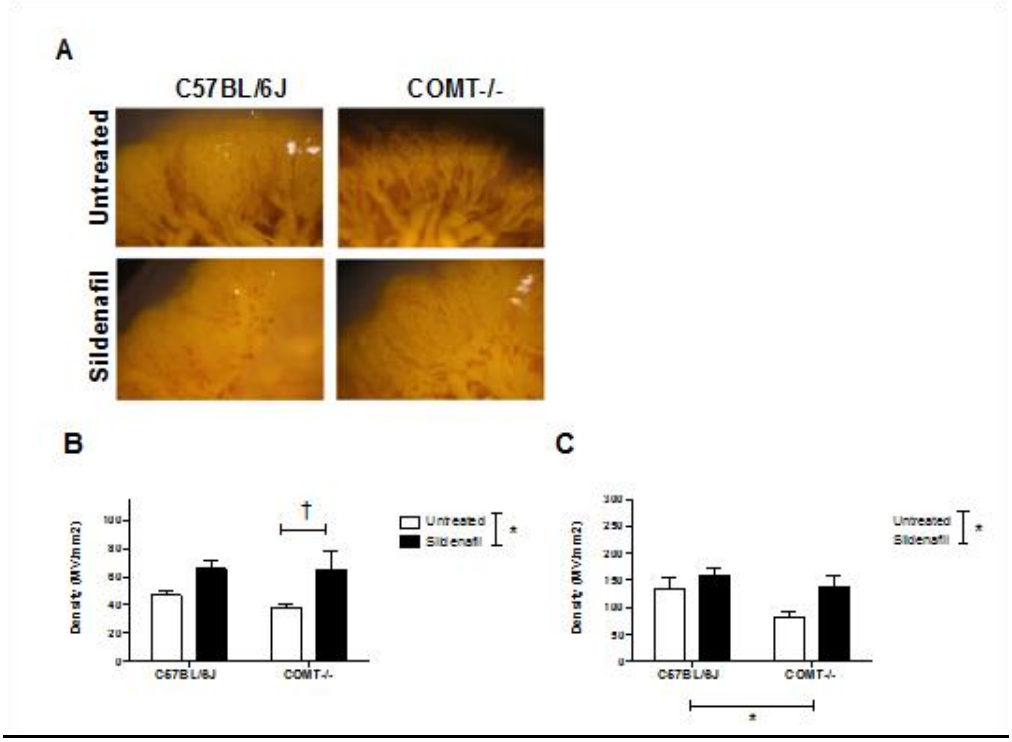
Figure 1: Change in daily abdominal circumference growth pre versus post-eligibility epochs[2].



1.6 Sildenafil and the Placenta

The placenta is highly likely to be the key to any effects of sildenafil. As illustrated in figure 2, placental morphology was markedly altered in the IUGR model (COMT-/-) compared to the control C57 mice. These changes were reflected in placental microvascular density (in both the 0-80µm range and 0-200µm ranges). We found differences in angiogenic markers, such as placental s-FLT1 expression ($p<0.05$). The differences between the IUGR and control animals were not apparent after Sildenafil treatment [12].

Figure 2: Rescue of placental vasculature with sildenafil in the COMT knockout mouse model of IUGR



1.7 Sildenafil and Maternal Vascular Changes

Studies have reported impaired maternal cardiac output (CO), and increased arterial stiffness and systemic vascular resistance (SVR) in pregnancies complicated by IUGR [24, 25]. Similar changes have been described in non-pregnant individuals with disorders associated with endothelial dysfunction, such as hypertension, coronary heart disease and heart failure [26-28]. Sildenafil intake in these cohorts was associated with a reduction in arterial stiffness as measured by pulse wave velocity (PWV), wave reflection, SVR, peripheral and aortic blood pressure [29, 30]. Sildenafil was also associated with an increase in CO [29]. In this study, repeat measurements were performed every 30 minutes for three hours; these cardiovascular changes were detected within a short period after administration of sildenafil [29, 30].

1.8 Trial Rationale and Risk Benefit Evaluation

Currently, there is no antenatal treatment for early-onset IUGR due to placental insufficiency. Management strategies involve intensive fetal surveillance with elective delivery performed when there is evidence of presumed fetal acidosis/distress. At gestational ages remote from term, such iatrogenic delivery is associated with significant perinatal morbidity and mortality. Intact survival is less than 25% for an infant weighing 600g born at 25 completed weeks' gestation, and is still only approximately 50% up to 28 weeks' gestation [31]. The key determinants of death and both short-term and long-term morbidity in severe early-onset IUGR are gestational age at birth and birth weight [32-35]. Importantly, an increase in neonatal survival of 2% is reported for each additional day in utero up to 32 weeks [31]. Clearly, any intervention that could prolong gestational age could have significant beneficial effects on both survival and short term health.

The long term health of growth restricted children is also likely to be improved by prolonging gestation and increasing birth weight, due to the growing recognition that an adverse intrauterine environment predisposes to significant health problems in adulthood, a concept termed "fetal programming". In particular, IUGR is associated with an increased long-term risk of developing cardiovascular disease, in both the mother and the fetus [8].

Sildenafil is a novel and innovative therapy which may improve feto-placental blood flow and fetal growth. Improved fetal growth is likely to delay the need for delivery and reduce the risk of prematurity related morbidity that contributes to long term handicap and disease. This RCT will provide new knowledge in the management of IUGR, initially in those with severe early onset disease. If successful, it may also be tested in later onset disease.

We have summarised the evidence of using Sildenafil in pregnancy in the section 1.4 and 1.5. Apart fom the IUGR cases series used as the basis for this protocol [22] the dosing rationale (25mg 8 hourly) has been based on two randomised controlled trials in pregnant women [21, 23]

Reference	Sildenafil dose used
Von Dadelszen et al [22]	25mgs tds
Samangaya et al [21]	20 mgs tds, increased to 40 mg on day 4 increased to 80 mg on day 7
Dastjerdi et al [23]	50 mg single dose

These studies have stated that ‘the medication was well tolerated, and no women withdrew from the trial due to side effects’ [21].Furthermore, follow up of the children in this randomised trial demonstrated no adverse effects (retinal examinations were specifically performed) (unpublished data)’. This is the rational for why each patient will receive a dose of 25mg 3 times per day.

2. TRIAL OBJECTIVES AND PURPOSE

The overarching aim is to determine whether maternal treatment with oral sildenafil citrate improves perinatal outcomes in pregnancies complicated by severe early-onset IUGR without increasing risks to the mother.

This study has a specific objective to evaluate the clinical efficacy of sildenafil i.e. its ability to lead to a delay of a clinical indication for delivery on fetal grounds by at least one week. The other specific objective is to add to our understanding of the mechanism of action of sildenafil by monitoring changes in the maternal, utero-placental and fetal circulation.

2.1 Primary Objective

To determine whether sildenafil compared to placebo therapy delays the need to deliver a severely growth restricted fetus by a minimum of one week.

2.2 Secondary Objectives

i. To investigate impact on fetal growth and fetal well-being by comparing differential effect on the vascular resistance in the uterine arteries, umbilical, fetal middle cerebral artery and fetal ductus venosus and differences in birth weight centiles in infants treated in-utero with sildenafil and placebo.

ii. To examine, through collaboration with an international consortium, the hypothesis that sildenafil therapy compared to placebo therapy increases the rate of infant survival free of major handicap.

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

iv. To investigate the impact on maternal cardiovascular parameters by measurements of maternal heart rate and peripheral blood pressure before and after administration of study medication.

v. To elucidate the precise mechanism and location of action of sildenafil in pregnancy by investigating the effects of sildenafil therapy on chorionic plate artery (placental vasculature) reactivity.

3. TRIAL DESIGN

3.1 Overview

The STRIDER study is a randomised double blind, placebo-controlled clinical trial to quantify the effects of administration of sildenafil on pregnancy outcome in severe early-onset IUGR. 112 women with affected pregnancies will be recruited and randomised to receive either sildenafil or placebo.

3.2 Settings

All participants will be recruited from hospitals participating in the study for which they have booked in for their delivery. The hospitals will be based within the United Kingdom.

The trial will recruit collaborating centres from the UK. Suitable collaborating sites and investigators will be assessed on the level of fetal medicine and neonatal service they provide and their ability to conduct the trial. In advance of the trial starting at a site the Principal Investigator must agree to adhere to the Good Clinical Practice Guidelines and all relevant regulations in their country. In addition, all relevant regulatory and ethics approvals will need to be in place.

3.3 End of Study

The study will end when the last recruited woman/baby is discharged from hospital after birth, or the baby has reached expected date of birth, whichever is later.

4. TRIAL POPULATION

Women reviewed in the participating fetal medicine with a diagnosis of a pregnancy affected by severe early-onset IUGR between 22^{+0} and 29^{+6} weeks of gestation will be considered for randomisation.

4.1 Subject Inclusion Criteria

- Singleton pregnancy with severe, early-onset IUGR between 22^{+0} and 29^{+6}**AND** a clinical decision to manage expectantly
- IUGR is defined by the presence of two criteria:
  I. either an Estimated Fetal Weight<10^{th} centile **OR** Abdominal circumference<10^{th} centile
  II. **AND** absent or reversed end diastolic flow in the umbilical artery
- 16 years of age or older
- Consent to take part in the trial

4.2 Subject Exclusion Criteria

- Multiple pregnancy
- Known or suspected structural or chromosomal fetal abnormality
- Maternal illness (such as pre-eclampsia) which is expected to require delivery for maternal reasons within 72 hours
- Maternal wish not to have active management of the pregnancy, such as a decision to have termination of pregnancy
- Inability to give informed consent
- Cocaine use in this pregnancy
- Contraindication to sildenafil therapy:
  - known maternal cardiac disease
  - left ventricular outflow tract obstruction
  - concomitant treatment with nitrates, nitrate drugs for chest pains/heart problems including nitroglycerin (glyceryl trinitrate, GTN), Isosorbide dinitrate , isosorbide mononitrate.
  - Nitrates – some recreational drugs contain amyl nitrate (“poppers”)

  Previous allergy to sildenafil, including hives, difficulty breathing, swelling of the face, lips tongue or face.

4.3 Subject Withdrawal

As participation in this trial is voluntary, subjects have the right to discontinue drug or completely withdraw from the trial at any time without giving reason. The investigator at the respective site has the right to discontinue a patient taking drug at any time if it is deemed to be in the patient’s best interest. The reason and circumstances for premature discontinuation will be documented in the eCRF.

If the participant is withdrawn due to a serious adverse event, the principal investigator will arrange for follow-up visits or telephone calls until the event has resolved or stabilised. However as the participants are pregnant women the data will be collected to outcome (i.e.

delivery) and used in the analysis unless the consent to participate to collect the outcome is specifically refused by the participant.

If the woman withdraws a previously given informed consent or refuses continuation in the trial, her data will be handled as follows:

- Data collected to the point of withdrawal of consent will be used as part of the intention to treat analysis
- All relevant adverse events identified will be reported as required to all relevant authorities

5. ENROLMENT and RANDOMISATION

5.1 Onsite Patient ID (Randomisation) Log

A patient ID or randomisation log must be kept at each trial centre detailing the patient's full name, data of birth, hospital number and contact details. This log will be maintained locally and will not be sent outside the trial centre, but may be monitored by authorised onsite personnel. Blank logs will be provided by the LCTU for completion.

5.2 Randomisation

Patients who have given written informed consent and meet eligibility criteria will be randomised by trained staff onsite who have been delegated the responsibility (as per the signature and delegation log).

STEP 1: Randomisation will be performed using a web-based randomisation service operating at the Clinical Trials Unit (CTU) British Columbia Women's Hospital (Vancouver, Canada). Passwords and login details will be provided to each centre at the point of site 'green light' authorisation by LCTU.

STEP 2: Once logged onto the system, users **MUST** confirm Informed Consent and all eligibility (inclusion/exclusion) criteria of the patient. If patient meets criteria, the system will proceed to randomise the patient and will assign and provide a Study Subject ID. If a patient fails criteria, the system will confirm and track this with a Screen Fail ID. A demonstration of the system will be given at site initiation and a step by step guide provided for each centre

Each participating woman will be allocated a Study Subject ID and a trial medication pack number to be collected from the hospital pharmacy.

Trial medication pack number should be transcribed onto the trial prescription and patient's notes and will be dispensed by pharmacy directly to the patient or responsible health care professional.

STEP 3: After randomisation a copy of the Informed Consent Form must be faxed to the LCTU for monitoring with 48 hours.

Fax number: **0151 794 8930**
(Please note the LCTU is open from 0900 -17.00 Monday to Friday, excluding public holidays)

Once a patient had been randomised onto the study she must be provided with a copy of the signed consent form and the patient information leaflet.

5.3 System Failure

In the event of a failure with the randomisation and drug allocation system the Clinical Trials Unit (CTU) British Columbia Women's Hospital should be contacted directly to conduct the randomisation.
Contact details: +1-778-709-2404

6. TRIAL ASSESSEMENTS and PROCEDURES

6.1 Visit Schedule

Trial Procedure	Screening	Baseline	48 hour – 72 hour assessment	Weekly assessment[b]	Labour and Delivery	Postnatal Assessment Mother/child
Day number:	-5	0	2-3	7,14,21,28,35,42		
Informed Consent	X					
Medical History		X				
Demographics		X				
Randomisation		X				
Urine Protein Analysis		X		X[c]		
Vital Signs (Including Height and Weight)		X				
Blood Pressure and Pulse		X[e]	X		X	
Blood Sample[a] (routine Haematology and Biochemistry)		X		X[c]		
Fetal Assessment – Ultrasound Scan	X			X		
Administration of Sildenafil/Placebo		X		X		
Treatment Compliance				X		
Record antenatal/postnatal management				X	X	X
Placental Sampling (OPTIONAL)					X	
Blood Samples for vascular profiling (OPTIONAL)		X		X[d]		
Cardiovascular Profiling (OPTIONAL)		X[e]	X		X	
Concomitant medications		X		X	X	
Adverse Event Reporting		X		X	X	

[a] Creatinine, Urea, Urate, Aspartate transaminase, Alanine transaminase, Albumin, Platelets

[b] to be conducted every week at 7 days, 14 days, 21 days, 28 days, 35 days, 42 days etc (weekly from recruitment to delivery)

[c] If clinically indicated

[d] max 6 samples within first 2 weeks as per protocol

[e] To be performed before and after first dose of IMP

6.2 Trial Procedures

Eligibility will be determined from the clinical information and no trial specific screening tests are required. Women eligible for inclusion should be randomised to receive either sildenafil or placebo treatment and the trial treatment started as soon as possible.

The STRIDER study procedures should be carried out as outlined in section 6.1 will involve consent, the oral administration of the trial drug, measurements of blood pressure, fetal assessment via ultrasound and collecting routine clinical information from participants' medical records. Clinical management for underlying conditions will remain as per each hospital's standard protocol.

For some participants in selected investigating sites the study may also involve maternal blood samples and the collection of the placenta after birth (see section 8).

The trial ends when mother/baby are discharged from hospital, or baby reaches the expected date of birth, whichever is later. However, all known SAEs will be collected until the end of the data collection for the last randomised woman/baby. The Trial Co-ordinating Centre (TCC) will develop plans to stay in contact will all trial participants by regular communication as appropriate (newsletters, text messages, emails) as there is an expectation that, in future, funding will be secured for long term follow-up of all survivors; this will be made explicit in the Patient Information Leaflet.

6.3 Procedures for Assessing Outcomes

6.3.1 Primary Outcome

Primary outcome is average prolongation of pregnancy for one week i.e. one week difference between two randomised groups in the mean randomisation to birth interval. Gestational age is determined by early pregnancy dating ultrasound examination. The primary outcome was chosen as a surrogate for long term morbidity as it has been shown that gestational age at birth remains the most powerful predictor of intact survival in early-onset IUGR cohorts. Recently published data from the 2006 English cohort of babies born between 22 and 26 weeks of gestation showed a step increase in survivors without major morbidity ranging from 15% at 23 weeks to 50% at 26 weeks.

6.3.2 Fetal, infant and maternal outcomes

Outcomes can be seen in the table below:

Fetal outcomes	Infant outcomes	Maternal Outcomes
Estimated fetal weight	Gestational age at birth	Mode of delivery
Abdominal circumference growth velocity	Survival to discharge	Standardised blood pressure and pulse monitoring during treatment
Serial measurements of	Birth weight centile	Pre-eclampsia

Doppler pulsatility index in the umbilical artery, middle cerebral artery and ductus venosus and uterine arteries		
Serial measurements of short term variability of the fetal heart rate recorded by transabdominal cardiotocography	Length of admission on the neonatal intensive care unit	Postpartum haemorrhage
	Bronchopulmonary dysplasia requiring oxygen 36 weeks corrected age	Recording of the side effects e.g. headaches, facial flushing
	Necrotising enterocolitis requiring surgery	In-patient postnatal stay
	Retinopathy of prematurity (requiring treatment such as laser, grade 2/3 or more)	
	severe central nervous system injury (detected by ultrasound and/or MRI) periventricular leucomalacia grade II or more, or intracerebral haemorrhage grade III or more or hydrocephalus;	
	confirmed sepsis by positive blood culture	
	Patent ductus arteriosus needing medical or surgical treatment	
	need for inotropes or vasopressors	
	Number of doses of surfactant	
	Ventilator days	
	Supplemental oxygen days	
	Number of days to full feeds	

Definitions and standardised methods for measuring and collecting secondary outcomes have been agreed amongst International STRIDER Consortium to facilitate prospective individual patient meta-analysis (IPD).

7. Trial Treatment

7.1 Introduction

ARM A (Experimental Arm): Sildenafil tablets 25 mg 3 times per day from baseline until delivery, or 31^{+6} weeks of gestation whichever comes first;

ARM B (Standard Arm): Placebo tablets taken as above

NOTE: As this is the first time that sildenafil has been used for the treatment of IUGR and an obvious dose response is unlikely to be observed, unlike in treatment of male erectile dysfunction, we have made the pragmatic decision to maintain the dose at 25mg TDS throughout the study period.

7.2 Investigation Medical Product (IMPS) – Sildenafil

7.2.1 Formulation, Packaging, Labelling and Storage and Stability

Trade Name	Sildenafil
Active Ingredients	Sildenafil citrate
Excipients	Lactose monohydrate
	Microcrystalline cellulose
	Povidone K29-32
	Croscarmellose sodium
	Magnesium stearate
Pack Sizes	Each bottle contains 30 x over capsulated sildenifil tablets
Manufacturers Name	Actavis
Suppliers Name	Sharp
Storage	The current shelf life is 36 months
	The tablets should be stored below $30^{o}C$

7.2.2 Supply and administration of trial treatment

The active trial drug sildenafil will be manufactured by Actavis and will conform to UK legislation. The active treatment will be encapsulated by Sharp Ltd. (UK) who will also provide matching placebo. The Marketing Authorisation will be obtained and guarantees that the product has been manufactured and released in accordance with the United Kingdom's Good Manufacturing Regulations.

Sharp Pharmaceuticals Ltd will be responsible for maintaining the Product Specification File (PSF) until final database lock and unblinding of the trial data. The LCTU will be responsible for assuring all relevant approvals are available before release of the trial treatment to a site.

Once a site has been activated by the LCTU on the Randomisation & Drug Allocation system, the first shipment of IMP will be sent to site. Medication will be delivered to each study centre hospital pharmacy, labelled to regulatory requirements and MUST be stored under appropriate conditions. Medication will be issued as 10-day (total 30 capsules) treatment packs to participants for self-administration if managed as an out-patient, or dispensed directly from pharmacy for those requiring in-patient care. The trial medication is for oral use only and capsules must not be halved.

Therapy will be started immediately after randomisation, between 22^{+0} and 29^{+6} weeks, and stopped at 31^{+6}weeks or delivery if sooner. Trial medication will be stopped at 31^{+6} weeks even if the pregnancy continues beyond this date. Therefore no participant will be taking the trial medication for longer than 10 weeks.

All other medications taken by a participant can be continued as normal, with the exception of nitrates and other medications listed in section 7.7 and the SMPC which should be avoided by users or potential users of sildenafil.

7.3 Medications Not permitted/Precautions required

It has been decided that no dose modifications/reductions will be required. Sildenafil should not be taken if the patient has an allergic reaction to Sildenafil.

Patients should stop taking Sildenafil:

- If they are taking medicines called nitrates, as the combination may lead to a dangerous fall in blood pressure, these medicines which are often given for the relief of angina pectoris (or "chest pain").
- If they are using any of the medicines known as nitric oxide donors such as amyl nitrite
- If they have a severe heart or liver problem
- If they have recently had a stroke or a heart attack, or if they have low blood pressure.
- If they have certain rare inherited eye diseases such as retinitis pigmentosa.
- If they have ever had loss of vision due to non-arteritic anterior ischaemic optic neuropathy (NAION)

Patients should speak to their doctor or midwife if they have:

- Vision changes or sudden vision loss
- Ringing in the ears
- Sudden hearing loss
- Chest pains or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling
- Irregular heartbeat
- Swelling hands, feet, ankles or feet
- Shortness of breath

- A light-headed feeling, feeling of passing out.

Common side effects may include:

- Warmth or redness in the face, neck or chest
- Headache
- Upset stomach
- Diarrhoea

7.4 Accountability procedures for IMP

Delegated study personnel within the pharmacy are responsible for maintaining accurate dispensing records using the agreed study accountability log. Further details can be found in the Pharmacy Operating Manual.

Under no circumstances will an investigator or pharmacist all the IMP to be used other than directed by the protocol.

7.5 Assessments of Compliance with IMPs

Compliance will be checked regularly during clinical review and when the participant returns to the pharmacy for reissue of a further treatment pack containing 30 tablets for 10 days of treatment.

Compliance data will be collected on accountability logs and the LCTU will enter data into the patient Case Record Form.

NIMP: There are no NIMPs for STRIDER (i.e. no rescue medications, no challenge medications or concomitant medications)

7.6 Overdose

STRIDER Risk Assessment does not identify overdose as a risk in this clinical trial. However, drug regimen compliance will be monitored at clinic visits by the clinical investigators to attempt to ensure participants are supported and fully aware with keeping to their capsule regimen. Dispensing of STRIDER IMP will be controlled by STRIDER specific dispensing and accountability procedures. STRIDER does not require rescue medications to be given or special measures for overdose.

7.7 Concomitant Medication

Sildenafil may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency the patient should inform their doctor or midwife. Sildenafil should not be taken if the patient is also taking nitrates, as a combination of these medicines may lead to a dangerous fall in the patient's blood pressure; these medications are often used for the relief of angina pectoris (or "chest pain").

Sildenafil should not be taken if the patient is using any medications known as nitric oxide donors such as amyl nitrite ("poppers") as the combination may also lead to a dangerous fall in blood pressure.

Sildenafil can be taken with protease inhibitors, such as for the treatment of HIV, but at a lowest dose 25mg.

Some patients who take alpha-blocker therapy for the treatment of high blood pressure may experience dizziness or light-headedness, which may be caused by low blood

pressure upon sitting or standing up quickly. Some patients have experienced these symptoms when taking Sildenafil with alpha-blockers. To reduce the chance that these symptoms might happen, the patient should be on a regular dose of the alpha-blocker before starting Sildenafil. The patient should be on the lowest dose 25mg.

For medications not permitted/precautions required for Sildenafil, the most current SmPCs should be referred to.

7.8 Data on Concomitant Medication

Data on concomitant medication will be collected at each treatment visit, day 7, 14, 21, 28, 35 and 42 and at the time of SAE reporting.

7.9 Unblinding

Randomisation codes will be generated and secured by the Clinical Trials Unit (CTU) British Columbia Women's Hospital. The codes will be made available to Sharp Pharmaceuticals Limited (UK) explicitly for the treatment packs to be created in accordance with the randomisation list.

Emergency Code break envelopes will be provided to each centre with each drug shipment.

Separate Unblinding procedures containing step-step guidelines on the process will be supplied to all centres at eth point of initiation and will be covered in initiation training.

8. Ancillary Studies

8.1 Vascular Profiling

Vascular profiling will involve clearly defined methods of assessing blood pressure and arterial stiffness using standardised equipment which will be covered in the specific SOP. Functional vascular studies will be coordinated by Dr Aris Papageorghiou and Dr Asma Khalil (St. Georges).

The effect of sildenafil upon maternal angiogenic markers will be assessed by maternal blood sampling. Blood will be drawn at randomisation; 2 hours post first treatment and every 3-4 days up to 2 weeks post randomisation (maximum of 6 collections per participant). Each sample will be of 30ml, with a total of up to 180ml drawn over the length of the study. Blood samples will be taken by a clinician trained in venepuncture and processed and stored in accordance with the specific SOP. Samples will then be sent to The University of Cork for analysis. Angiogenic marker studies will be coordinated by Professor Louise Kenny (Cork). All sample transfers will be covered by a specific MTA.

8.2 Placental Biobanking

Each participant will be requested to donate their placenta after delivery. This process will not prevent formal histopathological assessment if this is deemed necessary by the attending physician. Placental samples and fetal blood taken from the umbilical cord after it is separated from the fetus will be prepared and transferred to The University of Manchester for storage and analysis in accordance with the HTA, under the supervision of Dr Edward Johnstone. Future funding will be sought for functional placental studies. The laboratory preparation of placental samples is covered in a specific SOP. All sample transfers will be covered by a specific MTA.

8.3 Individual Patient Data meta-analysis

We are planning to conduct an Individual Patient Data (IPD) meta-analysis in collaboration with the STRIDER consortium across the world. This prospective analysis will address the issues of sildenafil effectiveness and safety focusing on substantive short and long term clinical outcomes. Separate protocol will be developed for this work. The data capture an analysis will be co-ordinated by CTU University of British Columbia, Department of Obstetrics & Gynaecology.

8.4 Cardiovascular profiling

Cardiovascular function will be evaluated where possible and is optional for patients. Cardiovascular profiling will be done using a combination of using impedance cardiography (ICG) and combined ECG. Arterial stiffness, pulse wave velocity, cardiac output and systemic vascular resistance will be measured. All tests will be performed in accordance with SOPs using standard equipment in selected centres.

9. Pharmacovigilance

The Liverpool Cancer Trials Unit Standard Operating is being followed for the STRIDER study. The processes for safety reporting are managed through the LCTU and will include notification to both co-sponsoring organisations LWFT R&D and the University of Liverpool Research Office (Sponsor).

9.1 TERMS and DEFINITIONS

The following definitions have been adapted from Directive 2001/20/EC and the ICH E2A document, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting". They are consistent with the LCTU SOP Pharmacovigilance (TM031).

Adverse Event (AE)	Any un-toward medical occurrence or effect [i.e. any un-favourable and un-intended sign (including abnormal lab results), symptom or disease] in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. A causal relationship between trial treatment and an adverse event is at least a possibility i.e. the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the Sponsor as having a **reasonable causal relationship** to the IMP qualify as ARs
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any adverse event or adverse reaction is classified as serious if: (a) results in death (b) is life-threatening* (c) requires hospitalisation or prolongation of existing hospitalisation** (d) results in persistent or significant disability or incapacity (e) consists of a congenital anomaly or birth defect (f) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
Possible Suspected Unexpected Serious Adverse Reaction (SUSAR)	For a blinded trial in which a patient has been randomised to either active treatment or placebo, it must be assumed that the patient has been randomised to active treatment for the initial assessment. The treatment allocation should only be unblinded is the event is classified as a 'possible SUSAR'
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction that is 'un-expected' (the nature and severity of which IS NOT consistent with the applicable Reference Safety Information (RSI) is termed as a suspected un-expected serious adverse reaction (SUSAR).
*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
** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations planned prior to informed consent for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE. A worsening of pre-existing conditions may be due to the IMP and so should be reported. Attendance to the accident and emergency department without admission to a ward would not need to be recorded as an SAE (unless the event met one of the other criteria)

9.2 NOTES on NON Serious Adverse Events

The protocol does not require the reporting of any non-serious adverse events. The non-serious adverse events of interest will be captured routinely on eCRF.

9.3 NOTES on Serious Adverse Event Inclusions and Exclusions

Sildenafil is a well-established drug with an extensively documented safety profile. This is a high-risk population and a large number of adverse events are anticipated in the absence of trial participation. The Sponsor's assessment of sildenafil safety during the trial will take account of this information.

9.3.1 Include

Investigators MUST REPORT ALL SERIOUS ADVERSE EVENTS including exposure to Sildenafil as well as treatment/study design related events that occur from informed consent until the end of the follow up period. In addition, maternal death and maternal life-threatening complications, stillbirths and neonatal deaths are also pre-specified outcomes to be reported in this trial immediately as SAEs. Stillbirths and neonatal deaths considered unrelated to severe IUGR should be reported immediately.

SAEs must be reported within 24 hours of sites becoming aware of them by entering information in the LCTU Pharmacovigilance MACRO database.

Examples of SAEs

Fetal

- Intrauterine fetal death following administration of IMP (SAE – report sent to trial coordinator)
- Emergency caesarean section for abnormal fetal monitoring (not SAE, recorded on eCRF form)

Maternal

- Maternal ECG or cardiac marker evidence pf cardiac event (SAE – report sent to trial coordinator)
- Maternal venous thromboembolic event (SAE – report sent to trial coordinator)

- Development of pre-eclampsia (not SAE, recorded on eCRF form)
- Flushing post IMP administration (not SAE, recorded on eCRF form)

Neonatal

- Unexpected fetal anomaly (SAE – report sent to trial coordinator)
- Prolonged admission to neonatal intensive care secondary to IUGR and/or prematurity (eCRF SAE, recorded on AE form)
- Neonatal death (SAE – report sent to trial coordinator)

9.3.2 Do not Include

The following events are anticipated from the presence of severe early onset IUGR and are therefore exempt from immediate safety reporting (unless the investigator deems there to be a causal relationship to the study procedures including potential exposure to sildenafil).These events will be reported in the eCRF as per the Pharmacovigilance Plan.

- Maternal prolonged hospital stay related to the diagnosis of IUGR
- Maternal prolonged hospital stay postnatally not related to the diagnosis of IUGR
- Termination of pregnancy in maternal interest
- Admission for:
    - any of the expected Adverse Events
    - 'rest'
    - maternal discomfort
- Pregnancy induced hypertension
- Pre-eclampsia
- • Threatened pre-term labour requiring administration of either tocolysis or steroids
- Preterm delivery in maternal interest
- Preterm delivery in fetal interest
- Caesarean section
- Postpartum haemorrhage >500mls
- Admission to neonatal intensive care
- Neonatal complications of prematurity

9.4 Reference Safety Information (RSI)

The Reference Safety Information for Sildenafil will be Section 4.8 entitled 'undesirable effects' of the SmPC produced and maintained by Actavis and obtained from EMC website.

Reference Safety Information will remain the same throughout each Development Update Safety Reporting Period and will be reviewed at least annually.

9.5 Relationship to Trial Treatment

Assessments of causality are to be performed by the site investigator responsible for the care of the patient using the below definitions. A second assessment of causality will be made by the clinical co-ordinator using the same definitions

In the case of discrepant views on causality between the local investigator and the clinical co-ordinator the highest assessment will be used for reporting and both opinions provided to the MHRA.

STRIDER Causality Assessment

ARs should be assessed for **causality** using the definitions below:

Unrelated: There is no evidence of any causal relationship.

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possibly: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probably: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

High Probable: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Any event graded as Possibly, Probably or Highly Probably related to the IMP will be classified as having a reasonable causal relationship, and will therefore be documented as an adverse reaction or a serious adverse reaction.

9.6 Expectedness

The clinical co-ordinator will evaluate each SAE as being expected or unexpected. An event is considered to be 'unexpected' if the nature and/or severity of the event is not consistent with the STRIDER Reference Safety Information (see section 9.4)

9.6.1 Serious Adverse Events

The site investigator **MUST REPORT ALL PROTOCOL DEFINED SERIOUS ADVERSE EVENTS IMMEDIATELY** to the Liverpool Cancer Trials unit Office[1]. The PI is responsible for reporting all SAEs that occur in trial patients at a trial site at which they are responsible for the conduct of STRIDER unless the event is specified as not needing immediate reporting because it is regarded as "anticipated" in this document. For purpose of the protocol immediately is interpreted as within 24 hours of becoming aware of the event. The initial report can be made either verbally or in writing.

Immediate reporting can be via:

[1] The LCTU has been delegated the responsibility of managing Pharmacovigilance on behalf of the Sponsor.

1. Fax using the STRIDER SAE report form. The STRIDER SAE forms can be obtained from the LCTU portal or by contacting the STRIDER trial team +44(0)151 794 8930. Copies of the blank form will also be supplied at site initiation and stored in the site file.

2. LCTU Pharmacovigilance system www.lctu.org.uk/macro/default.aspx. Step by step instruction will be provided at site initiation.

3. If both the computer and fax systems have failed and an SAE needs urgent reporting, as a last resort an answer phone message can be left on 0151 794 8930 detailing the SAE.

   For urgent safety queries including out of hours and for advice on un-blinding, the emergency STRIDER mobile held by one of the lead STRIDER clinicians should be contacted. Mobile number: 07812238459

Steps for reporting:

i. The online or paper SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed by detailed, written reports
   For electronic reports: An email is sent to the person completing the form, the Principal Investigator at the site, the co-sponsors and the STRIDER trial team.
   For faxed reports: A fax acknowledgement receipt of the SAE will be sent within 2 hours on the same day if sent on a working day between 9am – 3pm or the next working day by 11am. The data will be entered onto MACRO by the STRIDER trial team.
   NOTE: If NO acknowledgment is received by the site within the timeframes set out above the site should contact the LCTU on +44 151 194 8930 to confirm it has been received.

ii. The responsible investigator must then **notify** their R&D department of the event (as per standard local procedure).

iii. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information should be provided following step 1 and is noted on the same SAE form within the LCTU Pharmacovigilance MACRO database. The SAE type question at the top of the form should be marked as 'follow-up'. Extra, annotated information and/or copies of test results may be provided separately.

iv. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

The Investigator must institute appropriate therapeutic action and follow-up measures in accordance with Good Medical Practice but should notify the study co-ordinator of such actions.

The minimum dataset required for a preliminary report should include the following.

- Research subject trial number and initials.

- Date of onset of event.
- Brief description of event
- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name. Date of last administration of study drug.
- Outcome

ALL INVESTIGATORS MUST ENSURE THAT MULITPLE SERIOUS ADVERSE EVENTS ARE REPORTED SEPARATELY TO THE LCTU. ONE SAE REPORT SHOULD ONLY RELATE TO ONE OVERALL DIAGNOSIS.

9.6.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Chief Investigator and the Liverpool Cancer Trials Unit will ensure that all SUSARs are reported to the co-sponsors, regulatory authorities (MHRA Clinical Trials Unit) and ethical committees within the following timelines.

- Fatal or life threatening SUSARs within 7 days after receiving the initial information.
- All other SUSARs with 15 days after receiving the information.

The Chief Investigator and the Liverpool Cancer Trials Unit will **inform all investigators of SUSARs** as they occur.

All SUSARs are managed in accordance with the LCTU Pharmacovigilance SOPs and the STRIDER Pharmacovigilance plan

9.6.3 Annual reporting

A Development Safety Update Report (DSUR) will be submitted annually in line with the DIDB. The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product it will cover the following 4 areas:

(1) Examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety

(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects

(3) summarise the current understanding and management of identified and potential risks

(4) Provide an update on the status of the clinical investigation/development programme and study results.

9.7 Pharmacovigilance Plan

Prior to study green light The STRIDER Pharmacovigilance Plan (PV plan) will be put in place in accordance with the LCTU Pharmacovigilance SOP (TM031). The PV Plan contains much more detail on how safety information will flow; who is responsible for reporting to who, and timelines and methods of reporting. The STRIDER Pharmacovigilance plan provides details of how safety information is triaged at the LCTU and how all parties and sponsoring organisations are kept informed.

Staff in the LWFT R&D Office will take responsibility for expedited reporting to the Regulatory Authorities as / when necessary; this process will be led by the LWFT R&D Office in collaboration with the University JRO office and the Trial Coordinator at the LCTU

9.8 Follow-up of Adverse events

The Trial Co-ordinator takes responsibility for coordinating the follow up of SAE reports. Where a verbal or incomplete report of a safety event has been reported and inputted onto MACRO, the Trial Co-ordinator will liaise with the investigator at the reporting site to ensure key missing information is followed up in a timely manner. The LCTU MACRO PV database will be used to facilitate reporting and closure of safety events to ensure the wellbeing of the participant.

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

The LCTU and the Trial Co-ordinator will be mindful of data protection across sites at all times in sharing patient details pertaining to safety events. The Trial Co-ordinator will oversee the flow of information to ensure patient identifiers are not leaving NHS sites

9.9 Procedures for Unblinding

In general there should be no need to un-blind the allocated treatment. If a contraindication to sildenafil becomes apparent after randomisation the trial treatment should be stopped and all normal clinical care given. Unblinding will only need to be performed when the attending physician believes that the clinical management depends importantly upon the knowledge of whether the patient received sildenafil or placebo.

Separate unblinding procedures containing step-step guidelines on the process will be supplied to all centres at the point of initiation and will be covered in initiation training.

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled and unblinding has taken place.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the

clinical trials unit prior to reporting to the regulator and re-evaluated for expectedness in light of the administered treatment.

9.10 Oversight of trial safety

Trend analysis of STRIDER safety events will be performed by the Trial Oversight Committees and will be facilitated by reports generated by the LCTU and University of British Columbia CTU.

Line listings of STRIDER safety events will also go to the LWFT and UoL R&D Committee and also to the independent Data Monitoring Committee (DMC).

The LCTU will enter all SAEs into the eCRF system once they have been processed

9.11 Congenital anomalies

Congenital anomalies will be recorded in the CRF. The investigator must assess whether there is any likelihood that a congenital anomaly is causally related to sildenafil. If there is ANY likelihood that a congenital anomaly is causally related to sildenafil then that event is a potential SUSAR. A congenital anomaly that could have ANY likelihood of being related to sildenafil must be reported to the Sponsor within 24 hours of the investigator becoming aware of it. Congenital anomalies may be unrelated to sildenafil if the teratogenic window for that anomaly is complete before the participant gives consent to be included in the trial. In case of doubt the investigator must report the congenital anomaly to the Sponsor.

Formal assessment of congenital anomalies will continue up to and including the routine neonatal check prior to hospital discharge.

If the investigator becomes aware of concerns about congenital anomalies after discharge of the neonate from hospital they should report these concerns to the Sponsor.

10.Data Collection

10.1 Data Capture Methods

Trial data will be captured using an eCRF designed and hosted by the Clinical Trials Unit (CTU) British Columbia Women's Hospital (Vancouver, Canada) it will designed and built using REDCap software. All data with the exception of SAEs will entered directly into the eCRF by the suite staff at participating centres.

Initial information including baseline demographic data will be transferred from the hospital records to a bespoke electronic Case Record Form (eCRF) **within 3 days of randomisation**. Full eCRF will be completed after discharge from the randomising hospital, or on death (whichever occurs first) and will include neonatal status at the time of expected date of delivery (EDD).

After a patient has been randomised, outcomes will be collected even if the trial treatment is interrupted or is not actually given.

Eligibility criteria will be entered directly into the trial database. Subsequent data will be transmitted electronically to the CTU by entering the data directly into the trial database (eCRF) at two time-points: 3 days after randomisation and at the time of expected date of delivery or discharge from hospital if later. Each participating centre will also be provided with hard copies of CRFs (pCRF) after each patient has completed trial. The data at each participating centre will be handled in accordance with local regulatory legislation and Ethics Committee approval.

Each randomised woman and baby will be followed-up until discharge from the randomising hospital or death (whichever comes first). Some patients may be transferred out to another hospital and, therefore, neonatal outcome will also be assessed at term age (as close to the expected day of expected day of delivery as possible) by telephone or clinic visit.

There is an expectation that, in future, funding will be secured for long term follow-up of all survivors to contribute to the international IPD meta-analysis. This will be made explicit in the Patient Information Leaflet. To this end, the TCC will develop plans to stay in contact will all trial participants by regular communication as appropriate (newsletters, text messages, emails)

10.2 Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing

records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial.

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. Data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the CRF will be considered the **source document,** unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent including date of provision of patient information, trial screening number, trial number, study treatment and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

10.3 Data handling and Record Keeping

This trial will be coordinated by the LCTU and conducted in hospitals in the UK and Republic of Ireland. Data will be collected at each site by local investigators and securely transmitted electronically to the CTU based in British Colombia, Canada.

10.3.1 Site level

Any trial related documents (pCRF, SAE forms, and copies of histology, and post-mortem reports) should be kept in locked filing cabinets only accessible by authorised personnel. Investigator Site Files (ISF) and other files making up the TMF should be stored in lockable filing cabinets.

Any documents that must be transferred to the CTUs for data entry or data reporting such as AE/SAE forms, they should not contain any personal identifiers. Patient should be identified by trial number and initials ONLY. If any data/documents/ information is requested by either CTU to should be faxed directly to the CTU. A log of documents sent should be maintained at the Site. Copies of faxed documents must be retained in the ISF with the date of faxing logged.

Any personal identifiers should be kept within secure premises and secure systems. Personal identifiers should not be accessed via remote access unless the machine/device used to access the data is fully encrypted or the machine/device used to access the data is kept within the research site's premises at all times and held securely (i.e. locked away when not in use, not left unattended whilst in use and not used in a public or general access area). The downloaded

material on the machine/device used to access must be deleted as soon as no longer required. If electronic data transfer is used, this can be conducted via the EDC system.

10.3.2 Clinical Trials Unit Level

The eCRFs entered by sites will be stored on UBC servers and can only be accessed by the CTU data management team. The database management system on the server is password protected, with each member of the research team responsible for data entry and data quality check having their own password. The server will be backed up daily by IT system administrator according to the local IT policies.

If eCRFs are transferred or stored offline using removable media (including laptops, portable hard drives, USB key drives) they must be encrypted with a password. The transferred material on the removable media should be deleted as soon as data transfer is successfully completed.

The LCTU will also have access to the database to enter SAEs and monitoring the data collection in the UK.

10.4 Data Recording and Sharing

The principal investigator at each site is responsible for the quality of the data recorded into the eCRF. All patient information upon leaving each site will be identified in a manner designed to maintain patient confidentiality. All records will be kept in storage areas with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring, auditing or inspection by the relevant authorities. The trial team involved may not disclose or use for any purpose other than performance of the trial any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement must be obtained for the disclosure of any said confidential information to other parties.

All trial investigators and associated staff must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to clinical staff treating the participants.

Computers used to collate the data will have limited access measures by user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

11. MONITORING

This trial is a randomised, placebo controlled trial. The intervention has marketing authorisation in Europe and the UK and has been in clinical use for over 10 years and its safety profile in non-pregnant population is well established. The trial will routinely collect data on adverse events which may theoretically be associated with this product and the condition under investigation, and these will be reviewed routinely by the independent Data Monitoring Committee (DMC). The STRIDER study will involve consent, the oral administration of the trial drug, measurements of blood pressure, and collecting routine clinical information from medical records for the participants. For some participants in selected investigating sites the study may also involve additional maternal blood samples and collection of maternal blood samples and the placenta after birth (see Ancillary studies). Clinical management for underlying conditions will remain as per each hospital's standard protocol. Monitoring will be performed in accordance with the STRIDER Monitoring Plan A detailed Monitoring Plan will be developed to assure appropriate conduct of the trial which will incorporate 100% central monitoring in conjunction with procedures such as investigator training, meetings and written guidance. In addition, all data will be subject to statistical monitoring and at least 10% of data will be subjected to on-site monitoring.

Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial related and source documents must be kept for twenty-five years after the end of the trial.

12. STATISTICS

12.1 Introduction

This section includes an overview of the statistical considerations relevant to the trial including randomisation, blinding, recruitment and a brief overview of any planned analysis. A separate statistical analysis plan will be developed to give full details of the analysis of any data. A separate DMC report plan will also be developed which will detail the data that are presented to the DMC at each meeting. Both of these documents will be approved and signed off by a reviewing statistician as well as the Chair of the trial DMC and TSC.

12.2 Blinding

Strider is a double blind placebo controlled trial. Both the patient and any clinical staff will be blind to the treatment allocation. Any unplanned unbinding that occurs in the trial shall be reported as a major protocol deviation. Unblinded patients shall then be retained in the intention to treat population but removed from any per protocol analyses. Planned unblinding procedures are set for the event of a possible SUSAR, full details can be found in Section 7.9 of this protocol. Throughout the trial, the trial statistician shall remain unblind to treatment allocation to facilitate reporting to the DMC.

12.3 Randomisation

Randomisation will be performed using a web-based randomisation service operating at the Clinical Trials Unit (CTU) British Columbia Women's Hospital (Vancouver, Canada). Passwords and login details will be provided to each centre at the point of site 'green light' authorisation by LCTU.

Treatments were allocated with equal probability by means of computer generated random permuted blocks of sizes 2 and 4 in equal proportions, created by the Liverpool Cancer Trials Unit (LCTU) in accordance with their standard operating procedure employing the Stata add-in ralloc. The randomisation was stratified by two factors, the participating centres and the gestational age at diagnosis.

12.4 Outcome Measures

12.4.1 Primary Outcome

Primary outcome is randomisation to birth interval. One week difference in the mean randomisation to birth interval is considered to be clinically important.

12.4.2 Secondary Outcome

Secondary Endpoints are divided into sub-groups: Fetal, Infant and Maternal

Fetal Endpoints

I. Estimated fetal weight
II. Abdominal circumference growth velocity

III. Serial measurements of Doppler pulsatility index in the umbilical artery, middle cerebral artery and ductus venosus and uterine arteries
IV. Serial measurements of short term variability of the fetal heart rate recorded by transabdominal cardiotocography

Infant Outcomes

I. Gestational age at birth (days)
II. Survival to discharge
III. Birth weight centile
IV. Length of admission on the Neonatal Intensive Care Unit
V. Bronchopulmonary dysplasia requiring oxygen 36 weeks corrected age
VI. Necrotising enterocolitis (requiring surgery),
VII. retinopathy of prematurity (requiring treatment such as laser, grade 2/3 or more);
VIII. severe central nervous system injury (detected by ultrasound and/or MRI) periventricular leucomalacia grade II or more, or intracerebral haemorrhage grade III or more or hydrocephalus;
IX. confirmed sepsis by positive blood culture
X. patent ductus arteriosus needing medical or surgical treatment
XI. need for inotropes or vasopressors
XII. Number of doses of surfactant
XIII. Ventilator days
XIV. Supplemental oxygen days
XV. Number of days to full feeds

Maternal safety

I. Mode of delivery
II. Standardised blood pressure and pulse monitoring during treatment
III. postpartum haemorrhage;
IV. recording of the side effects e.g. headache, facial flushing;
V. in-patient postnatal stay

12.5 Sample size

Our internal audits of early-onset IUGR cohorts revealed an average diagnosis-delivery interval of around 20 days with standard deviation of 11 days. In order to confirm that sildenafil can prolong pregnancy by one week (7 days), we need to recruit a total of 104 women (alpha 5%, power 90%). Although we do not anticipate any loss to follow-up, we plan to recruit 112 women to account for any possible post-randomisation withdrawal of consent or missing data. As this is a placebo-controlled double blind study, it can be safely inferred that any difference in the timing of delivery will be caused by sildenafil.

Our secondary hypothesis is that sildenafil will improve utero-placental circulation and therefore delay the development of fetal cardiovascular changes (reduced short term heart rate variability, deterioration of fetal Doppler indices) that lead to the indication for iatrogenic delivery. With a complete data set for around 100 participants, we will be able to detect (with power of $\geq$80% and

α=5%) a clinically meaningful 20% difference in mean Doppler Pulsatility Index (PI) values of uterine artery (0.86, SD 0.20), middle cerebral artery (2.21, SD 0.39) and ductusvenosus (0.62, SD 0.22).

Previous randomised controlled studies using sildenafil in non-pregnant subjects demonstrated significant changes in the proposed maternal parameters using a modest number of participants (n<30). We are therefore anticipating that our sample size will yield sufficient information to assess maternal pulse and BP changes. Even assuming incomplete data for up to 10% of participants, a sample of around 100 women would allow us to detect (with power of 80% at significance of 5%) a difference of 7 mmHg in mean arterial pressure and a difference of 6 beats/min in heart rate.

Vascular functional studies typically have a standard deviation of approximately 8%. To detect a change of 15%, this requires 6 women per group. Therefore, for all experiments proposed, we will use vessel from 8 women per group to allow for possible experimental failure.

12.6 End of Study

The study will end when the last recruited woman/baby is discharged from hospital after birth, or the baby has reached expected date of birth, whichever is later. No interim analysis or stopping rules for efficacy are planned within the study although the DMC will be able to recommend stopping the trial in terms of safety

12.7 Patient Accrual

Patient accrual is anticipated to last 24 months. The aim is to recruit a total of 112 in this time scale. Based on having 18 sites open to recruitment with sites recruiting an average of 7.5 patients over a 2 year period.

12.8 Data Analyses

The main analyses will compare all those allocated sildenafil versus those allocated placebo, on an 'intention to treat' basis, irrespective of whether they received the allocated treatment or not. Results will be presented as appropriate effect estimates with a measure of precision (95% confidence intervals). Frequency and nature of interim analyses including safety analysis will be determined in discussions with DMC and recorded in DMC report plan.

12.8.1 Primary Outcome

The primary outcome of the difference in gestational length shall be analysed across groups using a Wilcoxon rank sum test. Further regression analysis shall be carried out including in the model treatment arm and stratification factors as main effects. Further key covariates of interest shall also be included. The primary analysis is to be carried out using the intention to treat principle on a complete case dataset. Sensitivity analyses shall be carried out both on a per protocol dataset and a dataset including missing data via multiple imputation. Full details are available in the Statistical Analysis Plan (SAP) separate to this protocol.

12.8.2 Secondary Outcomes

Analyses of secondary outcomes shall be analysed comparing each outcome across treatment arms using a Fisher/Chi-suare test for categorical data and a Mann Whitney U-test for continuous data.

Modelling to adjust for key covariates of interest is carried out where possible. Full details are included within a separate statistical analysis plan (SAP).

13. QUALITY CONTROL & ASSURANCE

13.1 Peer Review

The trial was extensively peer reviewed as part of the process of gaining grant funding from the MRC/NIHR. The trial will receive a favourable ethics opinion before the trial commences and will obtain clinical director approval from each site before recruitment commences.

13.2 Risk Assessment

A detailed clinical risk assessment has been carried out by the lead clinical site with input by the Chief Investigator, Trial Co-ordinator, R&D Manager and R&D Director. Input has also been given by the CTU. The University of Liverpool as sponsor has reviewed the documentation as are satisfied that the risk assessment has been carried out adequately and is fit for purpose.

In addition organisational and information governance risk assessments will be carried out before recruitment commences.

A monitoring plan has been designed by the lead clinical site, with input by the CTU. Again this has been approved for use by the Sponsor.

13.3 Trial Oversight

13.3.1 Sponsorship and Trial Management

The STRIDER study is jointly sponsored by the University of Liverpool and the Liverpool Women's NHS Foundation Trust and overseen by the Trial Steering Committee (TSC). Day to day running of the trial will be co-ordinated by the Trial Management Group (TMG) supported by the Liverpool Cancer Trials Unit Liverpool Women's Hospital. The TMG may delegate some responsibilities to third parties which will be outlined in relevant agreements.

13.3.2 Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final Protocol and, throughout the trial, will take responsibility for:

a) Major decisions such as need to change the protocol for any reason
b) Monitoring and supervising the progress of the trial
c) Reviewing relevant information from other sources
d) Considering recommendations from the DMC
e) Informing and advising the Trial Management Group on all aspects of the trial

The TSC will include experienced obstetric and neonatal experts, and clinical trialists. Meetings will be held at regular intervals determined by need, but no less than once a year. A TSC Charter will be agreed at the first meeting which will detail how it will conduct business.

13.3.3 Trial Management Group (TMG)

The Trial Management Group will consist of the Protocol Committee members plus the Trial Co-ordinator. The TMG will act on behalf of the Sponsor and will be responsible to the TMG to ensure that all Sponsors' responsibilities are carried out. The responsibilities will include (but are not limited to):

- Report to the Trial Steering Committee
- Maintain the Trial Master File
- Identify trial sites
- Confirm all approvals are in place before release of the trial treatment and the start of the trial at a site
- Provide training about the trial
- Provide study materials
- Data management centre
- 24-hour advice and unblinding service
- Give collaborators regular information about the progress of the study
- Respond to any questions (e.g. from collaborators) about the trial
- Ensure data security and quality and observe data protection laws
- Safety reporting
- Ensure trial is conducted in accordance with the ICH GCP
- Statistical analysis
- Publication of trial results

13.3.4 Independent Data Monitoring Committee (DMC)

Severe early-onset IUGR is associated with a high incidence of fetal/neonatal mortality and morbidity. To provide protection for study participants an independent data monitoring committee (DMC) will be appointed for this trial to oversee the safety monitoring. The DMC will regularly review the data from the ongoing trial and advise the Trial Steering Committee regarding the continued safety of the current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and each member will be given in the DMC charter which will be in line with that proposed by the DAMOCLES Study Group. Membership includes expertise in the relevant field of study, statistics and research study design.

The DMC charter includes, but is not limited to, defining:

1. The schedule and format of DMC meetings
2. The format for presentation of data
3. The method and timing of providing interim reports
4. Stopping rules

The DMC has the responsibility for deciding whether the unblinded results should be revealed to the trial steering committee whilst randomisation is on-going. The DMC will only follow this course of action if the following conditions are met, as per the DMC charter:

1. The results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of, participants in terms of the major outcome;
2. The results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with other trial results that exist.

Exact criteria for "proof beyond reasonable doubt" are not, and cannot be, specified by a predefined stopping rule. The DMC charter is in accordance with the Peto-haybittle stopping rule whereby an interim analysis of major endpoints would need to involve a difference between treatment and placebo of at least three standard errors to justify premature closure [36, 37]. Interim subgroup analysis would need an even greater burden of evidence to justify premature closure. The number and timing of interim analyses is not predetermined. In summary, the stopping rules require extreme differences to be present to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgement.

13.4 Collaborator Responsibilities

Coordination within each participating hospital will be through a local Principal Investigator whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- Ensure all necessary approvals are in place prior to staring the trial
- Delegate trial related responsibilities only to suitably trained and qualified personnel
- Train relevant medical and nursing staff who see obstetric patients and ensure that they remain aware of the state of current knowledge, the trial and its procedures
- Agree to comply with the final trial protocol and any relevant amendments
- Ensure that all women with severe early-onset IUGR are considered for the trial
- Ensure consent is obtained in line with local approved procedures
- Ensure that the patient entry and outcome data are completed and transmitted to the TCC in a timely manner
- Ensure the Investigator's Study File is up to date and complete
- Ensure all Adverse Events are reported promptly to the TCC
- Accountability for trial treatments at their site
- Ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements
- Allow access to source data for monitoring, audit and inspection
- Be responsible for archiving all original trial documents including the data forms for twenty-five years after the end of the trial

14. ETHICAL CONSIDERATIONS

At the time of diagnosis of severe, early-onset IUGR women will be given an information leaflet about the STRIDER study and asked to participate. The diagnosis of IUGR can be an extremely stressful time for parents and relatives. Whilst recruitment to the STRIDER study can occur at any point after diagnosis, it is not time dependent and time can be allowed for the potential participant to be fully informed prior to consent.

The requirements of the relevant ethics committee will be adhered to at all times.

A favourable ethics opinion has been received for the trial by: NRES Committee North East – Newcastle & North Tyneside 2.

15. Finance and Insurance

15.1 Finance

The MRC/NIHR is funding the run-in costs for this trial and up to 112 patients' recruitment. Funding for this trial covers meetings and central organisational costs only. The trial medications (active and placebo) have been purchased on the open market via a tendering process. The design and management of the study are entirely independent of the manufacturers of sildenafil, which is not a new product.

15.2 Insurance

The study is co-sponsored by the University of Liverpool and the Liverpool Women's NHS Foundation Trust; however tasks and responsibilities will be delegated to partner organisations (including Chief Investigator LCT and Canadian CTU). The sponsors are responsible for ensuring proper provision for insurance and indemnity to cover their liability and the liability of the Chief Investigator and staff.

The protocol has been designed by the Chief Investigator (Zarko Alfirevic) and researchers employed by the University of Liverpool (Andrew Sharp) and partner organisations (Phillip Baker, Keele University; Louise Kenny, University College Cork; Aris Papageorghiou, St. Georges Hospital; Edward Johnstone, University of Manchester). The University of Liverpool has insurance in place (which includes no-fault compensation) for negligent harm caused by such protocol design.

15.3 Indemnity

The Liverpool Women's NHS Trust and the University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Liverpool Women's NHS Foundation Trust and the University of Liverpool does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

16. Authorship and Publications

The success of the trial will be dependent entirely upon the collaboration of clinicians in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from a participating site as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to the TSC and then to trial collaborators.

The protocol and results from the STRIDER trial will be published in an established peer-reviewed journal. At least one publication of the main results will be made. Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients will take place via the media, trial website and relevant patient organisations. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients.

17. Protocol Amendments

17.1 Version 1 (17/DEC/2013)

Original document submitted for ethical review approved version

17.2 Version 2 (25/JAN/2011)

Main changes from version 1: Date: 17/12/13

1. Clarification on the end of study definition.

   Old text:

   The study will end when last recruited woman and her baby are discharged from hospital after birth

   New text:

   The study will end when the last recruited woman/baby is discharged from hospital after birth, or the baby has reached expected date of birth, whichever is later.
2. Addition of Cardiovascular profiling and blood pressure and pulse monitoring to study procedures table in section 6.1
3. Addition of Individual patient Analysis and Cardiovascular Profiling section 8.3 and 8.4 respectively in the ancillary studies section of the protocol
4. Removal of withdrawal due to bereavement – section 12.4

17.3Version 3 (30/06/2014)

Main changes from version 2: date: 25/01/2014)

1. Clarification on reporting of SAE's
2. A list of individual study drug discontinuation criteria included.
3. Inclusion of prohibited medications to the exclusion criteria
4. guidance about concomitant medication has been added with reference to the SmPC
5. Justification in to why only one dose range has been proposed. Rationale for why a dose of 25mg 3 times per day is deemed appropriate has been included.
6. Clarification on infant outcomes
7. Additional information added to the Placental sampling studies.

18. Examples of SAE'sReferences

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